

DEVELOPMENT AND APPLICATION OF AN AMBULATORY ESOPHAGEAL MANOMETRY SYSTEM

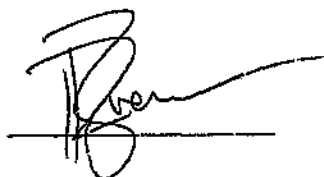
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For the Degree of Doctor of Philosophy (Medicine).

Johannesburg and Los Angeles, 1997

DECLARATION

I, Ross Macrae Bremner, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy (Medicine) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree of examination at this or any other University.

A handwritten signature in black ink, appearing to read 'Ross Macrae Bremner', is written over a horizontal line.

Fifteenth day of February, 1997.

DEDICATION

To my father, Cedric Gordon Bremner, who was never short of encouragement and advice. His love for the art of medicine and his constant endeavor for excellence will always inspire me.

PRESENTATIONS AND PUBLICATIONS IN SUPPORT OF THIS THESIS

Published Manuscripts and Book Chapters

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Using prolonged motor activity monitoring, what is the proportion of peristaltic esophageal contractions occurring in patients with achalasia? In Giuli R, Tytgat GNJ, DeMeester TR, Galmiche JP (eds): *The Gastroesophageal Junction*. Amsterdam: Elsevier Science B.V., 1997, In Press.

Presentations

Validation of computerized analysis of multichannel 24-hour esophageal motility. Presented at the 5th annual meeting of the American Association for Medical Instrumentation, Anaheim, California, 1992.

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Secondary peristalsis is rare and is not important in clearing the esophagus of refluxed gastric acid. Presented at the Annual Meeting of the American Gastroenterological Association, San Francisco, California, 1993

How can the sensitivity of the esophageal mucosa to acid be assessed quantitatively? Presented at the 4th world congress of O.E.S.O, Paris, 1993

Technical Aspects of Ambulatory Esophageal Manometry. Presented at the biennial meeting of the American Motility Society, Tahoe, California, 1993

Making Sense of Ambulatory Esophageal Motility. Presented at the biennial meeting of the American Motility Society, Tahoe, California, 1993

Pharyngeal Swallowing: The major factor in clearance of esophageal reflux episodes. Presented at the annual meeting of the American Surgical Association, Baltimore, Maryland, 1993.

A Cause of Non-Obstructive Dysphagia in Patients with Gastroesophageal Reflux Disease. Presented at the Annual meeting of the American Gastroenterological Association, Boston, 1994

Should the reproducibility of ambulatory esophageal manometry encourage more universal use of this technology? Presented at the 5th world congress of O.E.S.O, Paris, 1996

Using prolonged motor activity monitoring, what is the proportion of peristaltic esophageal contractions in patients with achalasia? Presented at the 5th world congress of O.E.S.O, Paris, 1996

Further evidence of altered sensation to reflux in patients with Barrett's esophagus. Presented at the Annual meeting of the American Gastroenterological Association, San Francisco, 1996

Clinical use of ambulatory motility studies. Presented at the annual USC esophageal course "Medical and Surgical aspects of Esophageal Disorders: Pathophysiology and treatment." TR DeMeester, DO Castell (Directors); Hawaii, 1993, 1994, 1996.

ABSTRACT

The aim of this project was to develop an automated system capable of monitoring intraesophageal pressures for prolonged periods of time, and to evaluate the clinical relevance of this system. Stationary esophageal manometry is, at present, the cornerstone of assessing esophageal motor function. Its shortcomings, related to the brevity of the test and the unphysiologic environment in which it is performed, have limited our understanding of esophageal motility abnormalities. The goal of this study was to overcome these shortcomings.

The thesis first describes the development of the hardware and software required to continuously monitor, and then analyze, pressures and pH from the esophagus in the ambulatory individual over a 24-hour period. Validation of the automated analysis and establishment of normal values are then described. The system was then used to evaluate patients with functional esophageal disorders in the esophageal laboratory at the University of Southern California (USC), Los Angeles.

Many patients with gastroesophageal reflux disease were found to have a profound motility defect of the esophageal body as evidenced by an inability to improve propulsive function during meals. This defect was not apparent on stationary manometry and has important implications for anti-reflux surgery. The increased sensitivity of ambulatory manometry in detecting poor motor function is now being used to tailor surgery in those requiring operative repair at USC.

Patients with primary esophageal motor disorders such as diffuse esophageal spasm, achalasia, nutcracker esophagus and hypertensive lower esophageal sphincter were found to have many overlapping features which inspired a new classification based on the *functional* defect as seen on ambulatory manometry. The basis and value of this is discussed.

The added advantage of combining a pH probe with the pressure manometer is the ability to detect clearance mechanisms in normal subjects and patients with

gastroesophageal reflux disease. The ability to record pharyngeal pressures using this system demonstrated the importance of pharyngeal induced peristalsis in clearing the esophagus of refluxed acid. Clearance mechanisms were found to be related to the state of consciousness and provided an explanation for the severe mucosal complications seen in patients with excessive nocturnal reflux. The clearance mechanisms of patients with Barrett's esophagus were shown to be compromised because of an alteration in the sensitivity of the columnar mucosal feedback mechanisms resulting in delayed and phlegmatic pharyngeal swallowing after the onset of a reflux episode.

This thesis describes the new insights afforded by ambulatory manometry and the benefits of having this information prior to instituting therapy in patients with esophageal disorders. The developed system can be performed with little added discomfort to the patient undergoing pH monitoring. It is hoped that the ease of performing the test and the added insight provided by the study will encourage the use of ambulatory manometry as the gold-standard for evaluating esophageal motor disorders.

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TABLE OF CONTENTS

DECLARATION	ii
DEDICATION	iii
PUBLICATIONS	iv
ABSTRACT	viii
ACKNOWLEDGEMENTS	x
LIST OF FIGURES	xviii
LIST OF TABLES	xxiv
ABBREVIATIONS AND NOMENCLATURE	xxvi
PREFACE	xxvii

CHAPTER 1: HISTORY OF ESOPHAGEAL MANOMETRY AND DEFINITIONS OF MOTILITY DISORDERS

1.1 HISTORY OF MANOMETRY	1
1.2 IDENTIFICATION AND CLASSIFICATION OF ESOPHAGEAL MOTOR	8
1.2.1 What is Normal?	8
1.2.2 Achalasia	9
1.2.3 Diffuse Esophageal Spasm (DES)	12
1.2.4 Nutcracker esophagus	15
1.2.5 Scleroderma and Other Secondary Motility Disorders	17
1.2.6 Non-specific esophageal motility disorders (NSEMD)	17
1.3 HISTORY OF AMBULATORY MANOMETRY	20

CHAPTER 2: DEVELOPMENT OF THE HARDWARE

2.1	HARDWARE REQUIREMENTS	25
2.1.1	Data Recorders	26
2.1.2	Catheters	27
2.1.2.1	Cardiac Interference	29
2.1.2.2	Development of a Swallow Channel	30
2.1.3	Personal Computer	34
2.2	ESTABLISHING OPTIMAL SAMPLING FREQUENCIES	36
2.2.1	Background	36
2.2.2	Methods	37
2.2.3	Results	38
2.2.4	Discussion	40
2.3	THE EFFECT OF EXTRA TUBES IN THE ESOPHAGUS	42
2.3.1	Background	42
2.3.2	Methods	42
2.3.3	Results	44
2.3.4	Discussion	45

CHAPTER 3: SOFTWARE DEVELOPMENT

3.1	OVERVIEW	47
3.2	GRAPHIC DISPLAY	48
3.3	DATA ANALYSIS	50
3.3.1	CONTRACTION ANALYSIS	52
3.3.1.1	Baseline	52
3.3.1.2	Threshold	52
3.3.1.3	Artefact Recognition	53
3.3.1.4	Contraction Descriptors	54
3.3.1.5	Multi-peaked Contractions and Repetitive contractions	56
3.3.2	PROPAGATION ANALYSIS	56
3.3.3	EFFICACY ANALYSIS	61
3.4	SCREEN DISPLAY OF ANALYSIS IN REVIEW MODE	63
3.5	SOFTWARE ANALYSIS OF THE SWALLOW CHANNEL	64
3.6	HARDCOPY OF REPORTS OF THE FINAL ANALYSIS	65
3.7	INCORPORATING ESOPHAGEAL pH ANALYSIS.	66

3.8	INCORPORATION OF GASTRIC PH ANALYSIS	67
-----	--	----

CHAPTER 4: METHOD OF PERFORMING THE 24-HOUR AMBULATORY pH AND MANOMETRY STUDY

4.1	INTRODUCTION	69
4.2	MEDICATIONS PERMITTED DURING THE STUDY	69
4.3	RADIOLOGY	70
4.4	STATIONARY MANOMETRY	70
4.5	CALIBRATION OF THE CATHETERS	72
4.5.1	Calibration of the pH Electrodes	72
4.5.2	Calibration of the Manometry Catheter	73
4.6	PLACEMENT OF THE PROBE	74
4.6.1	Anesthetizing the Nasopharynx	74
4.6.2	Positioning the pH Probe in the Esophagus.	76
4.6.3	Design and Placement of the Ambulatory Manometry Catheter	76
4.7	THE DIARY	77
4.8	DIET	77
4.9	ACTIVITY	79
4.10	SMOKING AND ALCOHOL	80
4.11	EXERCISE	80
4.12	DURATION OF MONITORING	81
4.13	INPATIENT VERSUS OUTPATIENT MONITORING	81
4.14	PATIENT TOLERANCE AND COMPLIANCE OF 24 HOUR PH AND MOTILITY MONITORING.	82
4.14.1	Background	82
4.14.2	Methods	82
4.14.3	Results	83
4.14.4	Discussion	83

CHAPTER 5: MANUAL VERIFICATION OF THE COMPUTER ANALYSIS OF 24-HOUR ESOPHAGEAL MANOMETRY

5.1	BACKGROUND	85
5.2	METHODS	85
5.2.1	Ambulatory Manometry	85

5.2.2 Manual Analysis	86
5.2.3 Computer Analysis	86
5.2.4 Statistics	87
5.3 RESULTS	88
5.4 DISCUSSION	90
5.5 CRITICAL EVALUATION AND COMMENT	93
 CHAPTER 6. ASSESSMENT OF ESOPHAGEAL MOTOR FUNCTION DURING MEALS	
6.1 MONITORING PRESSURES DURING EATING	94
 CHAPTER 7: NORMAL CIRCADIAN ESOPHAGEAL BODY FUNCTION	
7.1 INTRODUCTION	98
7.2 METHODS	98
7.2.1 Data Analysis	98
7.2.2 Statistics	99
7.3 RESULTS	99
7.4 DISCUSSION	101
7.5 CRITICAL EVALUATION AND COMMENT	104
 CHAPTER 8: ASSESSMENT OF ESOPHAGEAL MOTOR FUNCTION IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE (GERD)	
8.1 BENEFITS OF MEASURING PRESSURES SIMULTANEOUSLY WITH pH MONITORING	105
8.1.1 The temporal relationship between coughing and reflux	105
8.1.2 Interpreting the effect of "napping" on acid exposure.	107
8.1.3 Artefactual reflux	108
8.2 ESOPHAGEAL MOTOR DYSFUNCTION IN GERD PATIENTS	109
8.2.1 Background	109
8.2.2 Methods	109
8.2.3 Results	110
8.2.4 Discussion	115

8.3	CRITICAL EVALUATION AND COMMENT	117
 CHAPTER 9: CIRCADIAN ESOPHAGEAL MOTOR FUNCTION IN PATIENTS WITH TREATED AND UNTREATED ACHALASIA		
9.1	BACKGROUND	118
9.2	METHODS	118
9.2.1	Stationary and Ambulatory Manometry	119
9.2.2	Statistics	120
9.3	RESULTS	120
9.4	DISCUSSION	128
 CHAPTER 10: THE HYPERTENSIVE LOWER ESOPHAGEAL SPHINCTER: A MATTER OF A MORE SEVERE MOTILITY DISTURBANCE		
10.1	BACKGROUND	132
10.2	METHODS	132
10.2.1	Patient Population	132
10.2.2	Motility and pH studies	133
10.2.3	Statistics	134
10.3	RESULTS	135
10.4	DISCUSSION	138
10.5	CRITICAL EVALUATION AND COMMENT	141
 CHAPTER 11: AMBULATORY ESOPHAGEAL MANOMETRY IN PATIENTS WITH CLASSIC DIFFUSE ESOPHAGEAL SPASM		
11.1	BACKGROUND	142
11.2	METHODS	142
11.3	RESULTS	144
11.4	DISCUSSION	149
11.5	CRITICAL EVALUATION AND COMMENT	152

CHAPTER 12 THE VALUE OF AMBULATORY MANOMETRY IN PATIENTS WITH UNCLEAR DIAGNOSES

12.1	BACKGROUND	153
12.2	METHODS	154
12.3	RESULTS	155
12.4	DISCUSSION	156

CHAPTER 13: ASSESSMENT OF ACID CLEARANCE USING SIMULTANEOUS AMBULATORY PHARYNGOESOPHAGEAL MANOMETRY AND pH MONITORING

13.1	BACKGROUND	159
13.2	PATIENTS AND METHODS	160
13.2.1	Study Population	160
13.2.2	Ambulatory pH and motility monitoring	160
13.2.3	Analysis	160
13.3	RESULTS	162
13.4	DISCUSSION	167
13.5	CRITICAL EVALUATION AND COMMENT	169

CHAPTER 14: MECHANISMS OF ESOPHAGEAL ACID CLEARANCE IN PATIENTS WITH BARRETT'S ESOPHAGUS

14.1	BACKGROUND	170
14.2	METHODS	171
14.3	RESULTS	172
14.4	DISCUSSION	178

CHAPTER 15: CONCLUSIONS

15.1	HARDWARE AND SOFTWARE DEVELOPMENT	183
15.2	VALIDATION AND ESTABLISHMENT OF NORMAL VALUES	183
15.3	GASTROESOPHAGEAL REFLUX DISEASE	184

15.4	ACHALASIA	184
15.5	HYPERTENSIVE LOWER ESOPHAGEAL SPHINCTER	184
15.6	DIFFUSE ESOPHAGEAL SPASM	184
15.7	FUNCTIONAL CLASSIFICATION	185
15.8	CLEARANCE	185
15.9	AMBULATORY MANOMETRY IN THE FUTURE: IDEAS FOR FURTHER RESEARCH	186

CHAPTER 16. APPENDIX

APPENDIX A: SPECIFICATIONS OF THE MICRODIGITRAPPER . . .	187
APPENDIX B: TECHNICAL SPECIFICATIONS OF THE SOLID STATE CATHETERS	189
APPENDIX C: MODIFICATIONS OF THE KONIGSBERG CATHETER	191
APPENDIX D: DEFINITIONS OF TERMS	193
APPENDIX E: ALGORITHMS FOR MULTYPEAKED AND REPETITIVE CONTRACTIONS	197
APPENDIX F: DIARY FOR 24 HOUR STUDY	201
APPENDIX G: QUESTIONNAIRE AFTER 24 HOUR STUDY	202

REFERENCES	205
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LIST OF FIGURES

CHAPTER 1

Figure 1.1 The early apparatus used by Charles Code in the 1940's for measuring intraesophageal pressures.	5
Figure 1.2 The solid state pressure transducer used by Charles Code as early as 1953.	6
Figure 1.3 The low compliance perfusion system of Arndorfer and Dodds which has become the gold standard for esophageal manometry today.	7
Figure 1.4 The dilators of Alfred Jordan used in 1913 for the treatment of cardiospasm.	10

CHAPTER 2

Figure 2.1 Graphical representation of the ambulatory manometry system.	25
Figure 2.2 Photograph of the new generation 4 megabyte memory recorder.	26
Figure 2.3 The ambulatory esophageal manometry system in an ambulatory subject.	27
Figure 2.4 Photograph of the glass pH probe, the Sentron catheter, the Konigsberg catheter, and the standard water perfused manometry catheter from above, down.	28
Figure 2.5 Diagram to show the position of the Konigsberg and Sentron catheters for comparison.	30
Figure 2.6 An example of the simultaneous recordings of the two catheters in the same esophagus at the same time. Note the cardiac interference in the middle channel of the Konigsberg tracing.	31
Figure 2.7 Gross artefact introduced by cardiac interference in the lower most channel of the Konigsberg tracing.	32
Figure 2.8 Diagram to show the position of the catheter containing four transducers. The uppermost transducer is placed just proximal to the upper esophageal sphincter.	34
Figure 2.9 Comparison of the reconstruction of a contraction when the original pressure data is sampled and stored at different frequencies.	37
Figure 2.10 The difference in recorded amplitudes of contractions for the different sampling frequencies expressed as a percentage of the true amplitude.	39
Figure 2.11 Integrated monitoring of ambulatory esophageal pH, gastric pH,	

and esophageal manometry.	43
-----------------------------------	----

CHAPTER 3

Figure 3.1 The algorithm for development of the software for analysis of the recorded ambulatory manometry data.	48
Figure 3.2 An example of the screen display of the ambulatory esophageal pH and manometry recording (right) next to a graphical representation of the position of the transducers (left).	50
Figure 3.3 An example of the 24 hour pH and manometry recording in the compressed mode showing the full 24 hours of study.	51
Figure 3.4 Graphical representation of an esophageal contraction superimposed on the oscillating pressure changes of respirations.. . . .	53
Figure 3.5 An example of the ambulatory recording showing the intrathoracic pressure changes with coughing, nose-blowing and sniffing.	54
Figure 3.6 The calculation of wave duration by different definitions. Note the respiratory fluctuations superimposed on the same contraction at different phases of the respiratory cycle.	56
Figure 3.7 The algorithm for classification of contractions and waves.	57
Figure 3.8 Classification of the types of peristaltic waves.	59
Figure 3.9 Graphical representation of simultaneous waves	60
Figure 3.10 Graphical representation of the detection of low amplitude contractions by the modified program.	62
Figure 3.11 An example of the screen display of the recognized contractions after the analysis. This enables on screen viewing of the analysis of individual contractions and waves.	63
Figure 3.12 An example of the screen display of the pharyngo-esophageal manometry. The pharyngeal transducer is used to flag swallows.	64
Figure 3.13 An example of the pharyngo-esophageal manometry with the pharyngeal transducer in the region of the cricopharyngeus muscle.	65
Figure 3.14 An example of how an increased sampling frequency increases the recognized number of reflux episodes (arrows). Dot = sampled data point.	67

CHAPTER 4

Figure 4.1 A method of calibrating the manometry catheter.	73
Figure 4.2 The calibration column containing water in which the manometry catheter is placed.. . . .	75
Figure 4.3 A compressed example of the ambulatory recording showing the	

effect of ice-cream on esophageal motility..	79
--	----

CHAPTER 5

Figure 5.1 Correlation of the computer results for amplitude.	89
Figure 5.2 Correlation of manual and computer results for duration	89
Figure 5.3 Comparison of accuracies of propagation characteristics based on peak and on onset for the five subjects studied.	91

CHAPTER 6

Figure 6.1 An example of the recording of esophageal pressures in a normal subject when the interval between swallows is 20 seconds.	95
Figure 6.2 An example of a recording of esophageal pressures in a normal subject when the interval between swallows is 5 seconds.	96
Figure 6.3 An example of a recording of esophageal pressures in a normal subject during the eating of a meal..	96

CHAPTER 7

Figure 7.1 The normal ranges of contraction amplitude from ambulatory manometry (black) versus stationary manometry (grey)..	102
--	-----

CHAPTER 8

Figure 8.1 An example of a simultaneous pH and manometry record showing coughing preceding a reflux episode.	106
Figure 8.2 An example of the simultaneous record showing coughing following the onset of a reflux episode.	106
Figure 8.3 A compressed recording showing a post-prandial reflux episode. The addition of manometry shows that the lung episode is related to the patient falling asleep after lunch.	107
Figure 8.4 An example of how drinking acid drinks can cause a drop in esophageal pH which, in the absence of simultaneous manometry, would be construed as reflux.	108
Figure 8.5 The amplitudes of contractions for the upper, middle, and lower esophagus for normal subjects and patients with GERD during mealtimes.	112
Figure 8.6 The mean amplitude of contractions for the upright and meal periods in normal subjects and patients with GERD.	114
Figure 8.7 An example of a recording demonstrating the reflux induced "spasm" seen in two patients in this study.	114

CHAPTER 9

Figure 9.1	An example of the typical low amplitude isobaric esophageal pressure responses after a pharyngeal swallow.. . . .	121
Figure 9.2	An example of a compressed record (80 minutes) showing an elevation in the baseline pressure that occurs with eating.	122
Figure 9.3	An example of the repetitive low amplitude isobaric contractions seen in the esophagus during meals.. . . .	122
Figure 9.4	The mean contraction amplitude for the lower esophagus for the different physiologic periods for normals and the three patient groups.	123
Figure 9.5	A graphic representation of the mean number of repetitive contractions in the lower esophagus during meals.	123
Figure 9.6	The pre and postoperative LES resting pressures and the mealtime baseline pressures for the nine patients studied before and after myotomy.	125
Figure 9.7	The mean amplitudes of contractions during the meal period for the upper, middle and lower esophagus for normals and achalasia patients before and after surgery.	125
Figure 9.8	An example of the return of incomplete peristalsis that was seen occasionally after myotomy. Note that the peristaltic wave does not reach the lower esophagus.	126
Figure 9.9	An example of the recording from a patient before myotomy (A) showing no peristalsis and, (B), after myotomy with return of some peristaltic waves.	127

CHAPTER 10

Figure 10.1	Graphical representation of the measurement of the intrabolus pressure (X) during the meal periods	134
Figure 10.2	The pressure dynamics in the lower esophagus during a peristaltic contraction wave.. . . .	135
Figure 10.3	The diagnoses of the thirteen patients as assessed with stationary and ambulatory manometry.	136
Figure 10.4	The mean $\pm$ standard error for the intrabolus pressures in normal subjects and patients with HTLES.	138
Figure 10.5	An example of the ambulatory recording of a patient with HTLES during a meal (A) and during the interprandial period (B). Note the prominent intrabolus pressures in A (Arrows).	139

CHAPTER 11

- Figure 11.1** An example of the recording from a normal volunteer, A, and from one of the patients, B, showing the characteristic spastic contractions of the esophageal body. 147
- Figure 11.2** Example of the increased intrabolus pressure in the lower esophagus in a patient with DES (heavy arrow). Note also the esophageal pressurization between swallows (double arrow) 148
- Figure 11.3** The prevalence of peristalsis during the different periods in normal subjects and DES patients. 148

CHAPTER 12

- Figure 12.1** Classification of patients with non-obstructive dysphagia based on the functional defect. 156

CHAPTER 13

- Figure 13.1** An example of the simultaneous recording of pharyngoesophageal motility and esophageal pH showing clearance of the esophagus by a non-transmitted swallow. 161
- Figure 13.2** An example of the recording demonstrating a secondary peristaltic wave occurring soon after the onset of the reflux episode. A primary peristaltic wave cleared the esophagus of acid. 161
- Figure 13.3** An example of the recording which has been compressed to show an 80 minute period. Note the increased frequency of pharyngeal swallows during reflux episodes. 163
- Figure 13.4** The frequency of swallowing during the baseline non-reflux and the reflux periods for normal subjects and patients with reflux disease. 163
- Figure 13.5** The prevalence of types of waves occurring during reflux episodes in normal subjects and patients. 164
- Figure 13.6** The types of contractions that resulted in acid clearance from the esophagus. 164
- Figure 13.7** Types of contractions responsible for clearing daytime and nighttime reflux episodes in patients with reflux disease. 165
- Figure 13.8** The mean duration of reflux episodes and the number of primary waves per reflux episode in patients during the day and during the night. . . 166
- Figure 13.9** An example of a recording showing a reflux episode occurring at night. 166
- Figure 13.10** The swallowing frequency in patients during the baseline period, and during daytime and nighttime reflux. 167

CHAPTER 14

Figure 14.1	Graphical representation of a portion of the ambulatory recording showing the measurements made during reflux episodes.	172
Figure 14.2	The average time (mean $\pm$ SEM) to the first swallow for the normal subjects and patients with Barrett's esophagus.	175
Figure 14.3	The mean $\pm$ SEM of the swallowing frequency during daytime reflux episodes for normal subjects and patients with Barrett's esophagus. . .	175
Figure 14.4	The average time (mean $\pm$ SEM) to the first swallow for patients with short (SCL) and long (LCS) columnar segments.	177
Figure 14.5	The mean $\pm$ SEM swallowing frequency during daytime reflux for patients with short (SCS) and long (LCS) columnar segments.	177

APPENDIX

Figure A.1	Diagrammatic representation of the microdigitraper.	187
Figure B.1	Diagram of the design of the Sentron catheter.	190
Figure B.2	Cross-section of the Sentron catheter pressure transducer.	190
Figure C.1	Photograph to show the recessed silicone membrane covering the transducer on the modified Konigsberg catheter (above) compared to the original catheter (below).	191
Figure E.1	Graphical representation of multi peaked and repetitive contractions. . .	198

LIST OF TABLES

CHAPTER 2

Table 2.1 Comparison of the ambulatory recording using 4 and 8 Hz sampling frequencies for the total 24-hour period. (Channel 4, 5, and 6 are 15, 10, and 5 cm above the lower esophageal sphincter respectively)	40
Table 2.2 The mean $\pm$ SEM of the amplitudes of contractions for 1, 2, 3 catheters respectively.	44

CHAPTER 4

Table 4.1 Diagnostic categories based on stationary manometry	72
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CHAPTER 5

Table 5.1 Sensitivity of computer analysis for contraction recognition in each subject using different thresholds. The number of false positive contractions detected by the computer is also represented (in parentheses).	88
Table 5.2 Correlation coefficients for comparison between experts, and between experts and the computer for contraction duration.	90

CHAPTER 7

Table 7.1 Normal ranges for contractions characteristics (Medians with 5th and 95th percentiles).	100
Table 7.2 Normal Ranges for wave analysis (Medians with 5th and 95th percentiles)	101

CHAPTER 8

Table 8.1 Endoscopic classification of mucosal injury	110
Table 8.2 Stationary manometric data for normal subjects and patients with GERD.	111
Table 8.3 Ambulatory motility characteristics of normal subjects and patients with GERD.	113

CHAPTER 9

Table 9.1 Comparison of the LES features by stationary manometry.	121
Table 9.2 Ambulatory manometry wave analysis of meal periods before and after surgical myotomy in individual patients. The numbers are given as a percentage of all recognized waves.	126

CHAPTER 10

Table 10.1 Lower esophageal sphincter characteristics of normal subjects and patients with HTLES	136
Table 10.2 Ambulatory motility characteristics of normal subjects and patients with HTLES	137

CHAPTER 11

Table 11.1 Severity scoring of patients symptoms.	143
Table 11.2 Severity scores for the patients with DES	144
Table 11.3 Stationary manometric data	144
Table 11.4 Ambulatory motility characteristics of normal subjects and patients with DES.	146

CHAPTER 14

Table 14.1 Lower esophageal sphincter and esophageal body characteristics by stationary manometry.	173
Table 14.2 Ambulatory motility characteristics of normal subjects and patients with Barrett's esophagus.	174
Table 14.3 Ambulatory motility characteristics of patients with <u>SCS</u> and <u>LCS</u>	176

ABBREVIATIONS AND NOMENCLATURE

A complete list of definitions of terms used for developing the software in this thesis is included in Appendix D. It is suggested that this be read prior to reading the chapter on software development. The following is a list of abbreviations used in the thesis.

DES - diffuse esophageal spasm

GERD - gastroesophageal reflux disease

HTLES - hypertensive lower esophageal sphincter

LES - lower esophageal sphincter

NSEMD - non-specific esophageal motor disorders

UES - upper esophageal sphincter

USC - University of Southern California

PREFACE

The work for this thesis was begun in 1991 in the esophageal function laboratory at the University of Southern California (USC), Los Angeles. The goal was to develop an ambulatory esophageal monitoring system to overcome the shortcomings of stationary manometry. The system has provided insight into esophageal motor function in normal and dysfunctional states beyond that which was originally envisaged. The application of the system to disease states as described in this thesis, however, reflects only a beginning in our understanding of esophageal motor disorders and, like much research, has produced a lot more questions than answers.

The first half of the thesis describes the development of the system and the computer software required for automated analysis. Validation and establishment of normal ranges is then described. All human studies were performed with the approval of the Institutional Review Board of the University of Southern California. The second half of the thesis discusses the application of the system to patients with gastroesophageal reflux disease and to patients with esophageal motor disorders. A new classification based on functional disturbances is proposed. The last section of the thesis addresses the esophageal acid clearance mechanisms in normal subjects, in patients with gastroesophageal reflux disease, and in patients with Barrett's esophagus.

CHAPTER 1: HISTORY OF ESOPHAGEAL MANOMETRY AND DEFINITIONS OF MOTILITY DISORDERS

1.1 HISTORY OF MANOMETRY

"When the open end of a stomach tube is connected with a Marey's tambour, the lever of which writes on a revolving kymograph, while a small rubber balloon is attached around the opening of the other end of the tube, any pressure exerted upon the balloon will increase the pressure in the tambour and raise the lever, thus producing a curve upon the revolving drum.... Now if the balloon end of the stomach tube is placed within the esophagus, the balloon will be compressed by the contraction of the oesophagus, thus producing a characteristic curve on the revolving kymograph....

I shall not mention all the difficulties which had to be overcome; it will be sufficient to state that I finally learned to place both tubes in my own pharynx and oesophagus and keep them there continually for hours while drinking liquids or swallowing soft food..."

Samuel J Meltzer, 1884.¹

As early as the mid nineteenth century scientists were asking questions regarding the mechanism of food transport from the mouth to the stomach. Volkman postulated in 1841 that a pharyngeal contraction elicited a reflex movement of the esophagus which aided in bolus transport.² Wild, in 1846, thought that the important stimulus for esophageal contraction was local mucosal excitation independent of pharyngeal contractions.³ In an experiment in which he diverted the passage of food by cervical esophagostomy, he noted that the propagation of the peristaltic contraction from the pharynx to the distal esophagus was terminated. A few decades later Mosso reported evidence in support of a central nervous system control theory.⁴ Mosso was probably

also the first to attempt to quantitate the peristaltic "power" of the esophagus by attaching a wooden ball introduced through an incision in the cervical esophagus to a weight, and recording the movement of the weight with esophageal peristalsis. He noted that the thoracic esophageal peristaltic contraction could lift a weight of 250 grams, whereas the cervical esophagus could lift as much as 450 grams.

The manometric experiments of Hugo Kronecker and his student Samuel Meltzer shed light on the apparent controversies of the time, and as a result, Kronecker and Meltzer are now acknowledged as the fathers of esophageal manometry. Meltzer himself was probably the first human subject to undergo esophageal manometry as recorded above.¹ Meltzer, in 1899, summarized many years of experimentation in a paper entitled "On the causes of the orderly progress of the peristaltic movements in the esophagus."⁵ He had repeated the experiments of Wild and Mosso and explained the difference between the previous conclusions on the control of esophageal movements to the different parts of the esophagus studied: Wild had studied the cervical (striated muscle) esophagus, and Mosso the thoracic (smooth muscle) esophagus. Meltzer also noted a difference in the anesthetic techniques used, and showed that esophageal peristalsis could be abolished under conditions of deep anesthesia.

Kronecker and Meltzer used a dog model which involved placement of an olive shaped body of hard rubber through a cervical esophagostomy. A silk thread was attached to the olive body. Peristalsis was recorded when the esophagus contracted and the olive body descended into the stomach. Important contributions to our understanding of peristalsis were made from these experiments. Firstly, a distinction between primary and secondary peristalsis was made. The former was defined as being initiated by a pharyngeal swallow, and the latter as initiated in the esophageal body in the absence of a pharyngeal contraction. This distinction is still used today. Secondary peristalsis was not studied further until some sixty years later when Hwang repeated many of these experiments with more modern equipment.⁶ Secondly, it was noted when the dog swallowed rapidly, that the esophagus only responded with a sequence, or wave, of peristaltic contractions at the end of the train of swallows. This phenomenon formed the basis of much discussion on the nervous control of the gut at the time, and is known today as deglutitive inhibition. Kronecker and Meltzer's concepts of a central control

mechanism responsible for inhibition of contractions in the esophagus preceded Bayliss and Starlings "law of the intestine".⁷ Thirdly, their experiments with the olive helped further elucidate the contribution of the central and the intrinsic nervous systems to the organization of motility.

Meltzer, along with his teachers, Falk and Kronecker, developed a theory of "squirting" of liquids from the mouth through the esophagus and into the stomach without the aid of peristalsis.¹⁸ Davenport believed that the liquid used was beer!⁹ Two other observations at the time seemed to reinforce their theory: firstly, it was noted that cold liquids could be felt (and heard with a stethoscope) in the epigastric region almost immediately after being swallowed, and secondly, when strong corrosives were swallowed only some areas of the esophageal mucosa were noted to be damaged. This would not have been the case were the acid propagated by peristalsis alone.

In 1896 W.B Cannon, then a first year medical student, began a long interest in esophageal motility when he was directed to apply the newly discovered technique of X-ray imaging to study the "squirt" theory of liquid swallowing.⁹ To do this he needed a radio-opaque medium that could be swallowed. Knowing that heavy metals were reportedly radio-opaque he tested Bismuth subcitrate on a frog given a bismuth filled gelatin capsule. Bismuth subcitrate was freely available at the time for the treatment of "pyrosis and gastralgia".¹⁰ His discovery of the medium was then used for the next two decades in imaging studies until barium sulfate became the preferred contrast medium. The early use of Barium had had disastrous results when the sulfide, instead of the sulfate salt, had poisoned and killed a few subjects.¹¹

Cannon's first experiments were performed on a goose which had its head extended and fixed to a board to prevent movement of the neck.¹² He fed the goose bismuth subcitrate mixed with cornmeal mush and imaged its passage into the esophagus using their newly acquired Crookes tube. His experiments harmonized the findings of Kronecker and Meltzer by imaging the slow and regular movement of the bolus into the stomach by peristaltic contractions. He noted that it took approximately 12 seconds for the food bolus to pass through the length of the esophagus. Liquids did indeed pass more quickly than solids but they *were* accompanied by peristaltic movements. The "squirt" only occurred in the upper part of the esophagus and only in animals such as

dogs and cats. His goose did not display this phenomenon as "the parts forming the mouth are too hard and rigid." Later Hwang confirmed the conclusions of Cannon in the dog, but noted the importance of gravity in food transport in the upright position.⁶

At the beginning of this century the methods of studying contractions in the esophagus were limited to Cannon's X-ray studies and to esophageal balloon intubation studies as used by Meltzer. It was then realized that the presence of the balloon itself could affect the esophageal contractions. This may have been the reason for Meltzer's observations that some balloons tended to "smear" the peristaltic progression of esophageal contractions.⁹ Kinderman, in 1902, used a modified manometric system using much smaller balloons, and was able to time the onset of esophageal contractions with respect to the onset of swallowing.¹³ However, his smaller balloons did not achieve popularity.

Little progress was made over the next two decades although Payne made some important contributions in the early 1920's.¹⁴ By using a water filled balloon connected to an external water manometer he confirmed the regular nature of peristalsis. He also reported esophageal peristalsis after very slight movements of the larynx in the absence of voluntary swallowing.

The decades of the 1940's and 1950's saw a revolution in the interest of esophageal motility, possibly stimulated by the fascination of the phenomenon of relaxation of the cardia on swallowing. This had been reported in Cannon's and Meltzer's time but little attention was directed to it until Burget and Zeller reported the results of their animal studies in 1936.¹⁵ In the late 1940's Charles Code, whose work had been temporarily postponed by the second world war, resumed his activity in his physiology laboratory and set about devising a better method to study intraesophageal pressures. He initially tried smaller balloons attached to flexible catheters to which a glass spoon manometer was connected, (figure 1.1).¹⁶ This manometer was made by blowing a glass bulb on the end of a glass rod. This bulb was fashioned into the shape of a spoon with a 'U' shaped internal curvature. The glass spoon changed shape slightly when subjected to different internal pressures. A mirror was connected to the end of the spoon and light was reflected onto a moving strip of silver bromide.

This system, however, did not overcome the problem of the unreliable results of

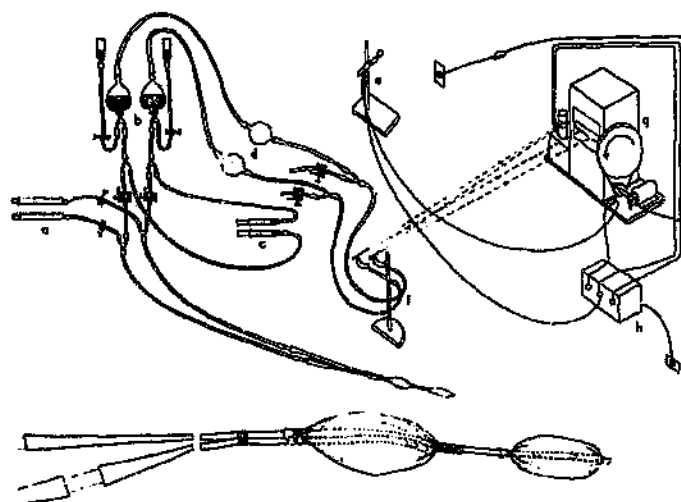


Figure 1.1 The early apparatus used by Charles Code in the 1940's for measuring intraesophageal pressures.

condom balloons which were now well recognized to cause secondary esophageal contractions.^{17,18} With this in mind Code then experimented with a new miniature electromagnetic transducer. This new technology was described in 1950 by Gauer but was initially designed as an intravascular pressure catheter.¹⁹ Butin and Code recognized the possibility of using the transducer in the esophagus and published their early work with the catheter in 1953, (figure 1.2).¹⁸ Unfortunately, owing to the size of the transducer, it was not possible to intubate the esophagus with more than one catheter, and in order to measure pressures from multiple sites in the esophagus, he needed yet another system. This came in the form of a bundle of small polyethylene tubes with openings five centimeters apart with each tube filled with water and connected to its own external transducer.²⁰

Independently, Franz Ingelfinger began developing a recording system and eventually came to use a catheter assembly that was similar to that which Code was using. Ingelfinger published a landmark treatise on esophageal motility in 1958 which summarized all that was known on the subject at the time.²¹ In this paper he discussed the fact that the peristalsis closely following a second swallow will have different



Figure 1.2 The solid state pressure transducer used by Charles Code as early as 1953.

characteristics to the peristalsis from the first swallow. Although this was noted by Meltzer²², Ingelfinger suggested that this was a phenomenon of the esophageal muscle itself, and called it the "refractory phase of the esophagus".

In the early 1950's Brody and Quigley began experimenting with the behavior of fluid filled elastic catheters.²³ It was demonstrated that in order to record pressures accurately the catheters needed to be perfused at a constant rate. With this information, the concept of water perfused catheters for the study of esophageal contractions was adopted, and such catheters have been used to the present day. The development of this system stirred an interest in esophageal manometry. The description of the manometric characteristics of the lower esophageal sphincter by Fyke and Code in 1956 added fuel to the fire.²⁴

Although infusion catheters were noted to produce a great improvement in recording fidelity²⁵, it was later noted that the catheters needed to be perfused at a rate of approximately 6-10 cc/min for accurate recording of pressures.²⁶ There was concern that the volume of infused liquid would affect esophageal contractions, or cause spontaneous activity.²⁷ Wylie Dodds published extensively in the early 1970's on esophageal manometry and its methods, but noted in a review article in 1976, that the performance of the infused catheter system was determined by the "rise rate" value of the system and that the rate of pressure rise should ideally be greater than 300 mmHg/sec.²⁸ He suggested that this may be improved by 1) decreasing compliance of the system by greasing the moveable parts such as the syringes and 2) increasing the infusion rate. Just a year later Ronald Arndorfer and Wylie Dodds published the results

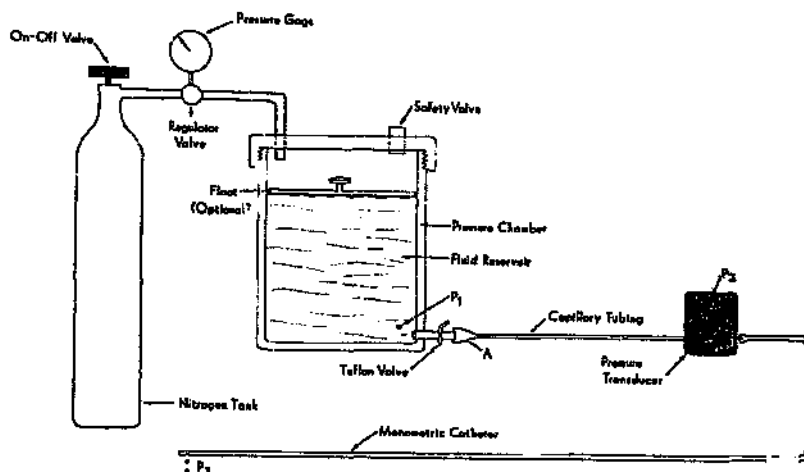


Figure 1.3 The low compliance perfusion system of Arndorfer and Dodds which has become the gold standard for esophageal manometry today

of a low compliance hydraulic-capillary infusion system which allowed low infusion rates (0.6 cc/min) with rise rates of approximately 300-400 mmHg, (figure 1.3).²⁹ In fact they had been working on this for a number of years and had first introduced their new concepts in 1974.¹³ The system is based on the principle that fluid flow from the catheter is proportional to the pressure difference across a capillary ($p_1 - p_2$ in figure 1.3). The pressure at the end of the capillary tubing approximates zero as the dimensions of the tubing (length 61 cm and internal diameter 0.2 cm) cause a high resistance to flow. Because the reservoir pressure is kept at high pressures (1000 mmHg) compared to the pressure generated by esophageal contractions (< 200 mmHg), pressure changes in the catheter result in an almost negligible reduction in flow. This system has become the gold standard for esophageal manometry, and while solid state transducers with high response rates are now available, many esophageal function laboratories still use the pneumohydraulic system, or "Arndorfer pump," as it has become known.

1.2 IDENTIFICATION AND CLASSIFICATION OF ESOPHAGEAL MOTOR DISORDERS

1.2.1 What is Normal?

The normal progression of peristalsis and the characteristics of "primary" and "secondary" esophageal contractions were described at the end of the last century but it was not until a few decades later that any attempt at defining normality was made. In order to compare the radiologic features of achalasia and scleroderma of the esophagus, Tenipleton first described the passage of barium in normal subjects.³⁰ He noted that in many of his "number of hundreds" of patients studied, most contractions were organized into peristaltic waves, but that occasional asymptomatic tertiary or segmental contractions occurred. The term "tertiary" was applied to the radiologic phenomenon of disorganized spontaneous contractions not related to a pharyngeal swallow. These tertiary waves were seen more frequently in the older age groups. He noted the similarity of these contractions to those seen in diffuse spasm, a condition known also as "non-sphincteric spasm" and, since his subjects were asymptomatic, he questioned their significance.

Kramer used a balloon system to quantitate pressures at the different levels of the esophagus and compared the results of normal controls with scleroderma and achalasia patients.³¹ In 1954 Dorn first and colleagues approached the problem of normality by using water filled polythene tubes, and measured pressures simultaneously with barium radiography.³² They performed studies on 6 normal volunteers and characterized "normal" swallowing. Esophageal contractions produced regular wave forms of 20-50 mmHg amplitude, were propagated at 4 cm/sec, and usually followed a pharyngeal contraction. Later when the perfused catheter systems were designed, Code and Ingelfinger quantified normal values and noted that the amplitude of contractions ranged from 40 to 80 mmHg, "but with occasional extremes of 20 and 140 mmHg."²¹

Since the development of low-compliance systems only a few reports have addressed the question of normal values. Clouse and Staiano reported values for

esophageal manometry from 40 volunteers but contraction parameters for different levels of the esophagus were not noted.³³ Richter *et al* published normal values for esophageal manometry in 95 volunteers in 1987 using the standardized water perfused Arndorfer system.³⁴ Motility parameters for different levels of the esophagus were reported which can be used by other centers using the same technique. Costantini *et al*, in a study of 136 normal subjects, have defined normal ranges by using 5th and 95th percentiles for each contraction parameter.³⁵ This large study also enabled a comparison of esophageal function for sex and age. No difference in contraction parameters were found in the different age groups or between sexes with the exception of older patients exhibiting a greater percentage of simultaneous contractions. These two studies have more clearly defined "normality" for stationary manometry.

1.2.2 Achalasia

The first description of achalasia was by Thomas Willis in 1672.³⁶ He also performed the first dilatation on this patient using a whalebone. An interesting account of this case is translated from Latin by Major and recounted by Ellis³⁷:

"A strong Man, and otherwise healthy, enough,....was wont, very often to cast up whatsoever he had eaten...That growing hungry he would eat until the Oesophagus was filled to the Throat... and he languished away in hunger, and every Day was in Danger of Death. I prepared an instrument for him like a Rod, of whale Bone, with a little round Button of Sponge fixed to the top of it; the sick Man having taken down meat and drink into his Throat, presently putting this down in the Oesophagus, he did thrust down into the Ventricle, its Orifice being opened, the Food which otherwise would have come back again; and by this means he hath taken daily his sustenance for fifteen Years and doth yet use the same Machine, and is yet alive, and well, who would otherwise perish for want of Food."

Kramer notes that Hoffman, as long ago as 1733, believed "cardiospasm" was caused by "irrational love" and "uncontrollable desires", reflecting the popular view of the time that the disorder was of psychogenic origin.³⁸ In 1821 Purton gave an account

of an overly distended esophagus found at autopsy of a patient of his that had suffered a lifetime of dysphagia. He described the cardiac orifice of the autopsy specimen as "much contracted".³⁹

Initially the disorder was known as "cardiospasm", a term given by von Mikulicz, as it was supposed that the cause was spasm at the lower end of the esophagus.^{40,41} In fact, some years earlier, Einhorn⁴² and later Rolleston⁴³ had thought that the condition was secondary to an inability of the cardiac sphincter to open. In 1898, Russell reported the first balloon dilatation of five cases of cardiospasm.⁴⁴ A few years later von Mikulicz described the surgical dilatation of the cardia through a gastrotomy.⁴¹ Alfred Jordan of Guy's hospital in London described the features of the disease in 1913 along with the treatment which he described as "typically American", although originally described by Russell, a fellow countryman.⁴⁵ Jordan noted that accompanying the cardiospasm was a grossly distended esophagus which could harbor a bismuth meal "for as long as six days". This had already been recognized by surgeons of the era as reflected by the plication operation of the dilated esophagus described by Reisinger.⁴⁶ The "typically American" treatment of Jordan consisted of dilatation by a balloon pulled back from the stomach across the narrowing of the lower esophagus. (Figure 1.4) The positioning of the balloon was aided by a string attached to

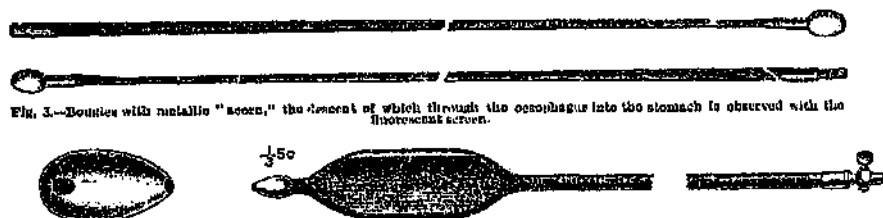


Fig. 1.--Bougie with metallic "acorn," the element of which through the esophagus into the stomach is observed with the fluorescent screen.

Figure 1.4 The dilators of Alfred Jordan used in 1913 for the treatment of cardiospasm.

a metallic "acorn" which was swallowed some days previously and allowed to be passed through the anus. By holding the string taut at both the oral and anal ends the dilating bougie was passed over the string into the stomach. Interestingly, he notes that repetitive

dilatations at intervals of a week or fortnight were usually required before "cure" could be claimed, and that relapse often occurred within 6 months. He made no mention of how long the string remained in position.

Plummer and Vinson published extensively on "cardiospasm" and reported their large series of 301 cases in 1921⁴⁷, but it was Hurst who first coined the term "Achalasia" (after the Greek, "does not relax")^{48,49}. Hurst had moved from Germany to England as a young man and his initial papers were published under the name A.F. Hertz. Hurst believed that the abnormality was not "spasm" but rather an inability of the lower esophagus to relax. Rake and Etzel, students of Hurst, later described changes in the Auerbach's plexus of the esophageal body.^{50,51} Templeton, after studying the loss of peristalsis associated with the condition, and well aware of the associated pathology, concluded that achalasia was a disease of the smooth muscle portion of the esophagus.³⁰ He hypothesized that the sphincter could not relax because there were no peristaltic contractions that reached the cardia to stimulate relaxation.

It was not until the late 1940's that manometric studies of achalasia were undertaken. Kramer and Ingelfinger described the manometric features of the disease in four patients and noted 1) decreased esophageal tone, 2) lack of propulsion of contractions and 3) an abnormal wave pattern.³⁸ These changes were noted in the mid and lower esophagus and were contrasted to the changes seen in scleroderma by the complete absence of peristalsis. Butin, in Charles Code's laboratory, used a new catheter containing a Gauer transducer for measuring esophageal pressures in 10 patients with cardiospasm.¹⁸ They noted a high occurrence of spontaneous esophageal activity in these patients which was reduced after dilatation of the cardia.

The diagnosis of achalasia, although often suggested by barium radiography, is now best made manometrically.⁵² A manometric pattern consistent with achalasia can also be secondary to carcinoma of the lower esophagus and endoscopy should be performed to exclude malignancy. The manometric features have been clearly described by Castell and others and include; 1) a total absence of peristalsis in the body of the esophagus, 2) an elevated esophageal resting pressure, 3) a hypertensive LES, and 4) incomplete relaxation of the sphincter with swallowing.^{52,53} The presence of low amplitude simultaneous esophageal contractions were said to be compatible with the

diagnosis and was thought by some to be an earlier form of the disease.⁵² The LES resting pressures, however, are not always increased, and Wong as well as Meshkinpour have found a poor correlation between LES pressure and esophageal emptying.^{54,55}

A subclassification of achalasia, called "vigorous achalasia", has been made to include patients with higher amplitude simultaneous contractions thought to be related to the symptom of chest pain.⁵⁶ However, the clinical significance of this entity is controversial. Bondi and colleagues in 1972 reported 5 patients with "vigorous" achalasia and found both symptomatic improvement and a decrease in esophageal contraction amplitude following myotomy.⁵⁷ They surmised that the contractions decreased not because of progression of the disease, but rather that "the esophagus no longer had to contract with such vigor to overcome the reduced sphincteric resistance produced by myotomy". They concluded that the vigorous form of achalasia represents an early stage of the disease and should be treated early with myotomy. Goldenburg and colleagues studied the manometric and radiologic findings of patients with classic achalasia and with vigorous achalasia, defined by amplitude of contractions.⁵⁸ They found no difference in symptoms nor outcome following dilatation, and concluded that use of amplitude as a criterion for classifying achalasia is arbitrary and of dubious value. The controversy continues in this area.

A non-relaxing lower esophageal sphincter and an "aperistaltic" esophageal body are thus the classical features of the disease. However, there appears to be some manometric overlap with other motor disorders of the esophagus such as diffuse esophageal spasm which may make the diagnosis difficult in some patients.

1.2.3 Diffuse Esophageal Spasm (DES)

The symptoms of diffuse esophageal spasm were first described by Osgood in 1889 in 6 patients who had intermittent episodes of intense pain and dysphagia while eating.⁵⁹ The radiologic characteristics were outlined sometime later by Moersch and Camp in 1934.⁶⁰ Moersch and others had noted the radiologic picture of "curling" or "corkscrewing" of the esophagus in patients with dysphagia and chest pain. The features included; 1) diffuse irregular spasm of the lower half of the esophagus, 2) narrowing of the lower esophagus, and 3) multiple spastic segments of concentric

narrowing. In two of their 8 patients the character and extension of the pain was such that a previous diagnosis of angina pectoris had been made. They felt that the origin of the disorder originated from "intra-abdominal pathology conditions of highly nervous individuals." It is interesting that Plummer and Vinson's report of 301 cases of "cardiospasm" noted psychoneurotic behavior in those patients with an undilated esophagus.⁴⁷ Ellis, commenting on the "tendency for diffuse spasm to develop in individuals with a highly nervous temperament", believes Plummer was discussing a subset of patients with diffuse esophageal spasm.³⁷

Schmidt, in Charles Code's laboratory at the Mayo Clinic, attempted to study the manometry of a patient with esophageal spasm. He noted that the balloon itself stimulated spasm of the lower half of the esophagus.⁶¹ Pressures in excess of 150 mmHg were measured. Creamer then detailed the manometric characteristics of the disorder⁶² and Gillies described the frequently associated thickened esophageal muscular wall.⁶³ Changes in the Auerbach's plexus were not seen as in achalasia, and no muscular ultrastructural abnormalities were noted on specimens taken at myotomy of six patients.

The exact diagnostic features of the disease have always been a subject of controversy. Simultaneous contractions, or so-called "spasm", may be seen occasionally in asymptomatic subjects and have been noted in increased frequency in older subjects.^{30,35,64,65} The syndrome as defined by Flesher of chest pain, dysphagia, or both, with a radiologic picture of non-progressive or tertiary contractions, and an increased incidence of simultaneous or non-peristaltic contractions on manometry, probably best defines the disease in terms of a clinical entity.⁶⁶ The exact manometric picture has been difficult to define. Eypasch and DeMeester have defined the disease in terms of a stationary manometric picture of more than 20% but less than 90% simultaneous contractions after 10 wet swallows.⁶⁷ Richter and Castell reviewed most of the published manometric data and found that the presence of simultaneous waves in more than 10 % of wet swallows with intermittent normal peristalsis in symptomatic patients was the most consistently described abnormality.⁶⁸ This also concurred with the data on normal subjects studied by Richter, in which none of 95 subjects exhibited more than 10% simultaneous contractions.³⁴ Achem and Benjamin have recently defined the manometric abnormalities in terms of "required" abnormalities and "associated"

findings. The required criteria include 1) greater than 10 % simultaneous contractions, and 2) intermittent normal peristalsis. The associated findings include 1) contractions with more than two peaks, 2) prolonged duration of contractions, 3) high amplitude contractions, 4) frequent spontaneous contractions, and 5) either incomplete relaxation or high resting pressures of the lower esophageal sphincter.⁶⁹

A further problem with the diagnosis stems from the apparent overlap of the disease with achalasia, and with other manometric abnormalities that cannot be classified into either diffuse spasm or achalasia. Furthermore, it has been suggested that one may progress to the other. Kramer, in 1967, described a patient who showed a transition from symptomatic DES to achalasia with time⁷⁰, and since then other publications have suggested that this may be a real entity.⁷¹⁻⁷³ Narducci has also described the transition from nutcracker esophagus to DES.⁷⁴ Mellow has reported that the manometric findings of DES are relatively stable but the manometric follow up in this study was limited to only 8 months.⁷⁵

The term "vigorous achalasia" was developed to categorize those achalasia patients with a DES-like pattern of esophageal motility⁵⁶, although the clinical significance of this entity has been questioned as discussed above⁵⁸. Moersch and Code coined the term "dyschalasia" to describe an incomplete picture of achalasia.⁷⁶ Frieling *et al* have also reported on the familial occurrence of achalasia and diffuse spasm and have suggested that the shared familial coincidence supports a close relationship between the two diseases.⁷⁷

Vantrappen has noted the frequent occurrence of intermediate types of motility disorders and the transition from spasm to achalasia, and has suggested that the two diseases are rather part of a spectrum of related motor disorders.⁷¹ Castell, in an editorial on Vantrappen's article, discusses his perception that achalasia and DES constitute two ends of a spectrum, with predominant sphincter dysfunction and aperistalsis at one end (achalasia) and predominant spastic activity of the esophageal body at the other (DES).⁷⁸ Further experimental evidence supports a primary defect in the relaxation of the lower esophageal sphincter. Little *et al* used a cat model in which a loose band was applied to the lower esophageal sphincter area.⁷⁹ This band allowed manometric relaxation but still produced an outflow obstruction. The obstruction

resulted in the development of high amplitude simultaneous contractions in the lower esophagus, suggesting that outflow obstruction of the lower esophageal sphincter may be the primary abnormality in this disease.

Simultaneous contractions may also be secondary to other disease states such as diabetes, connective tissue diseases, amyloidosis, alcoholism and gastroesophageal reflux.⁸⁰⁻⁸⁵ In fact, it has been suggested that the diagnosis of DES in the presence of increased esophageal acid exposure cannot be made, since the spasm may be solely acid induced.⁸⁵ On the other hand, the prolonged acid exposure may be a consequence of the poor clearance of non-peristaltic contractions of physiologic reflux in these patients and DES may be the primary disease.⁶⁷

One of the major problems with the diagnosis of these disorders is that the manometric picture is defined on only 10 wet swallows of 5 cc of room temperature water performed during stationary motility testing. However, motor abnormalities are frequently episodic and may not be seen during this limited period of study. Characterizing motility disorders with respect to symptoms is conjectural, at best, when the symptoms are not experienced during the study period. Furthermore, the symptom of dysphagia, the predominant symptom in DES, cannot be studied unless the patient is eating a meal. There are thus strong arguments for the application of a manometric system that can measure esophageal pressures for a prolonged period in an ambulatory subject. Opportunities for examining motility during reflux, during eating or during symptomatic episodes would be possible. Early studies have indicated that monitoring the esophagus for prolonged periods of time holds promise for better defining these abnormalities.⁸⁶

1.2.4 Nutcracker Esophagus

The finding that high amplitude esophageal contractions are more common in patients with non-cardiac chest pain has led some authors to suggest a causal relationship of the former to the latter.^{87,88} Benjamin and Castell described the entity and proposed the name "nutcracker esophagus" to draw attention to the prevalence of the manometric finding.^{89,90} It was not their intention to attribute the high amplitudes as a specific disease process responsible for symptomatology. The term is applied to the manometric

finding of a mean amplitude of contractions greater than 180 mmHg on stationary motility testing. This figure is generated from the upper limit of normal of contraction amplitudes. This correlates well with the normal limits in other studies. Costantini *et al* found the upper limit of normal to be 164, 180, 190 mmHg respectively for the three lowest levels in the esophagus.³⁵ Katz found that almost 50% of patients who were evaluated for non-cardiac chest pain met the criteria for this disorder.⁹¹ However, Achem *et al* have also found that the majority of patients with "nutcracker esophagus", as defined by manometric criteria, had increased esophageal acid exposure.⁹² Since it is known that some patients with GERD may have increased amplitudes of contractions, reflux disease should be excluded, or treated, prior to making the association of nutcracker esophagus with chest pain. Other manometric abnormalities have also been described with "nutcracker esophagus". Castell has noted the occasional association with a hypertensive lower esophageal sphincter⁹³ and others have found a striking feature of prolonged duration of contractions.⁹⁴⁻⁹⁶ The clinical significance of these findings is unclear as no definite functional disturbance in terms of bolus transport has been demonstrated in this disorder, and the association with chest pain has been largely conjectural.⁹⁷ There has been a further debate as to whether the high amplitudes are found diffusely or are confined to a specific segment.^{89,93,95,98} Achem, however, found that with long-term follow up, only 53% of patients with a diffuse picture, and 20% with a segmental disorder, retained their diagnosis, suggesting that the spectrum of high amplitude contractions constitutes an intermittent disorder.⁹⁹ They concluded that, at best, high amplitude contractions are a labile marker associated with noncardiac chest pain. Cohen and others have questioned the presence of high amplitude esophageal contractions as the source of pain in these patients since Nifedipine reduced the amplitude of contractions but had no effect on the symptom of pain.^{100,101} Kahrilas has questioned whether "nutcracker esophagus" should even be considered a distinct entity,⁹⁷ while others are confident that the entity is a source of significant symptoms and are applying the new technology of thoracoscopy to perform a long esophageal myotomy for the disease.¹⁰²

Like DES, the manometric finding of nutcracker esophagus may change with follow up. Dalton and Castell found after long term follow up that only 50% of patients

retained the diagnosis of nutcracker esophagus.¹⁰³ Others have reported an evolution from nutcracker esophagus to DES or to achalasia.^{74,99,103-107}

To date, the best that can be concluded from all the research in this area is that high amplitude contractions found in a patient with chest pain or dysphagia and no evidence of GERD, may indicate either a developing motor disorder or a disorder with episodic manometric characteristics.

1.2.5 Scleroderma and Other Secondary Motility Disorders

Esophageal motility may be affected by a number of systemic disorders, the most well known being progressive systemic sclerosis. The esophagus is involved in up to 85% of patients with this disease.^{105,108,109} The changes are secondary to progressive degeneration and fibrosis of the smooth muscle of the esophagus and are characterized by profound loss of peristalsis and an incompetent lower esophageal sphincter.^{81,110-112} Involvement of the esophagus is common in polymyositis and dermatomyositis.¹¹³ The esophagus may also be involved in systemic lupus erythematosus and rheumatoid arthritis although the severity of involvement is usually mild.^{114,115}

Diabetics commonly have abnormalities of the esophageal body when tested manometrically, but the functional significance of this is not known since most are asymptomatic. Those with a peripheral or autonomic neuropathy are most commonly affected and the pathophysiology is thus believed to be neurologic and not secondary to smooth muscle dysfunction.^{116,117} Variable abnormalities have been described and include a decrease in peristalsis, an increase in repetitive and spontaneous contractions, and an increase in multi-peaked contractions.^{118,119} Esophageal motor abnormalities have also been noted in amyloidosis, stroke and other neuromuscular diseases, chronic idiopathic intestinal pseudo-obstruction and in Chaga's disease.¹¹⁹

1.2.6 Non-specific esophageal motility disorders (NSEMD)

The previous discussion indicated that it is not always possible to categorize manometric abnormalities into achalasia, DES, nutcracker esophagus, or scleroderma. The widespread use of manometry has shown that there is a large group of patients with motor abnormalities that do not meet the criteria for any of the primary motor disorders.

These abnormalities have been termed "non-specific esophageal motor disorders".⁷⁸ Patients with gastroesophageal reflux disease with changes in the esophageal body motility form a large part of this group. The group of patients with NSEMD constitute the largest group of esophageal motility disorders.

Dodds noted almost 20 years ago after developing the low compliance system with Arndorfer:

*"After peristaltic pressure values in normal subjects are established, manometric diagnosis of subtle esophageal motility disturbances featuring hypotensive or hypertensive peristaltic pressures may become commonplace"*¹²⁰

Unfortunately, we have yet to understand the group of patients with NSEMD and the clinical significance of subtle abnormalities. Katz and colleagues have reported the association of NSEMD with symptoms.⁹¹ In a manometric study of 251 patients with the principle symptom of dysphagia, 30% met the criteria for DES, nutcracker esophagus and achalasia, while a further 30% were diagnosed with NSEMD.

Clouse and Staiano have attempted to reclassify manometric disorders on the basis of manometric findings of the esophageal body and the lower esophageal sphincter.^{33,121} Their system allows for recognition of the spectrum of distal contraction abnormalities without reliance on current nomenclature. Unfortunately the classification system has not been used widely.

Achem *et al* have studied 23 patients with NSEMD over a 3 year period and found that the NSEMD persisted in 57% of patients, while 29% were found to be normal on subsequent evaluation, and 14% developed DES.¹²² Symptoms correlated poorly with the manometric findings suggesting that the esophageal dysmotility was not the origin of the problem.

The association of esophagitis and motor abnormalities was noted first by Olsen and Schlegel in 1965¹²³. The motility changes seen in gastroesophageal reflux disease are multiple and include an increase in the number of dropped and interrupted contractions, and a decrease in the amplitude and duration of contractions.¹²⁴⁻¹²⁶ Increased simultaneous contractions, mimicking a picture of diffuse esophageal spasm,

may also be seen.⁸⁵ Peristaltic dysfunction appears to be more prevalent with increasing severity of esophagitis.^{127,128} Overall, about 50% of patients with GERD will be classified as having a non-specific motor abnormality after stationary motility testing.¹²⁹ The functional significance of the NSEMD in GERD patients is unclear. Recently, Hsu has noted a delayed emptying of semisolids using radioscintigraphic techniques, so it appears the disorder is an entity worthy of further study.¹³⁰ How this translates to esophageal function during eating will only become clear with the application of ambulatory manometry.

1.3 HISTORY OF AMBULATORY MANOMETRY

Ambulatory esophageal pH monitoring has become the gold-standard with which to measure increased esophageal exposure to acid. Its present day form was developed in the early 1970's by Johnson and DeMeester who believed the standard acid reflux test or SART was merely a "dip-stick" test and could not reflect accurately the physiological state.¹³¹ It took more than a decade for their method to be accepted, but today ambulatory pH monitoring is used world-wide in a standard form as a test for gastroesophageal reflux disease. Its value has been found in the ability of the test to measure what normally happens to the patient in their day-to-day life and enables documentation of symptomatic episodes which can be correlated with changes in intraesophageal pH.¹³²⁻¹³⁴ Naturally occurring reflux episodes are episodic and prolonged monitoring is necessary to detect unprovoked events.

It is not surprising that some of the earliest work in ambulatory esophageal manometry was also carried out in DeMeester's laboratory.¹³⁵ The impetus was the same: that the "dip-stick" test of stationary manometry has limitations. These include the non-physiological environment of the esophageal laboratory in which the test is performed, and the supine position the patient assumes for the duration of the study. Studies have now shown that the position of the patient, as well as anxiety and mental state affect esophageal contractions.^{136,137} Similarly, esophageal function is usually assessed on the results of only 10 swallows of small amounts of water, usually 5 milliliters. This does not give an accurate account of the physiological esophageal function as it is known that temperature, size, and consistency of a swallowed bolus affect manometric results.^{138,139-143} There are profound differences in esophageal contractions following wet and dry swallows, and following different intervals of time between swallowing.^{35,142,144,145} The limited number of controlled swallows in an unfamiliar environment may be very different from the situation of the patient eating a meal in the comfort of his or her home.

The short duration of standard stationary motility gives little opportunity for studying the patient with episodic symptoms of dysphagia or chest pain.¹⁴⁶ Kahrilas has

discussed the probability of detecting episodic disorders with stationary manometry.¹⁴⁷ Expressed mathematically, the probability of detecting an episodic abnormality (P) can be expressed as $P = 1 - (1 - p)^n$ in which p is the frequency with which the abnormal contraction occurs and n is the number of swallows in the study. If an abnormality occurs 10% of the time the likelihood of detecting it with stationary manometry performing 10 swallows is only 0.65. The probability, using this equation, approaches certainty if the thousand or more swallows occurring during a circadian cycle are analyzed.

The mechanisms of esophageal clearance of refluxed gastric juice are also of pathophysiologic significance, but have only been studied in artificial environments. The only means of studying clearance in the physiologic environment would be with simultaneous ambulatory pH and manometry recordings. This provided further impetus for developing the technique.

The concept of ambulatory motility is consequently a natural progression from ambulatory pH monitoring. Unfortunately, at the time of conception, available technology was limited. Wallin *et al* performed some of the first prolonged measurements of intraesophageal pressures.^{148,149} Twelve hour studies were performed with water perfused catheters and the data was stored on analogue tape recorders. The water perfusion system of the catheters demanded that the patient was lying flat in the laboratory so that calibration of the external pressure transducers would not be affected. Computer software at the time was unavailable for automated analysis and measurements had to be made manually. Solid state pressure transducers mounted onto fine catheters were then developed. These overcame the stationary position requirement, but a problem arose with how to store the results. Clouse was one of the first to use the solid state technology and to recognize the potential for long-term monitoring.¹⁵⁰ He measured intraesophageal pressures for periods of three or more hours in patients with non-cardiac chest pain. The catheter and pneumograph transducer were connected to a chart recorder by a 30 ft cable so that the recording could stay out of view of the patient.

The idea that esophageal dysmotility could cause non-cardiac chest pain became the stimulus for development of ambulatory manometry in the late 1980's. It soon became apparent that the problem with measuring esophageal pressures for prolonged

periods was how to deal with the large amount of data recorded. A number of techniques were used to overcome this. Firstly, as mentioned above, the data could be stored in an analogue form on tape recorders and then random "samples" from the recording could be printed and analyzed manually.¹⁵¹⁻¹⁵⁴ Secondly, the technology of analogue to digital conversion and storage of digital data, as used by pH monitoring, could be applied to ambulatory manometry. Solid state pH systems used the technology of solid state complimentary metal oxide semiconductor (CMOS) dataloggers for storage of data during prolonged studies. Unfortunately these had inadequate memory capabilities for the purposes of ambulatory manometry. Motility data needed to be sampled at much greater sampling rates than for pH monitoring. The amount of data recorded is in the order of 32 times that of pH monitoring (8 Hz vs 0.25 Hz) for a single level of the esophagus. This had implications on both the method of storing data and the method of analyzing the recording. Data needed to be reduced either by sampling digital data at a lower frequency, or by storing selected data such as pressure rises greater than a defined value. Selected data storage was initially performed by Smout, one of the European pioneers in ambulatory manometry.¹⁵⁵ The problem of data reduction during recording, however, is that the original tracings can not be recovered for later investigation.

Early work in DeMeester's laboratory utilized the new technology of a portable solid state CMOS memory logger with greater memory capabilities than the earlier pH dataloggers. The 192 kilobyte capacity of the datalogger unfortunately still did not enable continuous monitoring for 24 hours. To overcome this, a catheter with only 2 pressure transducers was used, and data were sampled intermittently, i.e., for 28 seconds every 17 minutes. This was validated by comparison with continuous monitoring in a few subjects and it appeared to correlate well. This system was used as a research tool to study the motor changes occurring in primary motility disorders, in gastroesophageal reflux disease, and in patients with noncardiac chest pain.^{124,146,156}

There were, however, limitations of these early systems. Intermittent monitoring may miss important episodic motility changes. Catheters containing only two transducers may not identify segmental disorders which can occur in spasm syndromes, nutcracker esophagus and in reflux disease.^{99,133,157,158} Furthermore, the early systems

did not incorporate simultaneous analysis of pH data, and analysis of motility related to reflux events was not possible.

In 1990 the recently developed dataloggers with memory capacities of greater than 2 megabytes became available for testing in the laboratory at the University of Southern California (USC). Together with the solid-state microtransducer technology the hardware for continuously monitoring pressures from three or more levels of the esophagus in an ambulatory individual became possible for the first time. However, storing data for 24 hours provided recordings of more than 1000 contractions from multiple levels of the esophagus. The need for automated analysis of the stored data became apparent.

The problem of analyzing the large amount of stored data was overcome by making use of the advances in computer technology. Troxell *et al* showed that it was feasible to write a software program to make reliable measurements of esophageal contractions recorded during prolonged monitoring periods.¹⁵⁹ Two groups in Europe developed software to measure amplitude and duration of contractions as well as the peristaltic nature of one pressure change in relation to a second pressure channel.^{160,161} These were validated and shown to correlate well with manual analysis. Unfortunately the systems were not available commercially and did not enable analysis of more than 2 pressure channels in the esophagus. Consequently, any center developing an ambulatory manometry system using more than two pressure transducers also needed to develop the software for analysis. The development and validation of a new software program for automated analysis of these recordings is discussed in this thesis.

The evolution of the simultaneous ambulatory pH and manometry system presented in this thesis was possible because of the interaction between the laboratory at the University of Southern California and Synectics Medical Incorporated, (Dallas, Texas) a gastrointestinal biomedical development corporation. Necessary changes in the dataloggers and catheters suggested by the results of my research in the laboratory, and presented in this thesis, were performed in Texas and in Sweden by Synectics medical. The development of the software to analyze the large volume of data stored using multichannel monitoring was performed in the USC esophageal laboratory with the cooperation of Hebert Shibberu, a computer programmer from Gastrosoft Incorporated, a

subsidiary of Synectics Medical. The software development constitutes a major part of this thesis. More than 46 versions of the software were developed and tested by myself in order to obtain a computer program that could reliably analyze the 5 megabytes of data recorded from each 24 hour study. The software developed has multiple unique features which will be discussed. The system was then validated against manual analysis and found to be accurate. Application of the system in asymptomatic volunteers was used to establish ranges of normality during eating, sleeping and during awake interprandial periods. The system was then applied to patients with primary and non-specific motility disorders as will be discussed. Integration of pH monitoring and a swallowing probe enabled evaluation of the normal and pathological mechanisms of clearance of refluxed acid from the esophagus.

The system has now been incorporated into the clinical workup of patients being studied with benign esophageal disorders at the University of Southern California, and ambulatory manometry assists in clinical decision-making affecting patient management. The system is now also available for use by other centers.

CHAPTER 2: DEVELOPMENT OF THE HARDWARE

2.1 HARDWARE REQUIREMENTS

The hardware requirements for ambulatory motility are:

1. A catheter containing solid-state micro-transducers,
2. A portable solid state data recorder,
3. A personal computer for transferring and analyzing recorded data.

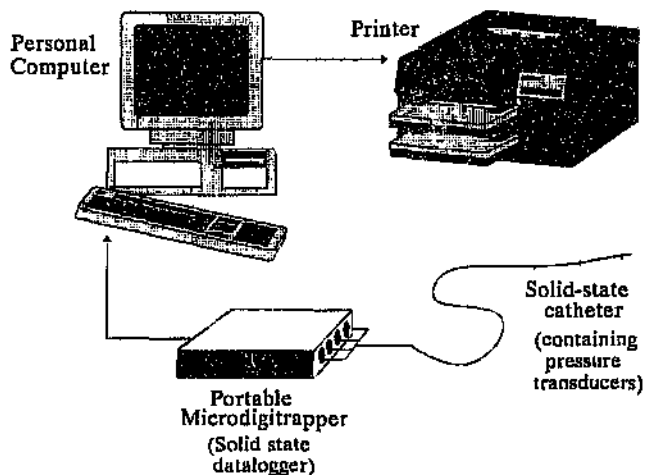


Figure 2.1 Graphical representation of the ambulatory manometry system.

A graphical representation of the complete system is shown in figure 2.1. The catheter containing the solid state pressure transducers is connected to the datalogger which is known as the "Microdigitrapper". This portable device stores the pressure readings continuously for the 24 hours of study after which the stored data is transferred to a personal computer. The personal computer allows visualization of the recording on screen, analysis of the data, and a hardcopy printout by a connected printer.

2.1.1 Data Recorders

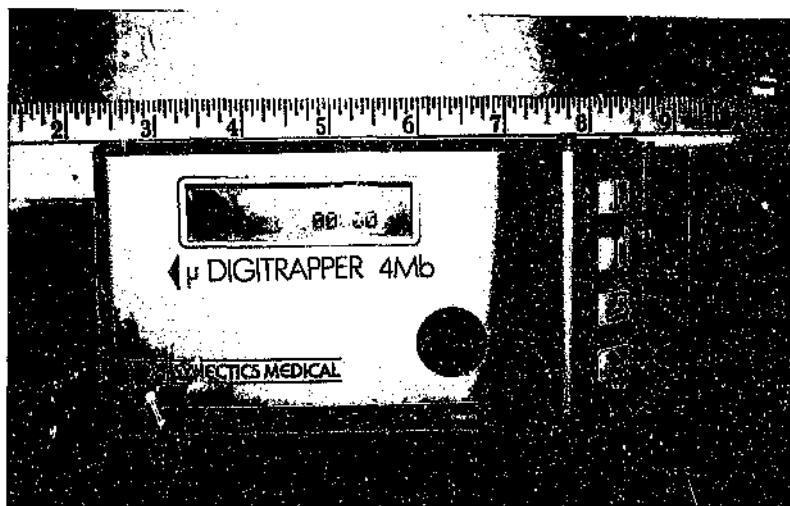


Figure 2.2 Photograph of the new generation 4 megabyte memory recorder.

The history of the development of CMOS (Complimentary Metal Oxide Semiconductor) memory storage devices is outlined in the first chapter. The value of the CMOS systems is that they operate with a very low power consumption and can be run with portable battery packs. At the outset of this project a new generation 2 megabyte Microdigitrapper was available for testing in the esophageal laboratory at the University of Southern California (USC). Initial bench-top tests were carried out using this machine and two different catheters. A newer generation 4 megabyte microdigitrapper was then released for testing (figure 2.2), and this machine overcame many of the problems of inadequate battery life, pre-amplifier failure, unreliable calibration, and corrupt memory storage that troubled the early generation machine. These modifications and improvements were performed in Texas and in Stockholm using input from Beta test sites of which USC was one. While the 2 megabyte generation machine was useful for the initial testing of the system, clinical use was unreliable and all the studies in this project made use of the newer generation 4 megabyte machine. Specifications of the device are listed in Appendix A.

The Microdigitrapper is housed in a leather case with a shoulder strap for easy

carrying. Figure 2.3 shows an ambulatory subject with the solid state manometry catheter placed transnasally into the esophagus and connected to the Microdigitrapper.



Figure 2.3 The ambulatory esophageal manometry system in an ambulatory subject.

2.1.2 Catheters

In order to record esophageal pressures in the ambulatory individual, a catheter system that maintains a calibrated baseline independent of the subject's position was needed. The standard stationary manometry system of Arndorfer ²⁹ makes use of a catheter with water perfused fine calibre tubes which are connected to external pressure transducers. The catheter is calibrated at the level of the transducers. For the purposes of measuring pressures the catheter must remain in this position to maintain the

calibrated baseline. The subject must consequently lie in the supine position and not move during the study. The advent of solid state microtransducers enabled development of catheters containing the pressure transducer in the catheter assembly itself (figure 2.4). Consequently, with the transducer in the esophagus there is no requirement for the subject to be stationary as the catheter will always maintain its "own" calibrated baseline.

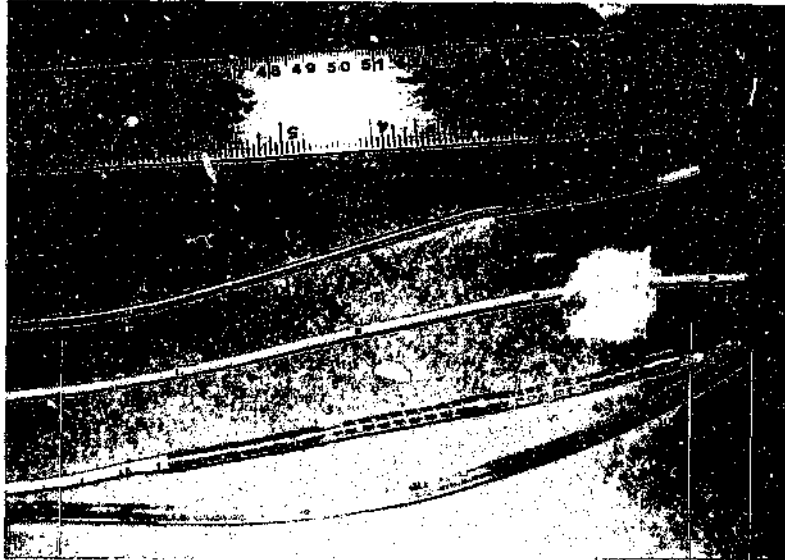


Figure 2.4 Photograph of the glass pH probe, the Sentron catheter, the Konigsberg catheter, and the standard water perfused manometry catheter from above, down.

The solid state transducers that were available for incorporation into esophageal catheters were either the piezoelectric crystal or the semi-conductor strain gauge type. The former could be made smaller but had the disadvantage of being fragile and sharp bumps e.g. against a table top, could shatter the transducer crystal. The piezo-electric transducer is the type used in the 7 French Sentron catheter which was custom made by Sentron, the Netherlands. The alternate catheter available for testing in the laboratory at USC, was the Konigsberg catheter manufactured by Konigsberg Inc. Pasadena, Ca. The proximity of the Konigsberg development site to the University of Southern California, allowed close interaction between myself and the director of Konigsberg instruments,

Efe Konigsberg. The Konigsberg catheter used transducers in the form of a micro-strain gauge array, and had the advantage of being far more durable than catheters containing piezoelectric crystals. The disadvantage of these catheters was the size of the transducer itself and the catheter diameter that housed the transducers. The assembly of transducers was contained in a catheter of 4.65 mm diameter (figure 2.4). The technical specifications of the two catheter systems and the design of the Sentron catheter used in this thesis are shown in appendix B.

2.1.2.1 Cardiac Interference

Initial testing on normal volunteers showed the occasional appearance of high frequency background noise in the channels 5 cm and 10 cm above the LES. This phenomenon appeared to be episodic, was not present in all studies, and usually affected only one channel at a time. However, when it occurred it raised the baseline and affected the recording of esophageal pressures. This appeared to occur almost exclusively with the Konigsberg catheter. A study was then performed using both catheter systems at the same time in the same subject (figure 2.5).

The catheters were positioned so that the transducers of one were each at exactly the same level as the other. Prolonged recording for 5 hours was performed and the data then uploaded onto a personal computer. Several periods of background "noise" were recorded on the Konigsberg catheter, whereas this did not appear on the Sentron recording. By expanding the recording on the x-axis it was possible to determine that the frequency of the "noise" was approximately 60 Hz which matched the heart rate of the subject studied.

Figure 2.6 shows the same time frame, i.e., the same esophageal contractions of the two recordings, and illustrates the "noise" in the middle channel of the Konigsberg catheter. This resulted in an artificial increase of the amplitudes of contractions in that channel. In figure 2.6 the amplitude of the measured contraction in the middle channel was recorded as 66 mmHg using the Sentron catheter and 92 mmHg with the Konigsberg catheter affected by cardiac pulsations. Occasionally the "noise" resulted in gross pressure changes as seen in figure 2.7 on the lowermost channel of the Konigsberg catheter. This might have been construed as spasm of the esophagus if the

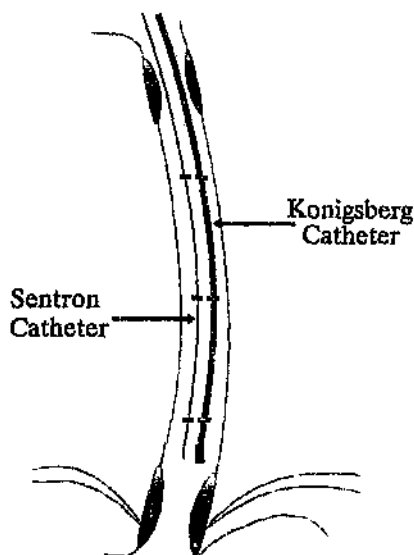


Figure 2.5 Diagram to show the position of the Konigsberg and Sentron catheters for comparison.

Sentron catheter did not show a regular smooth tracing.

An attempt to modify the Konigsberg catheter was made to limit this problem. This is discussed in appendix C. The costs, however, to modify the catheter to completely overcome the problem were too great and a decision was made to use the Sentron catheter. The single disadvantage of the Sentron catheter was its fragility, but although transducers occasionally did break, careful handling of the catheter overcame this problem.

2.1.2.2 Development of a Swallow Channel

The categorization of waves into simultaneous and peristaltic, as is discussed in the next chapter, prompted the question of which esophageal waves were stimulated by a pharyngeal swallow and which occurred in the absence of a swallow. Nearly a century ago, Meltzer recognized that contractions may be initiated either in the pharynx, or in the esophageal body in response to local distension. He made a distinction between

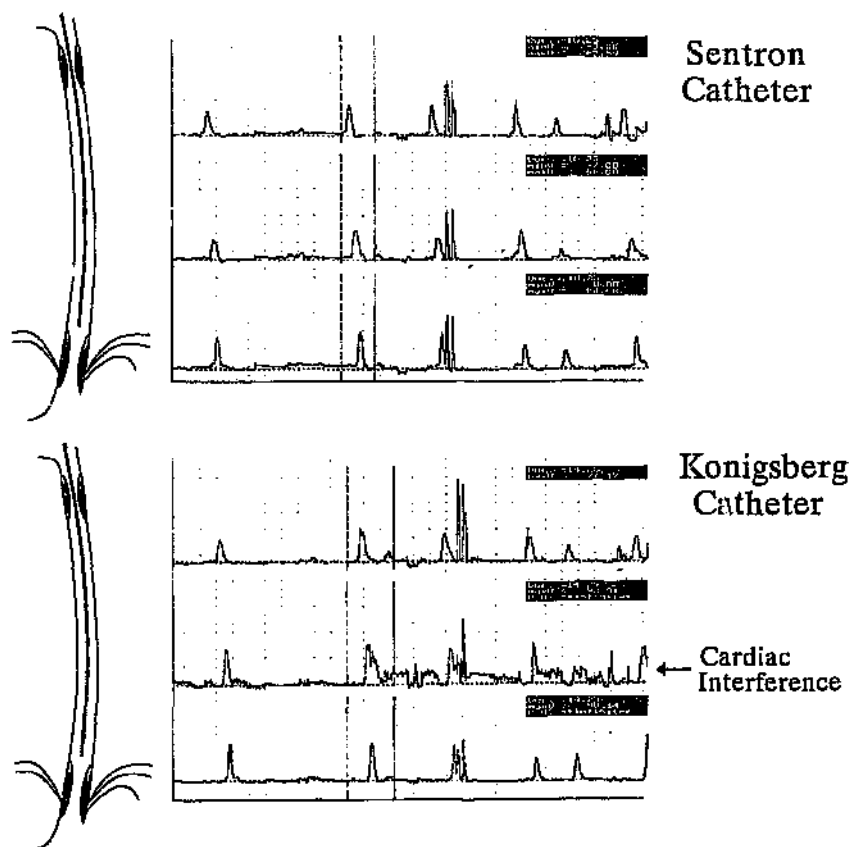


Figure 2.6 An example of the simultaneous recordings of the two catheters in the same esophagus at the same time. Note the cardiac interference in the middle channel of the Konigsberg tracing.

these waves and called the former "primary" peristalsis, and the latter "secondary" peristalsis.¹⁶² Kahrilas, recognizing that the terms may cause some confusion has suggested that the "secondary" waves be called "autonomous" which more correctly defines their nature.¹⁶³ The characteristics of these types of waves are discussed in a later chapter, but it is appropriate to describe the development of the swallow channel here. This was only implemented one year after the beginning of this project and consequently not all subjects (and not all normal volunteers) were studied with the catheter containing the swallow channel. In this thesis graphical representations of the ambulatory recordings may or may not show the swallow tracing.

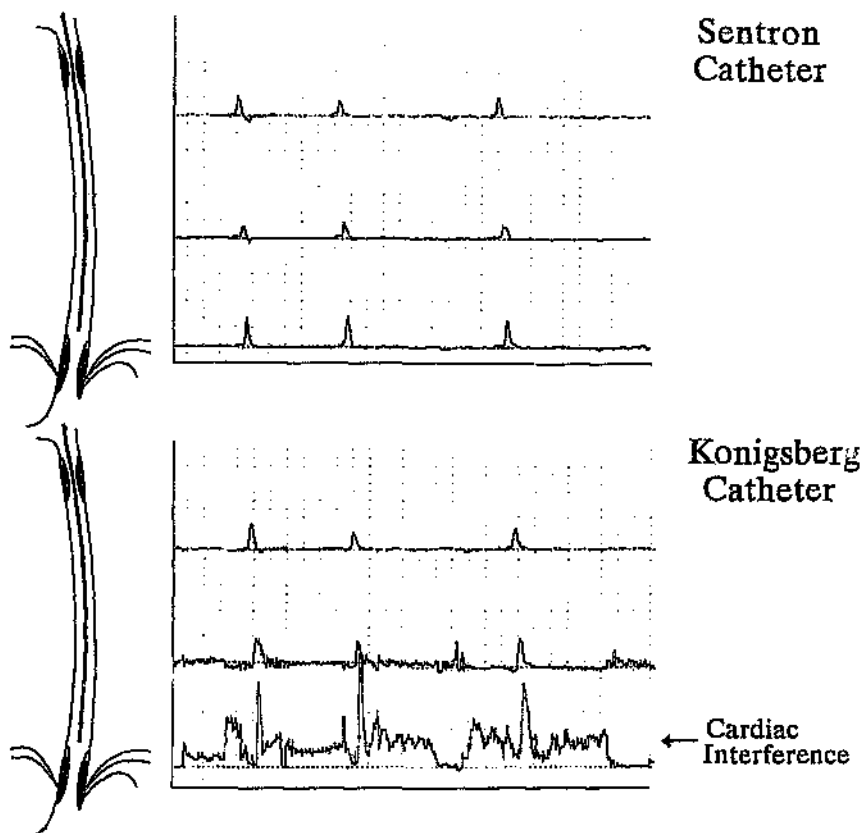


Figure 2.7 Gross artefact introduced by cardiac interference in the lower most channel of the Konigsberg tracing. The two catheters are recording the same pressures at the same time.

Ambulatory recording of pharyngeal swallowing was difficult. The swallow transducer that was applied to the external neck in the supine subject during stationary manometry could not be used in the ambulatory subject as it is sound-sensitive and would record talking and movement. Electromyography of the mylohyoid muscle would register swallowing but would also register movements that occurred with talking and a system to record swallowing in this way was not available to us. The ideal way would be to have a small pressure transducer positioned just above the cricopharyngeus muscle. This would have to be part of the esophageal manometry catheter as a

transducer on a separate catheter with a free-floating tip in the pharynx would be too irritant to the patient. The transducer would be used merely to flag the occurrence of swallows and not to provide information on the characteristics of the pharyngeal contraction as it is known that pressure changes in this area are far too rapid to be accurately recorded by a system sampling at 4-8 Hz.¹⁶⁴⁻¹⁶⁵ Also the pharynx is asymmetrical with respect to contraction amplitude which is greater in the antero-posterior direction than in the lateral direction.¹⁶⁶ This is not the case with the esophageal body which has been shown to exert equal pressures in all directions, so unidirectional transducers as used in this thesis accurately reflected pressures in the esophageal body.¹⁶⁷ A transducer placed above the cricopharyngeus muscle would, however, be able to flag contractions in the pharynx whenever a swallow occurred. The sampling frequency would only have to be rapid enough to detect a rise in pressure in the pharynx.

A catheter was designed to contain 4 transducers, the lower three each five centimeters apart and the most proximal transducer 10 cm above the second transducer (figure 2.8). This provided some flexibility as the high pressure zone that occurs in the pharynx during a swallow is 5-6 cm long.^{165,168} Placing the catheter with the distal most transducer 5 cm above the LES would place the most proximal transducer just above the upper esophageal sphincter in most subjects. Unfortunately the length of the esophagus between sphincters is variable in different people, as is the length of the upper esophageal sphincter itself. In subjects with a short esophagus the swallow channel is too high and is affected by movement of the posterior tongue. In those with a longer esophagus the pharyngeal transducer is too low and moves into the cricopharyngeus muscle with movement and with swallowing. This is discussed in the next chapter.

In order to design the optimal catheter for recording pressures from both the esophageal body and the pharynx, it became necessary to measure the manometric length of the normal esophagus and the esophagus in patients with GERD and hiatal hernia, in whom esophageal shortening was known to occur.¹⁶⁹ To overcome the differences in esophageal length 2 catheters were later designed, one with a distance of 12 cm and the other of 8 cm between the pharyngeal transducer and the most proximal esophageal transducer. The catheter to be used for the ambulatory manometry was

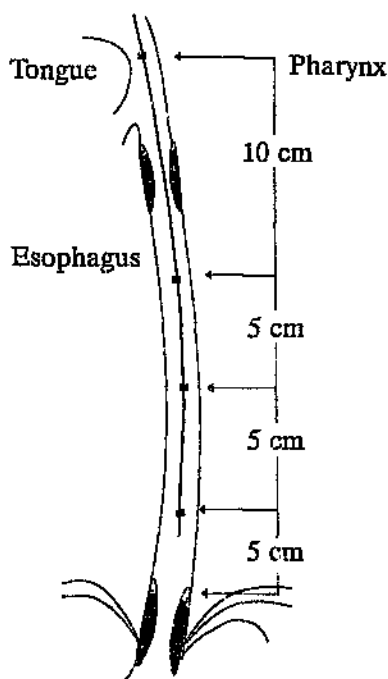


Figure 2.8 Diagram to show the position of the catheter containing four transducers. The uppermost transducer is placed just proximal to the upper esophageal sphincter.

chosen based on the esophageal length as measured by stationary manometry.

2.1.1.3 Personal Computer

Once the data was recorded in a digital format for the 24 hour period of study, it was transferred from the Microdigitrapper to a personal computer, a process called "uploading". This was necessary to display the recording on the computer screen and to enable computerized analysis of the recorded data. The minimal computer requirements for the upload and analysis were a 386 microprocessor with 640 Kilobytes of RAM (Random Access Memory). The rapid technical advances in personal computing over the last 5 years overcame any problems with early limitations of personal computing. Initially the automated computer analysis of a single recording took more than 20

minutes since more than 5 megabytes of data were generated. However, current computer technology reduced this to under 3 minutes. A dot matrix, deskjet or laser printer was necessary for hardcopy printouts of summaries and reports.

2.2 ESTABLISHING OPTIMAL SAMPLING FREQUENCIES¹

2.2.1 Background

The advent of portable dataloggers with larger memory capabilities allowed 24 hours of continuous recording of esophageal pH and esophageal motility monitoring in the ambulatory setting. However, in order to record data for 24 hours some form of data reduction was required as the memory of the datalogger, while much larger than previous prototypes was still limited. The new prototype dataloggers which were available to our laboratory were capable of storing 4 megabytes of data. The manageability of the stored data by the analysis software also needed to be considered. The larger the amount of data the more complex the software would have to be and the greater the potential for software errors.

One of the systems developed in Europe used an on-line method for data reduction.¹⁵⁵ The system utilized a microprocessor incorporated in the digitrapper which stored only pressure increases greater than 2 kPa (15 mmHg) which lasted longer than 0.8 seconds. The system utilized a catheter with only two pressure transducers which were 10 cm apart. The problem of data reduction during recording is that the original tracings can not be recovered for later investigation.

Another method of data reduction is to store data at lower frequencies. For example, if a contraction lasts two seconds then the storage of data at 60 Hz (optimal storage frequency for digital data collection for stationary manometry), would result in 120 data points for the entire contraction. On the other hand, if the data were stored at 2 Hz, then only 4 data points would be stored for that contraction. This method is illustrated in figure 2.9 which shows the potential for inaccurate data collection as the sampling frequency decreases.

A compromise between the amount of data that can be stored, the fidelity of the reproduced recording, and the analytic ability of the stored data by current software,

¹ This study was published in abstract form in *Gastroenterology* 102(4):A430, 1992.{1729}

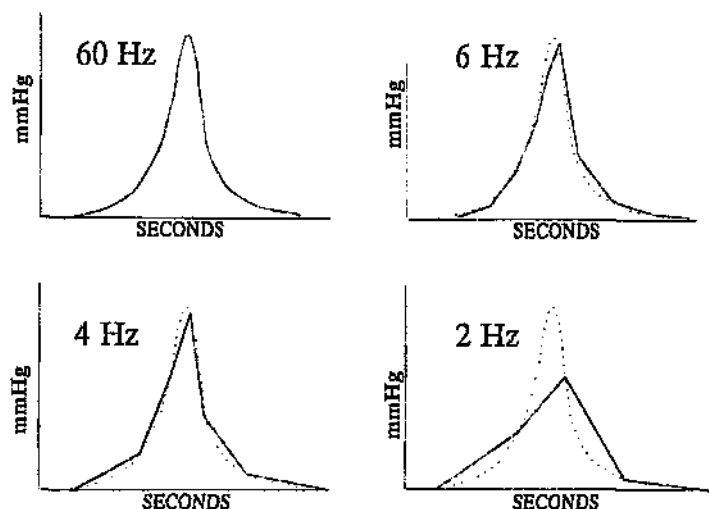


Figure 2.9 Comparison of the reconstruction of a contraction when the original pressure data is sampled and stored at different frequencies. The dotted line shows the original contraction.

needed to be reached.

In order to quantitate the effect of data compression by decreasing sampling rates, the amplitude of esophageal contractions from normal subjects and patients with a variety of motility disorders recorded at 60 Hz were compared to the amplitudes recorded at frequencies of 15, 10, 6, 4, 2 Hz.

Four normal volunteers also underwent dual 24 hour ambulatory esophageal monitoring using a storage frequency of 4 hz on one catheter assembly and 8 Hz on the other.

2.2.2 Methods

The stationary manometric records of 19 subjects studied in the esophageal laboratory at the University of Southern California were used. Two patients met the manometric requirements of nutcracker esophagus, two had diffuse esophageal spasm, seven had a non-specific esophageal motor disorder which included low amplitude

contractions, and eight had normal esophageal motility. All subjects underwent esophageal manometry according to the protocol described in chapter 4. Esophageal body function was assessed by a series of 10 "wet" swallows using 5 cc of water. A duration of 30 seconds separated each swallow.

The manometric data was recorded continuously in an analogue form with a Gould 2000 recorder and data underwent analogue to digital conversion with storage of digital data at a frequency of 60 Hz. This frequency accurately reflects the original analogue tracing when digital data is displayed on a computer screen in a graphical mode. It is the standard digital storage frequency for stationary manometry. This digital data was then reduced by sampling data from the original 60 Hz recording at different frequencies. This was done by taking every fourth data point (30 Hz), then every 6th data point (10 Hz), every 10th (6 Hz), 15th (4 Hz), and every 30th (2 Hz) for storage (figure 2.9). These data points were used to reconstruct contractions, and the amplitudes of the contractions for the data sets from different frequencies were compared. Data was used from all five levels of the esophagus providing 50 contractions for analysis for each of the 19 subjects. Amplitudes from these 950 contractions were measured for the 6 different sampling frequencies providing a total of 5700 measurements. The contractions chosen for analysis comprised a spectrum of abnormalities which included high and low amplitudes. A few mmHg difference for high amplitudes would be less significant than the same absolute pressure change for low amplitude contractions. For this reason a percentage difference from the true amplitude was chosen to reflect the difference of the reconstructed contractions for the different frequencies.

In the second part of the study 4 normal volunteers underwent 24 hour ambulatory motility using two identical catheters bonded together, and linked to two microdigitrappers. One microdigitrapper was set up to record data at 8 Hz while the second stored data at 4 Hz. These two frequencies were chosen because hardware limitations precluded 6 or 10 Hz sampling. Ambulatory manometry was performed as described in detail in chapter 4. Briefly, after placement of the solid state manometry catheter the subjects were allowed home and encouraged to perform normal daily activities.¹⁷⁰ Two meals were eaten and diaries were completed of all activities.

Patients returned the next day and data was uploaded onto a personal computer for analysis. The recorded data was analyzed using the software program developed and validated in our laboratory and discussed in chapter 5.¹⁷¹ Parameters of amplitude, duration, contraction recognition, and prevalence of peristaltic wave forms were compared for the two frequencies.

2.2.3 Results

Figure 2.10 shows the average difference in amplitudes as a percentage of the "true contraction" recorded at 60 Hz.

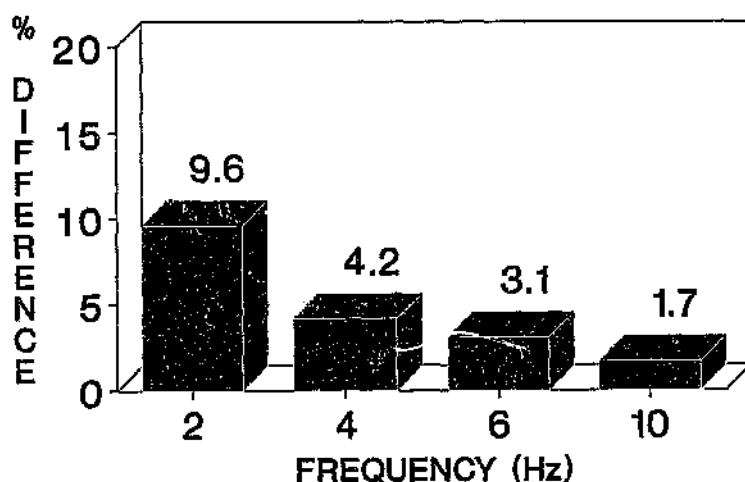


Figure 2.10 The difference in recorded amplitudes of contractions for the different sampling frequencies expressed a percentage of the true amplitude (60Hz).

Analysis of volunteers with simultaneous recordings at 4 and 8 Hz showed no significant difference in the detection and measurement of esophageal contractions. (Table 2.1). Propagation analysis of waves showed no difference between the 4 Hz and 8 Hz recordings for prevalence of peristalsis ($80.1 \pm 3.7\%$ vs $79.6 \pm 2.84\%$, $p=NS$).

Table 2.1 Comparison of the ambulatory recording using 4 and 8 Hz sampling frequencies for the total 24-hour period. (Channel 4, 5, and 6 are 15, 10, and 5 cm above the lower esophageal sphincter respectively)

VARIABLE	CHANNEL	4 Hz (MEAN $\pm$ SEM)	8 Hz (MEAN $\pm$ SEM)	SIG.
AMPLITUDE	4	31.7 $\pm$ 6.2	29.5 $\pm$ 4.1	NS
	5	28.8 $\pm$ 2.9	31.9 $\pm$ 2.9	NS
	6	34.0 $\pm$ 5.3	35.6 $\pm$ 5.9	NS
DURATION	4	1.5 $\pm$ 0.2	1.2 $\pm$ 0.2	NS
	5	1.7 $\pm$ 0.1	1.6 $\pm$ 0.1	NS
	6	1.8 $\pm$ 0.3	1.6 $\pm$ 0.3	NS

2.2.4 Discussion

The need for data reduction can be accomplished by storing data at lower frequencies. Unfortunately, the optimal sampling frequency for this purpose is not known. In this study this was evaluated from two perspectives. The first part of the study examined the effect of decreasing the sampling frequencies on the amplitude of contractions. The amplitude was chosen as this is the most important characteristic of a contraction in terms of its functional significance, and in terms of contraction recognition by available software programs. The manometric tracings from patients with different disorders were chosen in order to examine the whole spectrum of esophageal contractions from multi-peaked high amplitude contractions of DES to low amplitude contractions of non-specific motor disorders. Overall the difference in amplitude of contractions between 4 Hz and 60 Hz was 4.2 percent. This is equal to about 2 mmHg for the average amplitude of contractions for normal volunteers which is 52 mmHg (see chapter 7). This is insignificant when one considers that transducer drift of up to 5 mmHg over the twenty-four hour period of study is considered acceptable.¹⁵⁶ By increasing the sampling frequency to 10 Hz the difference decreases to 1.7 percent

but this would be at the expense of storing 2.5 times the data for recording and for software analysis. Sampling, then, at a frequency of at least 4 hertz is adequate for ambulatory manometry.

The second part of the study examined the effect of two different sampling frequencies on the ambulatory recording from four volunteers. In this study the amplitudes and duration of contractions and the peristaltic nature of contraction waves were examined. This was done to ascertain the difference in the clinical situation and to examine parameters other than amplitude. No differences were found between the sampling frequencies of 4 and 8 Hz either for individuals or taken as a group, confirming the previous conclusion that 4 hertz is adequate.

We can expect that technology will continue to advance and provide larger memory storage devices and more efficient computer software programs. However, for the purposes of ambulatory esophageal manometry, sampling data at a frequency of at least 4 Hz is optimal in terms of preserving fidelity of the data, complying with memory limitations of dataloggers, and meeting the analytic abilities of available software. Later it was found that 8 Hz was necessary to reliably flag pharyngeal swallows because of the rapid contractions of the pharyngeal muscles. For this reason, the equipment was modified to store data at 8 Hz for all the pressure channels.

2.3 THE EFFECT OF EXTRA TUBES IN THE ESOPHAGUS²

2.3.1 Background

The new generation digitrappers with larger memory capabilities provided the opportunity not only to measure esophageal pressures over 24 hours, but also to integrate esophageal and gastric pH monitoring. Combined esophageal and gastric pH had been used in the Esophageal laboratory at USC for some time and was performed with two catheters each containing a glass pH electrode with built-in reference electrodes.¹⁷³⁻¹⁷⁵ It was policy to always use glass pH electrodes as these are considered superior to antimony probes.^{133,176} By protocol, one pH catheter was placed 5 cm proximal to the upper border of the LES for esophageal monitoring, and the other was placed 5 cm below the LES for gastric monitoring. As the length of the LES varies between individuals (Normal range 2.6 - 5.0 cm)³⁵ it was not possible to construct a single catheter containing two pH electrodes which could be placed with the same position with respect to the LES in all studied subjects.

With the advent of ambulatory manometry a further catheter was needed for integration of 24-hour manometry with gastric and esophageal pH (figure 2.11). While the catheters are only 7 Fr in size, a potential for interference of the pressure monitoring by the pH probes was considered. It has been reported that the greater the diameter of the catheter used for stationary motility, the greater the amplitude of esophageal contractions.¹⁷⁷ Furthermore, a question arose as to whether abutment of the pH catheter against the pressure transducers would dampen the recording of esophageal contractions. This study aimed to determine the effect of extra esophageal pH catheters on the pressure recording of the ambulatory manometry catheter in five normal subjects and five patients with gastroesophageal reflux disease.

2.3.2 Methods

Five normal asymptomatic volunteers and five patients with gastroesophageal

² This study was published in abstract form in *Gastroenterology* 102(4):A430, 1992.{1727}

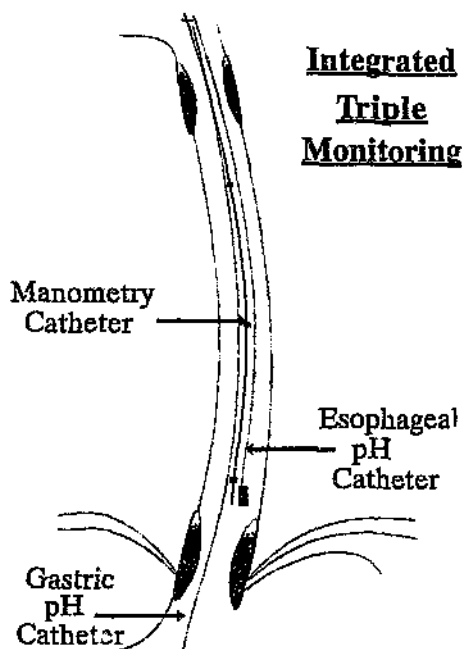


Figure 2.11 Integrated monitoring of ambulatory esophageal pH, gastric pH, and esophageal manometry.

reflux disease proven by 24 hour pH monitoring were studied. All subjects had stationary manometry performed as described in chapter 4.¹⁷⁸ Three 7 French diameter catheters, (one three channel Sentron manometry catheter and two glass Ingold pH probes) were introduced transnasally into the esophagus using 2% lidocaine jelly for topical anaesthesia. The catheters were placed so that one of the pH probes was 5 cm below the LES and the other 5 cm above the upper border of the LES. The manometry catheter was placed so that the distal transducer was at 5 cm above the upper border of the LES, i.e., at the same level as the esophageal pH probe. These are the standard positions for pH and motility studies. At least one hour was allowed for the esophagus to accommodate to the probes before starting the recording. Patients were placed in the supine position as for stationary manometry. Ten swallows with 5 ml boluses of water were performed with all three catheters in situ. Twenty seconds were allowed to elapse between each swallow. If the patient inadvertently swallowed during the 20 second

interval a further 20 seconds were allowed to pass before the next swallow. This was to negate the influence of the refractory period of the esophagus from the study. One of the pH catheters was then removed and 5 minutes were allowed for the patient to accommodate. A second set of ten wet swallows were performed in the same manner as before. The second pH catheter was then removed and a third set of 10 swallows was performed. Contraction amplitudes were recorded 5, 10, and 15 cm above the LES for all swallows. Collectively, a total of 1125 contractions were analyzed. Statistical analysis was performed with the aid of a computer program. Multifactor analysis of variance and the Kruskal Wallis test for non-parametric data sets were used to assess the effect of the number of catheters on contraction amplitude.

2.3.3 Results

Table 2.2 shows the means and standard error for the amplitudes (in mmHg) of contractions for the different number of tubes in the different levels of the esophagus.

Table 2.2 The mean $\pm$ SEM of the amplitudes of contractions for 1, 2, 3 catheters respectively.

CM ABOVE LES	AMPLITUDE* 1 CATHETER n=125	AMPLITUDE* 2 CATHETERS n=125	AMPLITUDE* 3 CATHETERS n=125	SIG.
15	57 $\pm$ 2.6	60 $\pm$ 2.6	60 $\pm$ 2.6	p=NS
10	72 $\pm$ 2.1	73 $\pm$ 2.2	70 $\pm$ 2.4	p=NS
5	68 $\pm$ 2.7	64 $\pm$ 2.4	64 $\pm$ 2.7	p=NS

* n amplitude (mmHg) $\pm$ SEM.

Multifactor analysis of variance confirmed that the number of catheters in the esophagus caused no difference in the amplitude of contractions ($p=0.85$), but that a large variation in amplitude occurred between patients and between swallows within any single patient. Similarly, when taken collectively, the overall mean amplitude for all contractions was similar for 3 tubes (64.5 ± 1.5 mmHg) and 2 tubes (65.3 ± 1.4 mmHg) and for 1 tube (65.5 ± 1.5 mmHg), $p=0.91$ by Kruskal-Wallis test.

2.3.4 Discussion

Monitoring pressures at the same time as monitoring esophageal pH provides the opportunity to observe the interaction between the two. Similarly, integrating esophageal pH with gastric pH has been shown to be useful for detecting duodenogastroesophageal reflux.^{179,180} Also, the pH probe would be 1 cm below the lowest pressure transducer, and not at exactly the same level. To preserve the fidelity of each test when integrating the three it was necessary to use three separate catheters since a single catheter containing all transducers and probes was not available. Because the tubes were narrow they were well tolerated by patients as is discussed in chapter 4. However, it was necessary to study the effect of the extra pH probes on the manometry catheter to make sure that the presence of the pH catheters did not affect the recording of pressures. The study of 10 wet swallows is the standard for stationary manometry and we chose to study 10 swallows with three catheters, then two catheters, then only the manometry catheter in situ. The results show that there is no difference in the recording of the contraction amplitudes with the presence of the pH probes in the esophagus. This is probably because the transducers are recording the intraluminal pressure and not the pressure exerted by direct "squeeze" of the esophageal muscle on the pressure transducer. This is in keeping with the previous observation by Dodds that the intraluminal pressures are radially symmetrical in the esophageal body.¹⁶⁷ It also appears as if the increase in the combined diameter of the three tubes does not affect the amplitude of contractions.¹⁷⁷ This appears to contradict the findings of Lydon *et al* that contraction amplitude increases with increasing diameter of the manometry catheter.¹⁷⁷ However, the catheters used in Lydon's study were up to 6.7 mm diameter which is larger than the combined diameter of the three 7 Fr catheters in this study (4.45 mm). In Lydon's study a difference in contraction amplitude on the smooth muscle of the esophagus was only found between the 4.8 mm diameter catheter and the 6.7 mm diameter catheters. There was no difference in amplitude between the 3.3 and 4.8 mm diameter catheters. It is possible that an effect of additional pH catheters may be seen if combined with a Konigsberg manometry catheter, which is 4.65 mm in diameter, in place of the Sentron catheter (2.23 mm diameter) as used in this study.

The presence of pH probes in the esophagus at the same time as the Sentron 7

French manometry catheter did not affect the recording of pressures in this study. Consequently, integrated monitoring of esophageal pH, gastric pH, and esophageal manometry is possible using three separate probes without affecting the integrity of each separate test.

CHAPTER 3: SOFTWARE DEVELOPMENT

3.1 OVERVIEW

Definitions of terms developed in this chapter and used throughout the thesis are listed in appendix D.

Once each 24-hour ambulatory recording was completed, the stored data was loaded onto a personal computer for analysis. Early development of ambulatory manometry was limited by the lack of comprehensive software for automated analysis of the large amount of data acquired from the 24-hour record. Complex software was required to analyze the amplitude, duration and morphology of contractions, and the resulting wave form derived from three or more levels of the esophagus. This chapter outlines the development of the software at USC and the basis for the algorithms used. The rapid advances in technology in the area of personal computing facilitated both the graphic screen display and the software analysis of the recorded study. The release of the IBM pentium processors with 16 megabytes of RAM (Random Access Memory) in 1995, enabled analysis of a 24-hour manometry study in less than 3 minutes whereas this took more than 20 minutes with the personal computers available at the beginning of the study. While the minimal requirements for running the software program are a 386 microprocessor with 640 kilobytes RAM, the newer model computers enabled more rapid analysis.

Figure 3.1 shows an algorithm depicting the three aspects of the software development and the features considered under each aspect: 1) the graphical display of stored raw data, 2) analysis of the data, and 3) a hardcopy report summarizing the analysis. The user-friendly interface of the graphical display was the product of Gastrosoft, Inc. Dallas Texas and was developed for the most part prior to the start of this study. Modifications were made during the software development to enable easier access to the data at any point in the recording. The largest part of the development was in the area of data analysis which included algorithm development and testing, and

OUTLINE FOR SOFTWARE DEVELOPMENT

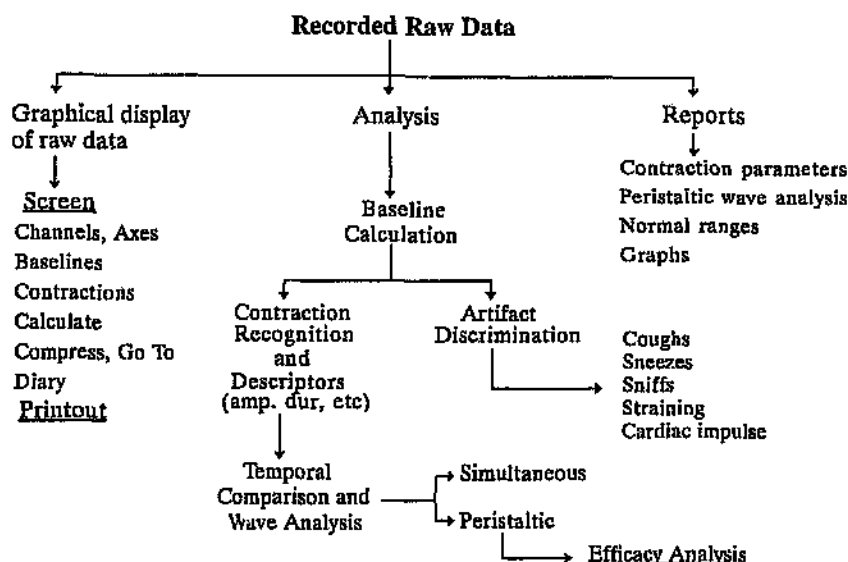


Figure 3.1 The algorithm for development of the software for analysis of the recorded ambulatory manometry data.

validation of the fully automated analysis. Forty-six versions of the program were tested and, in each, errors were identified and corrections made for incorporation into a newer version for further testing. The final version was validated by comparison with manual analysis and is discussed in chapter 5. This final version has been released by Gastrosoft for commercial use with the Microdigitrapper described in the previous chapter. Here we discuss the concepts and definitions developed for the analysis of the 24 hour manometry data, highlighting the difficulties encountered in the ambulatory setting compared to stationary manometry.

3.2 GRAPHIC DISPLAY

In order to display the stored digital data it was necessary to convert digital information (transferred from the microdigitrapper) into an analogue format to be displayed on screen or printed out as a hardcopy. Certain functions were needed to

display the data in a user-friendly environment. The goals for the graphic display as defined at the outset are listed below:

1. The screen display should show contractions in a way which is familiar to the physician. This was done by using the stationary manometry format. Different colors were used for different channels.
2. The program should have the ability to display simultaneous pH data.
3. Baselines and axes should be shown, the scales of which should be user determined and flexible.
4. There should be a facility to move to a particular part of the recording eg. "GO TO" a certain page or time.
5. A compression mode should enable variable durations of the recording to be displayed on screen at any one time. This would enable the full 24 hour of study to be displayed on screen or any part thereof.
6. There should be a function that facilitates insertion of diary times from the graphic screen display (review mode). This allows accurate insertion of meal times as well as the ability to "IGNORE" certain periods or enter a new diary period.

An example of the screen display of part of a recording is shown in figure 3.2. The top channel shows the esophageal pH (5 cm above the LES). The other three channels show esophageal pressure at 5, 10, and 15 cm above the LES. The Y-axis provides a scale in mmHg for each channel. The interval between "dots" for the X-axis is shown in the lower right hand corner where the time of the beginning of the displayed page is also shown. At a sampling frequency of 8 Hz, 2 seconds between dots is possible for the fully "uncompressed" or expanded mode. In the uncompressed mode, approximately 2000 pages, or screens, make up the entire 24 hour study. The total number of pages for that compression is shown in the bottom left hand corner of the screen. The entire recording (2000 screens) could be "paged" through on computer screen. The screen display could be variably compressed to include progressively larger durations of the recording all the way to depiction of the full 24 hours of study (figure

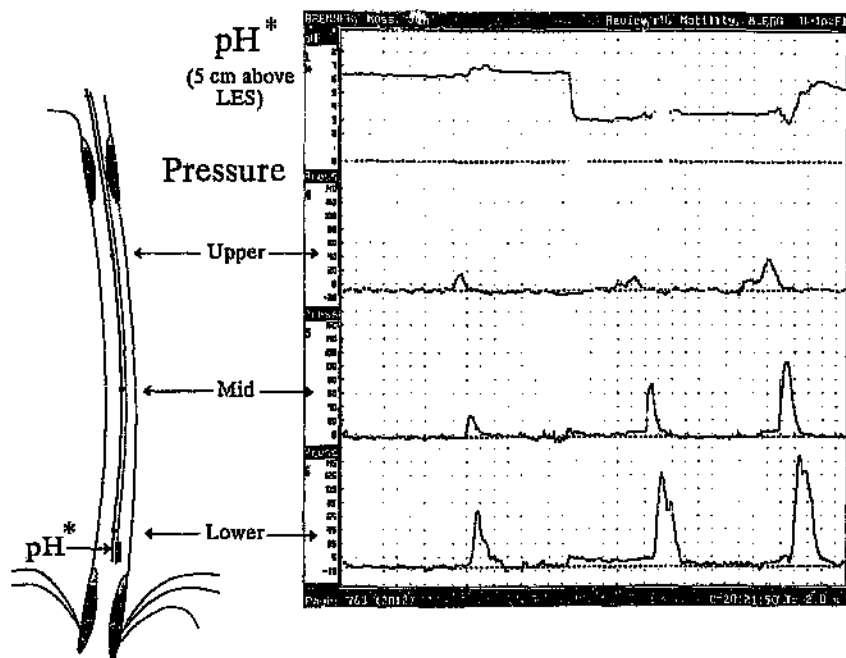


Figure 3.2 An example of the screen display of the ambulatory esophageal pH and manometry recording (right) next to a graphical representation of the position of the transducers (left).

3.3). The vertical cursor on screen could be placed at any point of the recording and can be "decompressed" at this point of the study for further on-screen evaluation. Calculations for individual contractions could be performed on screen by use of the function keys. Further channels such as a swallow channel can be represented as is discussed later.

An additional on-screen feature was the display of the analyzed contractions after automated analysis of the entire recording was completed. This provided the ability to display the contractions as recognized by the computer. This is discussed later.

3.3 DATA ANALYSIS

The accumulation of pressure data at a frequency of 4-8 times per second from multiple levels of the esophagus for prolonged periods of time resulted in a large body

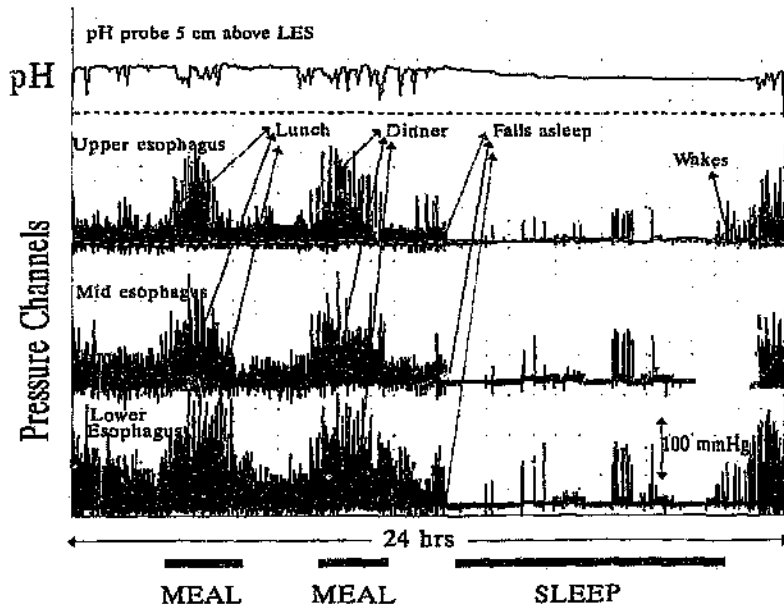


Figure 3.3 An example of the 24 hour pH and manometry recording in the compressed mode showing the full 24 hours of study.

of data for analysis. It has been estimated that manual analysis of the 10 wet swallows obtained from stationary manometry takes 60 - 90 minutes¹⁸¹. Manual analysis of more than a thousand contractions, by extrapolation, would take approximately 250 hours. This was obviously not practical and computer assistance was required. Fortunately, a rapid advancement in personal computer and software technology occurred in tandem with the development of miniature pressure transducers and solid state portable dataloggers. Consequently, the concept of automated computer analysis became feasible. In order to do this, definitions and algorithms for computer recognition of the desired pressure events had to be developed. Early use of computer technology had been used by Castell for analysis of stationary manometry and showed that computer analysis correlated well with manual analysis.¹⁸²

For the purposes of ambulatory motility analysis the analysis of the recorded contractions was broken down into three main areas:

- I. Contraction analysis and recognition of artifacts.
- II. Propagation analysis using a temporal comparison between contractions of different levels of the esophagus. This enabled a distinction between peristaltic and simultaneous waves.
- III. Efficacy analysis which relates manometric data to propulsive function.

3.3.1 CONTRACTION ANALYSIS

Standardized parameters as used to define esophageal contractions by stationary manometry were used in order to develop computer algorithms. These included contraction amplitude, duration, area under the curve, slope of contraction i.e., rate of rise of pressure, and the morphology of the contractions in terms of double or multi-peaked and repetitive contractions.

3.3.1.1 Baseline

In order to measure contraction amplitude, it was necessary to define a baseline from which to take measurements. In order to minimize the effect of minor transducer drift occurring over the 24 hour period a dynamic baseline was used. This was done by resetting the baseline every sixty seconds based on the mode value for that period. This also facilitated accurate baseline settings to account for the slight negative intrathoracic pressure with respect to atmospheric pressure in normal subjects¹⁵³ and the esophageal pressurization that occurs in patients with achalasia.

3.3.1.2. Threshold

There are physiologic intrathoracic fluctuations in pressure that constitute a "background noise" with respect to esophageal contractions. Respiratory excursions are the most ubiquitous intrathoracic pressure changes recorded. Figure 3.4 shows a graphical representation of a typical esophageal contraction on the background of these respiratory fluctuations. Because the respiratory fluctuations can result in pressure

changes of up to 15 mmHg with deeper breathing, it was necessary to define a threshold with which to measure the contraction parameters. This threshold was defined as an amplitude (pressure) that had to be exceeded before consideration of a contraction was made. Once a pressure event exceeded this value, a further criterion of a specified duration above the threshold value was made. Defining the optimal thresholds required comparison of computer analysis using different thresholds to manual analysis by physicians experienced in analysis of stationary manometry.¹⁷¹ The optimal threshold values provided by the validation study were 15 mmHg for a duration of 1 second. While it was important to standardize this for the purpose of defining normal ranges the option of changing these parameters was still included in the software program.

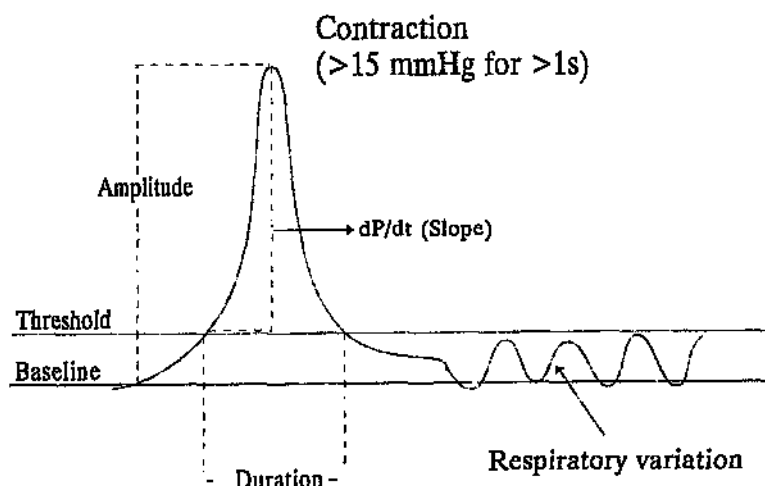


Figure 3.4 Graphical representation of an esophageal contraction superimposed on the oscillating pressure changes of respirations. dP/dt = the rate of change of the pressure increase.

3.3.1.3 Artefact Recognition

Besides respirations, coughing, sneezing, nose blowing, and sniffing cause intrathoracic pressure changes that are recorded from the intraesophageal catheter (figure 3.5). It was necessary to develop algorithms to detect these pressure changes to ensure

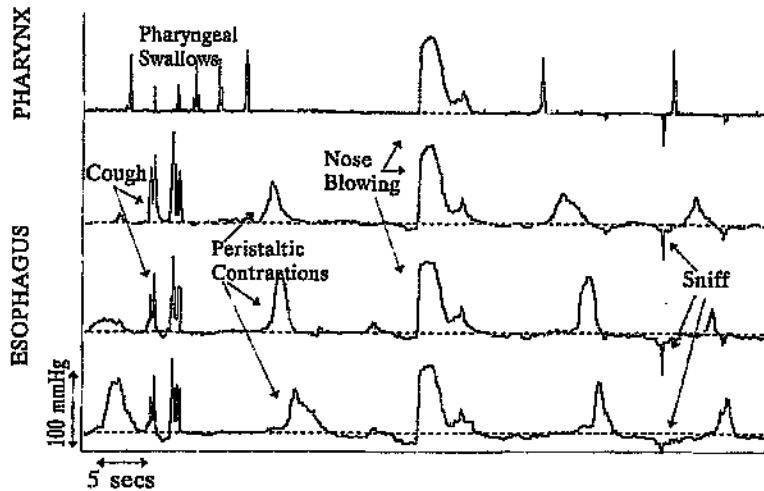


Figure 3.5 An example of the ambulatory recording showing the intrathoracic pressure changes with coughing, nose-blowing and sniffing.

accuracy of recognition of valid contractions and exclusion of the "artifacts" from the contraction analysis. The application of the criteria for valid contractions excluded most of the artifacts from being recognized as contractions but further criteria for coughing and sneezing were necessary. Coughing and sneezing have similar characteristics, namely a rapid rate of rise in pressure (dP/dt), a simultaneous nature of the pressure change, and a similar amplitude in all levels of the esophagus. The algorithm developed to recognize these pressure changes included these characteristics in the following way: When a contraction wave was recognized as simultaneous (see later) the dP/dt of the pressure change was noted. If this exceeded a certain value (later defined as 100 mmHg/sec) then the amplitude of all contractions was compared. If the amplitude of all three pressure changes was within 10% of each other, then the "wave" was labelled "c" (for cough) on the screen and was excluded from the contraction analysis. Coughing and nose-blowing were categorized together.

3.3.1.4 Contraction Descriptors

Figure 3.6 depicts the computer algorithms for recognition of contraction

duration and amplitude. If a pressure increase exceeded the threshold value for a period of 1 second, the pressure increase was recognized as a valid contraction. Derivation of threshold values is discussed in chapter 5. The amplitude was then measured as the maximum pressure with respect to the baseline. Duration was defined as the time that the pressure exceeded the threshold level. These measurements were then saved for that particular contraction along with exact times that each of these parameters occurred. This was important for later analysis of peristaltic progression of contraction waves.

Measurement of the amplitude of contractions with respect to the baseline was standard for stationary manometry. The measurement of duration was more complex. Castell had used a computer algorithm for measuring contraction duration for automated analysis of stationary manometry based on the beginning of the rapid upstroke of the wave.¹⁸² Duration of the contraction was measured from this point to the point where the downslope reached the baseline. There were two problems with this in the ambulatory setting, both related to the background respiratory fluctuations (figure 3.6). The measurement of duration of the contraction was dependent in part on the onset of the contraction with respect to the phase of the respiratory oscillations (x_1 and x_2). Similarly, the return to baseline was affected by the respiratory oscillations, y_1 and y_2 . The figure shows that by using this definition, the recorded duration of the contraction d_1 is very different from the recorded duration of the contraction d_2 , even though these are identical contractions occurring at different times of the respiratory cycle. The transducer only records the highest pressure at any point in time and therefore records the respiratory pressure if this is greater than the start or end of a contraction. Consequently a different definition for measuring duration was necessary. The threshold, which had already been used for contraction recognition was used, and the contraction duration was defined as the time that the pressure in the esophagus was greater than the threshold pressure of the "valid" contraction (d_3). While this underestimated the true duration of muscular contraction of the esophagus it represents a reliable and objective measurement. As can be seen from the figure, the measured duration of both contractions using this definition is the same, d_3 , regardless of the phase of respiration. Correlation of computer measurement of duration using this algorithm with manual analysis was better than previously reported even for stationary

manometry programs.^{171,182}

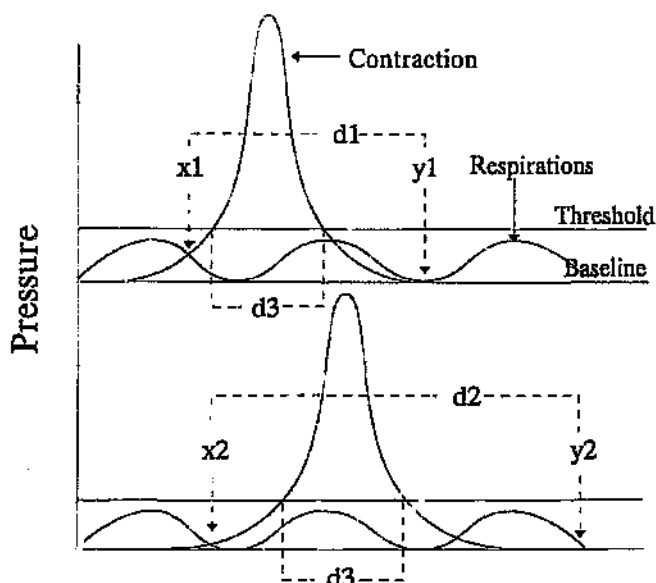


Figure 3.6 The calculation of wave duration by different definitions. Note the respiratory fluctuations superimposed on the same contraction at different phases of the respiratory cycle.

3.3.1.5 Multi-peaked Contractions and Repetitive Contractions

A "double-peaked" wave was defined as one with two definite peaks while "multi-peaked" waves have more than two peaks. Repetitive contractions are contractions that recur after a single stimulus, i.e., a pharyngeal swallow. There is no universal definition of multi-peaked or repetitive contractions and their functional relevance is not clear. A discussion of these contraction forms and the algorithms developed to recognize them is included in appendix E.

3.3.2. PROPAGATION ANALYSIS

An analysis of the temporal relationship of the propagation of contractions down the length of the esophagus allowed a definition of the concepts of peristalsis and

simultaneity. The sequence, or train, of contractions that are propagated down the length of the esophagus was called a "wave". This term was used to embody the concept that contractions, as seen on manometry, are part of a single event, i.e., propagation of the impulse from the pharyngeal swallow down the esophagus. A contraction at a particular level of the esophagus should not initially be regarded in isolation. The mechanical equivalent of peristalsis is the "stripping wave that milks the esophagus clean from its proximal to its distal end."¹⁶³ Figure 3.7 shows the algorithm used for classification of contractions into waves.

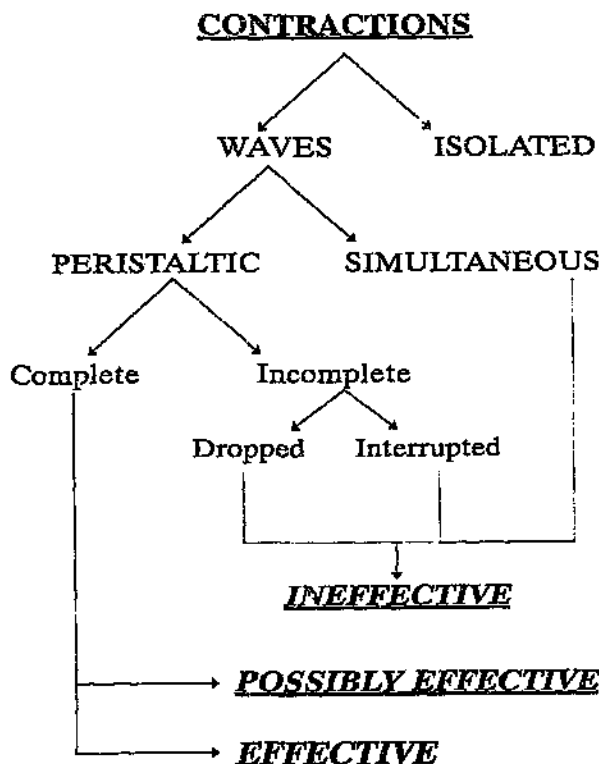


Figure 3.7 The algorithm for classification of contractions and waves.

The software was programmed to relate a valid contraction in one channel to any other pressure changes in the other two levels of the esophagus. A contraction was

therefore either part of a wave, or it bore no relation to any other pressure event and was called "isolated". As the normal propagation speed of contractions is between 1 and 4 cm/sec, it was specified that the time interval for recognition should be less than 5 seconds between consecutive channels (5cm apart) and less than 10 seconds between the uppermost and lowest channels (10 cm apart).

The analysis by the software program began with the upper channel. When a valid contraction was recognized the contraction was related to the other two channels. If another contraction was recorded then a wave, or sequence, was recorded. Figure 3.8 shows the definition of the types of peristaltic waves recognized by the software. If valid contractions were recognized in all channels and they were peristaltic then a "complete peristaltic wave" was recorded. If a contraction was not recognized in either the uppermost or the middle channel, but was recognized in the other two channels, then an "interrupted" wave was recorded. If a contraction was not recognized in the lowest channel, but was recognized in the other two channels, a "dropped" wave was recorded. The distinction between "dropped" and "interrupted" was made to differentiate between a loss in peristalsis in the lower esophagus as was seen frequently in end-stage gastroesophageal reflux disease, and motor abnormalities that may affect other parts of the esophagus. The software then performed the same temporal comparisons for the second channel so that if a wave was interrupted in the first channel (proximal esophagus) the wave could be recognized by virtue of its propagation more distally. This demonstrates how an increase in the number of channels in the esophagus increases the complexity of the analysis. Applying the concept of wave recognition to the automated analysis also increased the sensitivity for contraction recognition and decreased the percent of "isolated" contractions which were felt to be part of a "wave" when analyzed manually.¹⁷¹

Once the software program recognized the relationship between contractions in different channels it defined the relationship as either peristaltic or simultaneous. If contractions in two different levels of the esophagus occurred at the same time the contractions were said to be simultaneous with respect to one another. As a corollary, if the wave of contractions progressed in an orderly sequential manner with a definite period of time between the proximal contraction and the distal contraction, then the

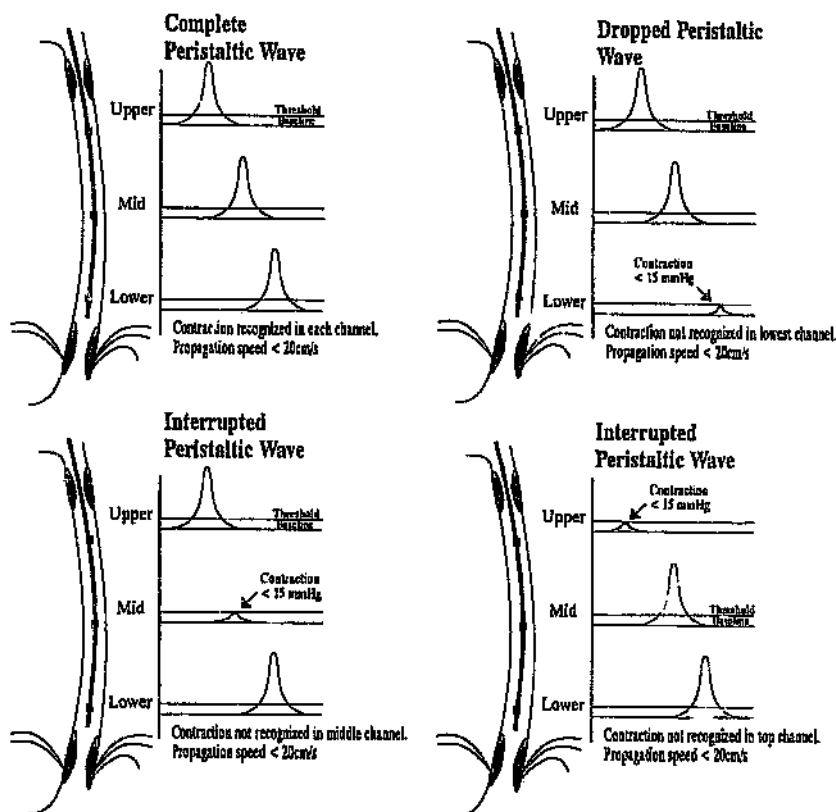


Figure 3.8 Classification of the types of peristaltic waves.

contraction wave was defined as peristaltic. However, defining numerical parameters to the definition was more difficult. There is a controversy concerning the definition of "simultaneous" and the way the propagating measurements should be made.

Richter³⁴ defined simultaneous contractions as those with a propagation speed greater than 10 cm/sec.³⁴ It has also been noted using fluoroscopic studies that a propagation speed of greater than 6.25 cm/s was associated with occasional escape of barium proximally in the supine subject.¹⁸⁴ Supine swallowing of barium, however, does not necessarily reflect swallowing of food or liquid in the upright period. It had been the policy in the laboratory of Tom DeMeester at USC to err on the side of

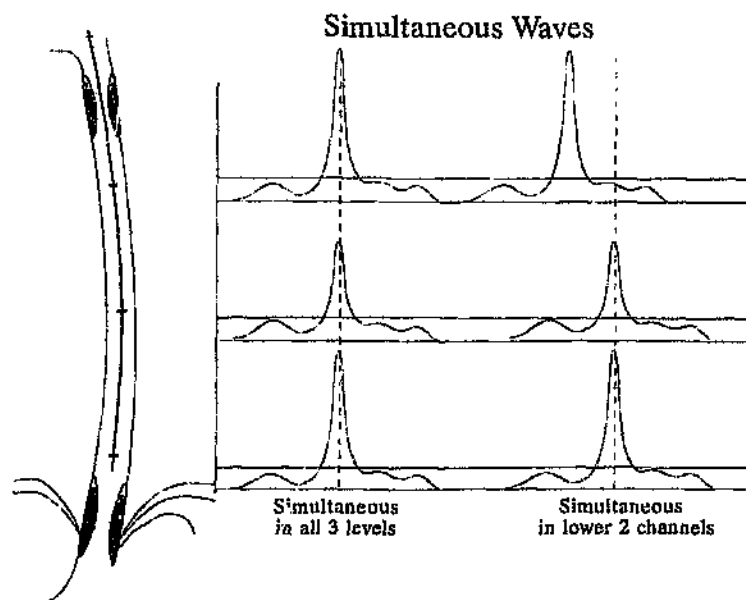


Figure 3.9 Graphical representation of simultaneous waves

specificity when defining spastic motor disorders that are defined by the prevalence of simultaneous contractions. For this reason a rapid progression speed of 20 cm/sec had been the defining limit at USC to discriminate between simultaneity and peristalsis using stationary manometry and this definition was adopted for the analysis of ambulatory recordings. It has been observed that spasm of the esophagus may be diffuse or segmental,⁹⁹ and bolus propagation of barium is usually impeded by simultaneous contractions even at the segmental level. Consequently it was decided to classify a wave in which either two or three contractions were simultaneous as a simultaneous wave (figure 3.9). Data regarding the position of simultaneity was preserved for later analysis so that the level of "spasm" could be determined.

Another controversy concerned the reference point with which to measure the propagation speed. The manofluoroscopic observation that bolus movement coincides with the onset of the contraction, prompted Richter and colleagues to use the contraction upslope as the reference point with which to measure simultaneity.³⁴ For the purposes of ambulatory manometry this definition had to be modified because the onset of

contractions was difficult to define from a standpoint of computer analysis. This point has been dealt with above in the discussion on the measurement of the duration of contractions and is related to the respiratory fluctuations. The computer analysis of peristalsis, using onset or peak of contractions, was compared to manual analysis and found to be more accurate when peak-to-peak propagation was used.¹⁷¹ This study is discussed in chapter 5.

An important modification of the software program was made utilizing the wave analysis which improved the sensitivity of contraction recognition. It was noticed during manual analysis that occasionally contractions of low amplitude were recognized by virtue of their relationship to contractions in other channels. However, being of low amplitude, the contraction did not meet the criteria for a valid contraction (of sufficient amplitude but not sufficient duration) and was consequently labelled as a "missed" contraction for that channel by the computer (X in figure 3.10 A). The software was then modified to accept pressure changes in any one channel if they met the threshold amplitude alone (and not the duration threshold), if valid contractions (meeting both amplitude and duration criteria) were recognized in the other channels (Figure 3.10B). This changed the "I,X,X" (isolated, no contraction, no contraction) to "P,P,P" (peristaltic, peristaltic, peristaltic) which correlated with manual recognition of lower amplitude contractions. The increase in sensitivity from this modification is discussed in chapter 5.

3.3.3. EFFICACY ANALYSIS

Elegant studies performed by Kahrilas defined the amplitude and propagation speed necessary to adequately move a bolus down the esophagus.¹⁵⁸ He performed videoesophagography simultaneously with manometry using liquid barium in the supine subject. Contractions invariably had to be peristaltic and required amplitudes of approximately 20, 25, 30 mmHg in the upper, mid and lower esophagus to prevent escape of barium proximally. If contractions were of lower amplitude, were simultaneous with another level of the esophagus, or were dropped or interrupted, then residual barium was left in the esophagus at the end of the wave. Unfortunately no work has been done in subjects in the upright position or in subjects eating solid food.

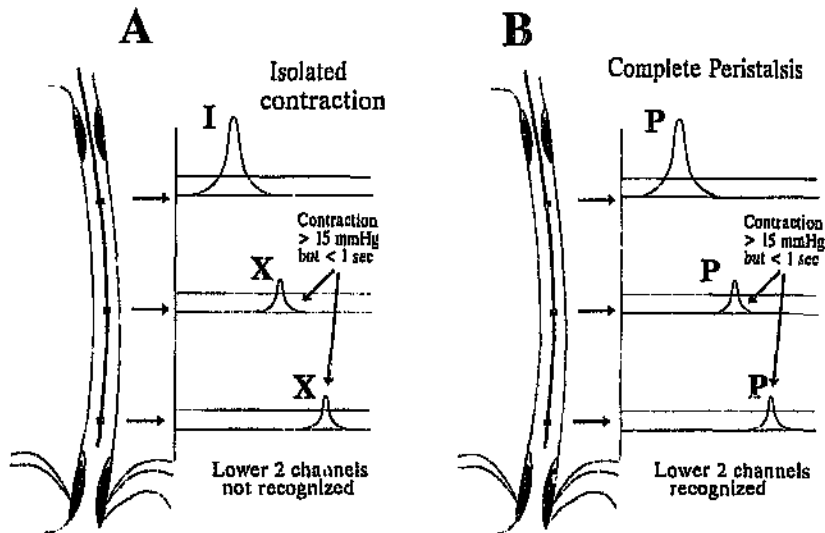


Figure 3.10 Graphical representation of the detection of low amplitude contractions by the modified program.

The physiologic requirements for adequate bolus transport had, therefore, yet to be studied. Nonetheless, using criteria to define efficacy was useful to define manometric function. Using Kahrilas' findings, an **effective wave** was defined as a peristaltic wave with contractions exceeding 20, 25, and 30 mmHg for the upper, mid and lower esophagus respectively. As a corollary, an **ineffective wave** was one in which simultaneity was identified between 2 or 3 channels, or in which the waves were dropped or interrupted. There remained, then, the peristaltic waves with contractions recognized in all levels of the esophagus but with insufficient amplitudes to qualify as an effective wave. These waves were considered **possibly effective**, since the ability of these waves to move a bolus, with the aid of gravity in the upright position, was unknown. The summarized "efficacy" analysis was stored in a separate computer file for the purposes of printed reports and for viewing on screen.

3.4. SCREEN DISPLAY OF ANALYSIS IN REVIEW MODE

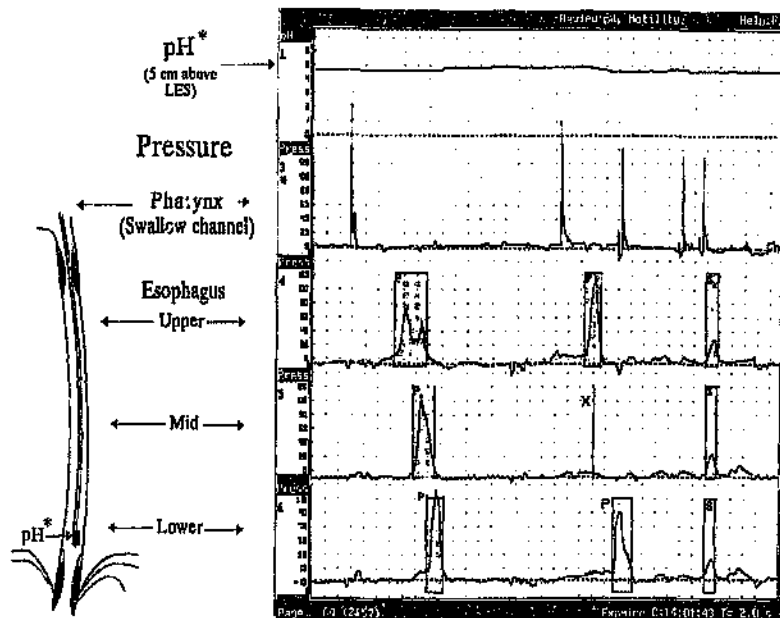


Figure 3.11 An example of the screen display of the recognized contractions after the analysis. This enables on screen viewing of the analysis of individual contractions and waves.

In order to view which waves had been recognized by the analysis on the computer screen, the program was modified to superimpose a band of light blue on each analyzed contraction - the width of which indicated the recognized duration of the wave. This feature, called the automatic event insertion, also displayed the propagation analysis (Figure 3.11). A "P" (peristaltic) or an "S" (simultaneous) was placed above the contraction if the contraction was recognized to bear a relationship to a contraction in another channel, or an "I" (isolated), if not related to a recognizable contraction in any other channels. The wave analysis enables identification of dropped and interrupted waves on screen by placing an "X" at the channel of the "missed" contraction. This enabled the person analyzing the recording to visualize the computer's recognition of contractions and propagation. A similar feature was incorporated in the pH analysis

which also displayed on screen the automated recognition of reflux episodes (R = reflux).

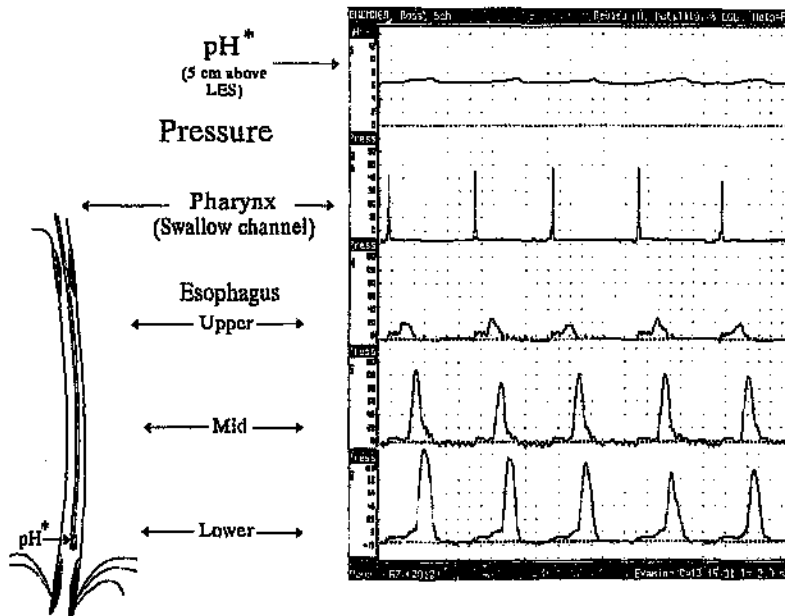


Figure 3.12 An example of the screen display of the pharyngo-esophageal manometry. The pharyngeal transducer is used to flag swallows.

3.5 SOFTWARE ANALYSIS OF THE SWALLOW CHANNEL

As discussed in the previous chapter the pharyngeal transducer was used only for recognizing the occurrence of a pharyngeal contraction and not for providing descriptive information on the nature of the contraction itself. To this end it was necessary only to provide a threshold amplitude with which to flag the swallow (Figure 3.12). This was user defined and could be set at any level depending on the recording for any particular subject. The pharynx did not show the background "noise" of respirations as was seen in the esophageal recordings but movements of the head did cause movements of the catheter in the pharynx. This changed the character of the swallow from high amplitude contractions to low amplitude contractions since the contraction amplitudes recorded in

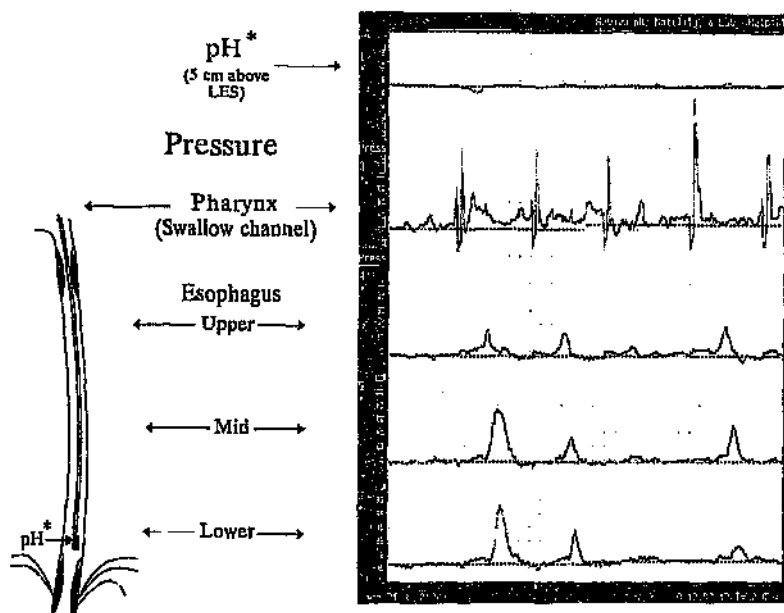


Figure 3.13 An example of the pharyngo-esophageal manometry with the pharyngeal transducer in the region of the cricopharyngeus muscle.

the pharynx are positional. Occasionally the swallow analysis was complicated by the movement of the catheter into the cricopharyngeus muscle which resulted in rapid changes in high amplitude pressures (figure 3.13). The later development of two different catheters with different distances between the pharyngeal and esophageal transducers overcame these problems.

3.6 HARDCOPY OF REPORTS OF THE FINAL ANALYSIS

Summaries of the results of the analysis and graphic representations of motility patterns were presented on screen and could be printed in hardcopy form. The report was flexible and could be user defined so that reports could be customized. As there was a large body of data concerning contraction forms for the different channels as well as the propagation and efficacy analysis, a brief summary report containing tables with values and graphs with superimposed normal values was designed.

3.7 INCORPORATING ESOPHAGEAL pH ANALYSIS.

The integration of pH analysis with the ambulatory manometry data became possible with the advent of the larger memory capacity dataloggers. One of the input channels on the digitrapper could be set up to receive pH data while the others received pressure data. The idea was to have a single system able to analyze both pH and manometry data, as well as provide the ability to correlate one with the other. Correlating pH with manometry would allow assessment of esophageal clearance of refluxed acid as well as the ability to identify the effects of esophageal acidification on esophageal motility.

"EsopHagram" (Gastrosoft, Inc. Dallas, Tx) was the computer program used for automated analysis of 24-hour pH studies in the USC esophageal laboratory. The program was a product of Gastrosoft but the software was written in a different language to that of Multigram. Incorporation of the pH analysis into the software required that the pH analysis software be re-written in Turbo Pascal. This required a comparison of the newly written program in Multigram with the EsopHagram program so as to be certain that both programs were analyzing pH tracings in exactly the same way. One of the problems that had to be overcome was that the motility data was being sampled at 8 Hz while the old pH programs utilized systems that sampled data only at 0.25 Hz. The normal values for pH monitoring had been established using systems sampling data at this lower frequency.¹⁸⁵ The single parameter most affected by a higher frequency sampling rate was the number of reflux episodes detected when the pH hovered around pH 4. The analysis of this situation was previously examined in detail by Johnson and DeMeester and the conclusion reached was to register each drop below pH 4 as a reflux episode.¹⁷³ The total number of reflux episodes was an important parameter in the generation of the DeMeester score and an artificially raised increase in the number of episodes increased the reflux score. When sampling at 8 Hz it was found that the total number of episodes was greater than when sampling only at 0.25 Hz. When 8 Hz was used any small change below pH 4 during clearance of a reflux episode was recognized as a separate reflux episode (figure 3.14). It was not possible to change the sampling frequency for a single channel on the digitrapper so this problem was overcome by adding a feature in the software during analysis. Extraction

of every 32nd data point stored for the pH channel was equivalent to storing data at only 0.25 Hz. Comparison of Multigram with EsopHagram subsequently was shown to be the same for the pH analysis. Reports of the pH analysis as previously shown in the EsopHagram program were incorporated in the final report of the ambulatory analysis.

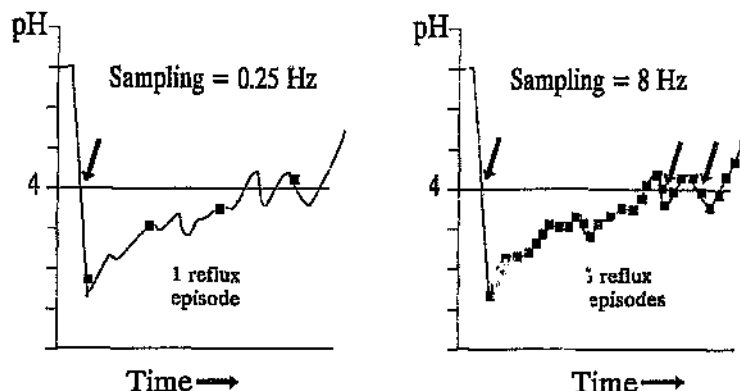


Figure 3.14 An example of how an increased sampling frequency increases the recognized number of reflux episodes (arrows). Dot = sampled data point.

3.8 INCORPORATION OF GASTRIC pH ANALYSIS

Gastric pH monitoring had been used for the indirect detection of duodenogastric reflux by Fuchs and others,^{174,175,186} and to detect a hypersecretory state.¹⁸⁷ Dual monitoring of gastric pH with esophageal pH monitoring had also been used to assess the presence of duodenogastroesophageal reflux.^{179,188} In order to preserve the protocols for gastric and esophageal pH monitoring and include ambulatory manometry at the same time as the pH studies, it was necessary to include the software used for analysis of gastric pH. This was incorporated in the Multigram program and validated against the EsopHagram program. The calculation of the Fuch's score and the graphic representation of the pH profile of the recording were included in the analysis. While this was incorporated in the program so that gastric analysis could be performed, further analysis of gastric pH was beyond the scope of this thesis. Furthermore, the gastric pH

study has been replaced by a new spectrophotometric device (Bilitec 2000) which measures the presence of bilirubin in the stomach.

CHAPTER 4: METHOD OF PERFORMING THE 24-HOUR AMBULATORY pH AND MANOMETRY STUDY

4.1 INTRODUCTION

It was necessary to standardize the 24-hour test so that it was performed in the same way for all subjects. Important aspects in this regard included medications permitted before and during the study, calibration and positioning of the catheters, optimal duration of the study, and lifestyle limitations necessary to minimize any variables that may adversely influence the results. In order to comply with the protocols of pH monitoring the same limitations were applied in this study, since pH and motility monitoring were performed simultaneously. Ambulatory esophageal manometry is a new test and little has been written about how to perform the study. Consequently it was necessary to address all factors that may have had an effect on both the recording of pH and motility. The methods discussed in this chapter were used in all the studies presented in the subsequent chapters.

4.2 MEDICATIONS PERMITTED DURING THE STUDY

All drugs that affected gastric acid output were discontinued long enough before the test for normal gastric acid output to return. Omeprazole was discontinued for at least 2 weeks prior to the study as the non-competitive nature of the binding of the drug to the proton pump inhibits acid output for the life of the parietal cell. It had been reported that some patients show a decreased basal acid output for up to 2 weeks after discontinuing omeprazole.¹⁸⁹ H₂-receptor antagonists were stopped for 48 hours prior to the study.¹³³ Those patients on omeprazole were allowed to substitute an H₂-blocker for up to 2 days prior to the study if necessary. Antacids were permitted up to the night before the study.

Medications that potentially had an effect on gastrointestinal motility were also stopped well in advance of the study. These included Cisapride which has been shown

to have an effect on esophageal contraction amplitude,¹⁹⁰⁻¹⁹³ and Erythromycin, a motilin agonist which has been shown to have an effect in increasing motility throughout the gastrointestinal tract although its effect on the esophagus is questionable.¹⁹⁴ Similarly other prokinetic agents such as metoclopramide were discontinued. Benzodiazepines (especially those taken to assist sleep) have been shown to have an effect on the motility and acid exposure of the esophagus¹⁹⁵ and were also stopped before the study.

4.3 RADIOLOGY

All radiological studies were performed at USC. The normal subjects and patients underwent radiological assessment according to the standard protocol of the USC Swallowing Center. Studies were performed on normal subjects to exclude the presence of anatomical abnormalities. Videoesophagography was recorded during 5 swallows of 10 cc liquid barium performed in the prone oblique position at intervals of 30 seconds. Rapid swallowing to produce full column films were performed on all patients. Upright swallows were again assessed with 2-5 swallows of liquid barium. Patients were also assessed with solid bolus swallows. Solid boluses consisted of cooked minced beef mixed with liquid barium. Bite sizes were determined by the patient.

4.4 STATIONARY MANOMETRY

All normal subjects and patients underwent stationary manometry prior to the ambulatory studies. This was done to assess the position of the lower esophageal sphincter for later placement of the catheters, to establish the competency of the LES, and to assess the esophageal body function.^{35,178} Standard manometry was performed after an overnight fast. A single catheter assembly was used consisting of five polyethylene tubes bonded together with five lateral openings placed at 5 cm intervals from the distal end of the catheter and oriented radially around the circumference. The diameter of the lateral openings was 0.8 mm. The catheter was perfused with distilled water at a constant rate of 0.6 ml/min using an Arndorfer pneumohydraulic low compliance perfusion pump (Arndorfer Medical Specialties, Greendale, Wisconsin).

Overall length, abdominal length, i.e., length below the respiratory inversion

point, and resting pressure of the lower esophageal sphincter were measured with a standardized station pull through technique as previously described.¹⁷⁸ The catheter was withdrawn one centimeter every 20 seconds and measurements taken at each station. Relaxation of the lower esophageal sphincter was assessed by a series of five wet swallows with 5 cc room temperature water with one pressure transducer positioned within the sphincter, the distal side hole within the stomach and the proximal side holes within the esophageal body. Relaxation was expressed as the percentage of resting sphincter pressure.

The function of the esophageal body was assessed by placing the most proximal side hole 1 cm below the cricopharyngeal sphincter and the remaining 4 side holes trailing at 5 cm intervals over the whole length of the esophageal body. The reason for placing the catheter with respect to the cricopharyngeus muscle is the ease of identification of the high resting pressures of this sphincter. The lower esophageal sphincter frequently has a low pressure (especially in patients with gastroesophageal reflux disease) and determination of its position while performing stationary manometry is difficult. This unfortunately placed the lowermost side hole at a variable distance from the lower esophageal sphincter in different patients.¹⁶⁹ Nonetheless, this was the convention at USC for stationary manometry. The rationale for placement of the ambulatory manometry catheter is discussed shortly.

Ten wet swallows with 5 cc room temperature water were performed at 30 second intervals to assess esophageal body function. The median amplitude and duration of contractions from the different levels of the esophagus were calculated from the 10 swallows performed. Amplitude and duration were calculated with respect to the baseline.

The time delay between the peak of esophageal contractions at various levels of the esophagus was used to calculate the speed of propagation. According to this information, the esophageal contraction wave following a swallow was classified as peristaltic (speed < 20 cm/sec), simultaneous (speed > 20 cm/sec), or interrupted (contraction amplitude falling to < 10 mmHg in any of the distal recording channels following a pharyngeal swallow). The 5th and 95th percentiles of historical normals were used to establish normal ranges for the measured parameters.^{35,178}

The classification of the motor disorders discussed in chapter 1, based on stationary manometric results at the University of Southern California, is shown in table 4.1.

Table 4.1. Diagnostic categories based on stationary manometry

DISORDER	SPHINCTER CHARACTERISTICS	ESOPHAGEAL BODY CHARACTERISTICS
Achalasia	Incomplete relaxation	No peristalsis
Diffuse esophageal spasm	Incomplete or complete relaxation	Greater than 20 % simultaneous contractions
Nutcracker esophagus	Normal	Amplitudes > 180 mmHg and > 190 mmHg in the lower 2 levels of the esophagus, respectively*
Hypertensive lower esophageal sphincter	Pressure > 26 mmHg*, normal relaxation	Not meeting the criteria for achalasia or diffuse spasm
Non-specific motor disorder	Variable	Not meeting the criteria for any of the above named disorders but outside the normal range

* Above the 95th percentile of normal subjects^{35,178}

4.5 CALIBRATION OF THE CATHETERS

4.5.1 Calibration of the pH Electrodes

The probes in this study were calibrated in standard solutions of known pH which were compatible with the glass electrodes used (Ingold, Sweden). In this study only glass pH electrodes were used as were considered more reliable and more accurate than antimony probes.^{133,195} Fresh batteries were used for each study and were inserted just prior to calibration. Calibration was performed in solutions of pH 1, 4 and 7 at room temperature. Since the recorded pH of a known solution changes with increasing temperature, a correction factor for this temperature difference was incorporated in the software program used for analysis. At the end of the study the catheter was advanced

into the stomach to record the gastric pH. This was done to ensure an acidic gastric pH as a few patients have achlorhydria and may have a false negative pH study despite significant reflux disease. The probes were re-calibrated in the same pH solutions (pH 1, 4 and 7) at the end of the study to exclude any drift in the recording over the 24-hour period. Studies with an electrode drift of greater than 0.2 pH units were discarded and the test was repeated where possible.

4.5.2 Calibration of the Manometry Catheter

Soaking the catheters in sterile water was necessary prior to calibration because of the hygroscopic potential of the silicone coating of the pressure transducers. As water is absorbed into the silicone lattice an increase in pressure is recorded until saturation is reached. The Konigsberg catheter required longer periods of pre-calibration soaking (> 1 hour) because of a thicker silicone coating than the Sentron catheter which reached saturation within 5 minutes.

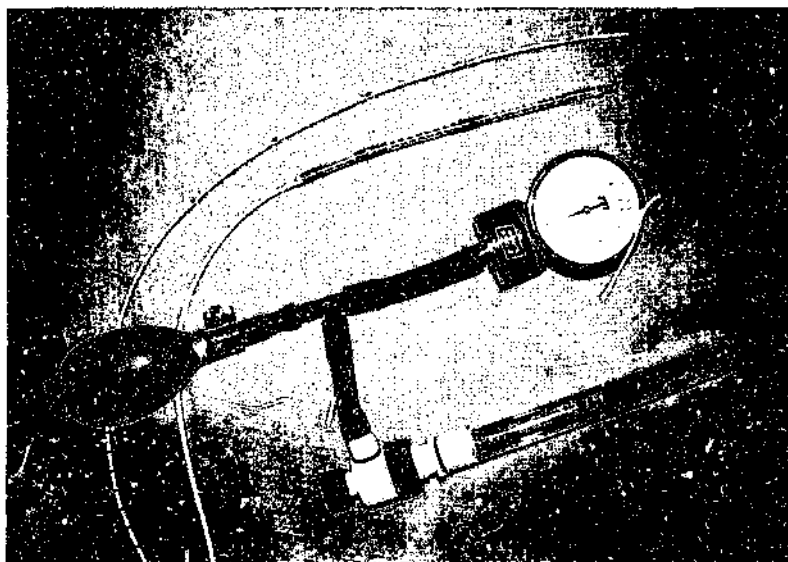


Figure 4.1 A method of calibrating the manometry catheter. The catheter is placed in a sealed glass tube which is connected to a bulb and a pressure gauge.

The manometry catheter was calibrated in a known pressure environment using pressures similar to those likely to be encountered during the recording of esophageal contractions. A tube with a baumanometer bulb was initially designed for calibration of the transducers (figure 4.1). However, this was found to be inaccurate because of a difficulty in maintaining a seal on the tube during calibration. An alternative method was designed which entailed placing the catheter in a calibration column containing water of known depth (figure 4.2). The catheter was placed so that the middle transducer was at a depth of 68 cm (equal to 50 mmHg). The software for the upload was programmed to accept the calibration pressures so that all measurements were made with respect to this. At the end of the study the catheter was again inserted into the calibration column to exclude transducer drift. Studies in which a transducer drifted more than 5 mmHg were discarded and were repeated where possible. The calibration column was cleaned after each use. In each study the Microdigitrapper was set to record during the calibration so that this could be confirmed on screen at the beginning and end of the 24 hour period. The Microdigitrapper clock was set prior to the start of each study. The liquid crystal display of the time on the Microdigitrapper ensured that accurate recordings of events were made by the studied subjects.

4.6 PLACEMENT OF THE PROBE

4.6.1 Anesthetizing the Nasopharynx

A number of local anesthetic agents were available for naso-esophageal intubation. Topical cocaine does not anesthetize the esophageal body mucosa and shrinks the nasal mucosa to aid in the passage of the probe. The disadvantages of cocaine is that it is a controlled substance and application to the nasopharynx is unpleasant. Spraying the nasopharynx with topical xylocaine is effective but the spraying itself causes a "burning" sensation. An alternative was to use 2% Lidocaine jelly. In this study the jelly was placed in a 5 cc syringe and given to the patient. The patient, in his or her own time, injected the jelly into the nose and sniffed it into the nasopharynx while lying supine. This maneuver was easily done with minimal

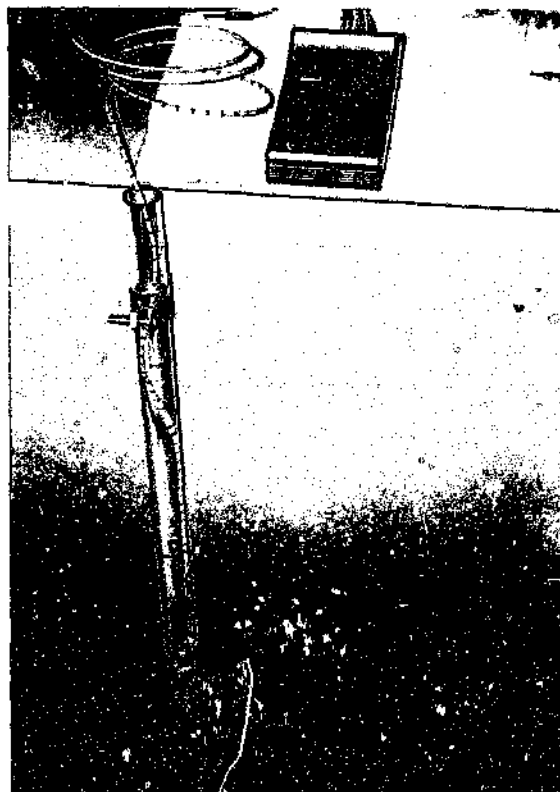


Figure 4.2 The calibration column containing water in which the manometry catheter is placed. This was the most accurate means of calibration and was the way it was performed in this study.

discomfort to the patient. The catheter was then introduced into the nostril and the patient was asked to extend his or her neck in order to straighten the angle between the nose and the oropharynx. This facilitated passage of the catheter tip past the soft palate into the back of the mouth. The patient was then given small sips of water and asked to swallow with the head fully flexed with the chin on the chest. This facilitated passage through the cricopharynx into the upper esophagus. Difficulty passing the catheters was only experienced in patients with a Zenkers diverticulum. The effect of lidocaine lasted approximately 15 minutes, so its effect on pharyngoesophageal motility was minimal.

4.6.2 Positioning the pH Probe in the Esophagus.

The results of pH monitoring have been shown to be affected by the distance of the probe from the LES. Significantly less acid is refluxed higher in the esophagus.^{197,198} Also, the LES has been shown to move upward with swallowing and respiration.^{199,200} It has also been noted that the lower esophageal sphincter moves into the chest transiently during peristalsis and it is estimated that the sphincter can move cephalad 2 to 2.5 cm.²⁰¹ There is also movement of the catheters with respect to the sphincter when the patient flexes or extends the head. In order to exclude the possibility of the electrode advancing through the sphincter and thereby being exposed to gastric juice which has not refluxed, it was necessary to place the electrode well above the upper border of the manometrically defined LES. By convention, and with regard to the studies just mentioned, the pH probe was positioned 5 cm above the upper border of the manometrically defined LES in this study.¹⁷² The alternate techniques used to determine correct positioning of the pH probe have been found to be inaccurate and were not used in this project.²⁰²⁻²⁰⁴

4.6.3 Design and Placement of the Ambulatory Manometry Catheter

In order to evaluate the entire esophageal body it was felt that sufficient transducers to span the length of the esophagus should be used. At least three transducers have been recommended for the use of stationary manometry.²⁰⁵ As mentioned, the problem of increasing the number of transducers is the increase in the amount of memory required on the datalogger, as well as the complexity of the software needed for analysis. Other systems developed in Europe used only two transducers but this limited the amount of information obtained from the study.^{206,207} In this thesis a 7 French Sentron catheter (Sentron, Amsterdam, The Netherlands) with three transducers placed 5, 10 and 15 centimeters above the lower esophageal sphincter was used. This enabled evaluation of the body of the esophagus in terms of peristaltic function, with a manageable amount of data as discussed in the previous chapters. Later development of the swallow channel placed 25 cm above the LES enabled sampling of pharyngeal pressures.

The lowermost transducer was placed at the same level as the pH electrode.

This ensured that the transducer did not move into the LES during the study and enabled evaluation of esophageal motility with esophageal acidification. It also enabled recording of pressures in the lower esophagus in a similar position with respect to the LES in all patients.

4.7 THE DIARY

Patients were asked to keep as accurate a diary as possible during the 24-hours of study. The sheet that was given to patients explaining the diary and providing a place to record events is included in appendix F. Subjects were asked to document, to the nearest minute, the start and finish of a meal and the occurrence and nature of any symptoms. Recording exact times was important as the characteristics of esophageal contractions were found to be very different during meals, between meals, and during sleep. Accurate diary keeping by the patient was also important for exclusion of the meal periods from the analysis of the pH study, and for discrimination between upright and supine reflux.¹³³ The Microdigitrapper had event "markers" which could be used by the patient during the study. These were used to mark the beginning and end of meals, the time of lying down for sleep at night and the occurrence of any symptoms. However, patients were reluctant to use these and a hand written diary was found to be more reliable. A questionnaire to assess the accuracy of the diary and the tolerance of the patients to the tubes is discussed in chapter 4.13.

4.8 DIET

The patients were allowed to eat normal sized meals during the course of the study. These were usually lunch and dinner if the study was initiated in the morning, and dinner and breakfast if the study was initiated in the afternoon. The only restrictions were the times of eating and the pH of the foods eaten to comply with the protocols for pH monitoring.^{172,208} Patients were given a list of foods with a pH of between 5 and 7 (Appendix G). Only water was allowed between meals and subjects were asked to document times of drinking on their diaries. Carbonated beverages were forbidden because of their acidic pH and their potential to encourage belching and augment reflux. Patients were asked not to eat within four hours of lying down to sleep

as eating prior to lying down may precipitate reflux.

In order to understand the patterns of motor activity in different physiological settings the circadian cycle was divided into different physiological periods for analysis. These were 1) the eating of meals, 2) the awake interprandial period, and 3) the supine or sleeping period. Reasons for this were based on previous studies which showed that oophageal motility is affected by the nature of the swallowed bolus, by body position, and by sleep.^{21,34,35,137,141,144,209-211} These are discussed in subsequent chapters.

Subjects were asked to eat their meals in one sitting so that motor activity could be assessed without the interruption of periods of "dry-swallowing". However, patients were asked not to rush their meals. An increase in swallowing frequency has the potential to affect the amplitude and organization of contractions because of neural inhibition and the refractory period of the esophageal muscle.

Langevin has noted that although the characteristics of a swallowed bolus affect individual wave forms, the nature of a whole meal does not affect the overall analysis of esophageal function with prolonged monitoring.²¹² In this study meals were not "standardized" and patients were encouraged to eat whatever they liked with the only limitation being the abstinence of acidic foods and ice-cream. Patients were asked only to drink water between meals and that these events should be noted on the diary. These periods were included with the meal period in the final analysis.

Assessment of the early recordings revealed that during the eating of ice-cream, the amplitude of contractions and the prevalence of complete peristalsis was decreased. Castell previously noted that when cold liquids are swallowed rapidly that esophageal contractions are diminished in amplitude.²¹³ This has not previously been reported in the ambulatory setting. Figure 4.3 shows an example of a compressed recording during a meal. The uppermost channel shows the pH recording. The pharynx, upper, middle and lower esophageal pressure recordings are shown in the next four channels from above, down. At the arrow, the patient documented precisely the start of eating a bowl of ice-cream. The recording shows that from this point, there was continued pharyngeal swallowing but a marked decrease in the esophageal body response. The amplitudes of contractions were decreased and the esophageal baseline pressure increased. It is possible, in this situation, that the same mechanisms responsible for the

depression of normal peristalsis cause inadequate relaxation of the sphincter resulting in esophageal pressurization. Research is presently in progress in this area at USC. Nonetheless, for the purpose of this thesis, the patient diets were modified to exclude ice-cream (Appendix G). All previous studies in which the patient ate ice-cream were re-analyzed to exclude this effect from the meal period.

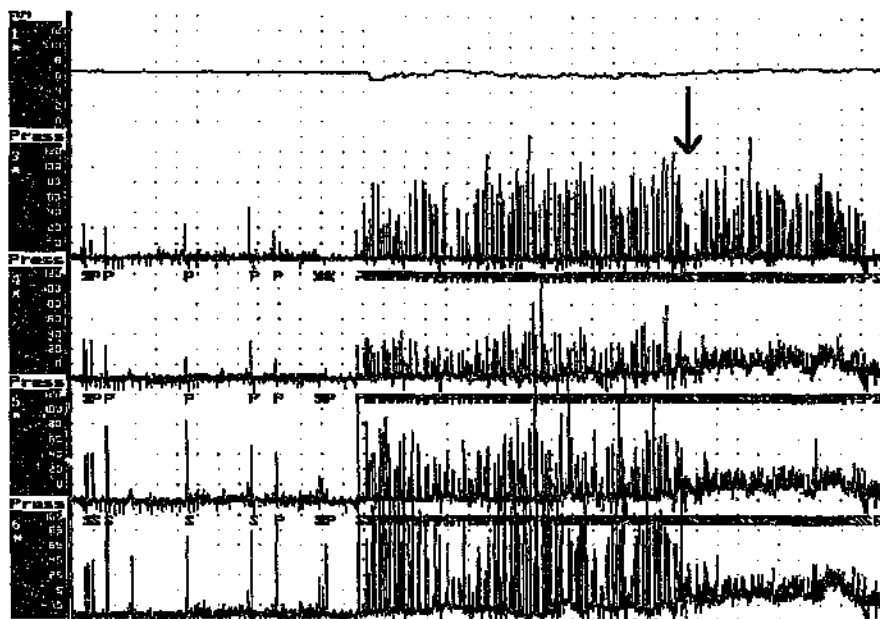


Figure 4.3 A compressed example of the ambulatory recording showing the effect of ice-cream on esophageal motility. The arrow marks the time the patient started eating ice-cream.

4.9 ACTIVITY

The patients were asked to sleep only at night since sleeping during the day, especially after lunch, can alter the motility patterns. During sleeping esophageal activity is markedly decreased and contractions have different characteristics from either the upright or the meal periods as is discussed later.^{214,215} Esophageal clearance of acid

is also markedly diminished when sleeping.^{170,316,217} The subjects were asked to document on the diary the times of retiring for the night and the time of rising in the morning. A more accurate means of documenting actual sleeping times was difficult. DeMeester had previously used a "supine" period during pH monitoring to represent reflux occurring at night. This included time spent asleep and time supine but awake.¹⁷² The ambulatory records revealed that the onset of sleep was accompanied by a marked decrease in both swallowing and esophageal motor activity and this was used to more accurately define the "sleep" period. If the patient managed to document periods of being awake and upright then these periods were included in the upright and not the supine analysis.

4.10 SMOKING AND ALCOHOL

Some centers allow patients to smoke and drink alcohol during pH monitoring if they normally do so. However, most evidence suggests that smoking and alcohol increase esophageal exposure to gastric juice over a 24-hour period. Ethanol has been shown to acutely decrease the LES pressure in healthy volunteers with an associated increase in nocturnal reflux.²¹⁸ It also has a chronic effect on the body of the esophagus.^{84,219,220} Smoking decreases the LES pressure, at least for the time of active smoking and increases the number of reflux episodes.^{221,222} Smoking is also associated with increased coughing which increases gastroesophageal reflux and makes analysis of ambulatory motility more complex.²²³ For these reasons smoking and alcohol were not permitted during the 24 hour period in this study.

4.11 EXERCISE

Although it was felt important to evaluate the patient in the most physiological conditions, subjects were asked to avoid excessive exercise during the study period. There is evidence that certain forms of exercise may increase the esophageal exposure to acid and affect the esophageal body activity. Clark and colleagues showed that reflux was increased significantly in running subjects.²¹⁸ Soffer *et al* found that the number of gastroesophageal reflux episodes and the duration of esophageal acid exposure was significantly increased in trained cyclists during exercise.²²⁴ The duration, amplitude

and frequency of esophageal contractions also declined with increasing exercise intensity. No subjects in this study were studied under strenuous exercise conditions.

4.12 DURATION OF MONITORING

Experience with ambulatory pH monitoring revealed that the longer the duration of study the more chance of correlating patients symptoms with reflux episodes.^{131,208,225} Monitoring during actual sleep was also important to document "nocturnal" reflux which has a different pattern to upright reflux.²²⁶ Similarly, it was felt that ambulatory manometry should record motor patterns from the periods of eating, awake interprandial, and sleeping. In this study subjects were studied for a complete circadian cycle with at least 12 hours of upright awake time, two full meals, and a full nights sleep. This prolonged period also provided the optimal period for detecting episodic motility abnormalities such as could occur with non-cardiac chest pain.

4.13 INPATIENT VERSUS OUTPATIENT MONITORING

Schlesinger and colleagues found that inpatient monitoring greatly underestimated the reflux which occurs in the outpatient ambulant subject.²²⁷ When ambulant outpatient monitoring was compared to inpatient monitoring, DeMeester found that in 18 normal subjects outpatient monitoring revealed a greater number of reflux episodes only in the upright position.¹⁸³ This was not so in 10 patients with GERD.²²⁸ The greatest advantages of outpatient monitoring are the decreased cost and convenience to patient and physician. While ambulatory manometry was not compared for inpatients and outpatients in this study, the conclusions reached by ambulatory pH monitoring were applied here. The patient is more likely to eat, drink and sleep more "normally" in his or her home environment, and assessment of esophageal motor function in this situation is probably a more accurate reflection of physiological motor activity.

4.14 PATIENT TOLERANCE AND COMPLIANCE OF 24 HOUR PH AND MOTILITY MONITORING.³

4.14.1 Background

During ambulatory pH and motility monitoring naso-esophageal intubation was necessary. It was not known whether the presence of the catheters limited the patients ability to eat or sleep or perform other tasks of daily living. Furthermore, accuracy of patient diary keeping was not known. In order to assess these aspects for the purposes of ambulatory manometry a post-study questionnaire was performed on 50 consecutive patients who underwent simultaneous pH and manometry testing.

4.14.2 Methods

Fifty consecutive subjects undergoing ambulatory pH and motility testing for workup of foregut symptoms comprised the study group. Stationary manometry followed by simultaneous ambulatory pH and motility monitoring was performed as described above.

Before the 24 hour study patients were informed about the importance of accuracy of the diary. This was also stressed in the diary sheet given to the patient on which the patient documented daily events (Appendix F). Patients were unaware, however, that they would be asked to complete a questionnaire after the study was completed.

Patients returned from the 24-hour study the next morning and the catheters were removed, re-calibrated, and then uploaded onto an IBM personal desktop computer for analysis. Each patient was then asked to complete the post-study questionnaire (Appendix H) in their own time prior to leaving the laboratory. Patients were informed that the results of the questionnaire would in no way compromise their future care and that the results of the questionnaire were for research purposes only.

³ This study was published in abstract form in *Gastroenterology*, 1994; 106(4), part 2:A471.

4.14.3 Results

Forty six (92%) of patients noted that they were able to mark events accurately at the time of occurrence. Forty six (92%) were able to eat the stipulated 2 meals and only 4 (8%) felt restricted by the suggested menu. Forty nine patients (96%) who admitted to eating or drinking between meals documented these times on the diary. Thirty subjects (60%) slept at some time during the day, but only 15 (50%) documented this on their diaries. Forty-three (86%) woke at some time during the night, but 31 (72%) failed to document these times accurately. Most patients described the test as uncomfortable but bearable and only 5 (10%) said they would not repeat the test should this be necessary.

4.14.4 Discussion

It is important to ascertain how reliable patients are in documenting occurrences during the 24-hour period of study since the analysis depends in part on the patient diary. It has previously been noted that the motility parameters during meal periods differ markedly from the interprandial period which is also different from the motility during the supine period. In order to accurately analyze these periods the patient diary needs to be accurate and, for this reason, the importance of the diary was emphasized to the subjects prior to the study. In reality it was usually evident from the recording when normal subjects ate and drank, and when they fell asleep (see chapter 3, figure 3.2), but this was not always obvious in patients with motility abnormalities. This study showed, however, that patients were reliable in documenting various occurrences when awake. On the other hand documentation of nighttime events was poor. Seventy-two percent of patients who woke in the night failed to document this on the diary. The implication of this is that some patients may have an increase in nocturnal motor activity that is due to periods of being awake and not to abnormal motor function. The poor documentation at night is also related to the poor correlation between symptoms and reflux episodes during this period.²²⁹

The fact that many patients slept during some part of the interprandial "awake" period has important implications. Decreased esophageal motor activity and compromised esophageal clearance function are characteristics of sleep.¹⁷⁰ Long reflux

episodes that occur during a post prandial "nap" may be a result of these factors. Whether these reflux episodes should be considered as part of the supine period or not is debatable, but in some patients a single long reflux episode in this setting may make the difference between a normal and an abnormal reflux score, (see chapter 8). In this study daytime sleeping was included in the supine period only if it was clearly documented by the patient.

The recording of snacking and drinking liquids outside of meal times was well documented. For the same reasons as above it is important to be able to know this prior to analysis, as the increased amplitude and organization of esophageal contractions that occurred with eating may sway an otherwise grossly abnormal interprandial period toward normal if the snacking is included as a non-meal period. When patients clearly documented these periods of snacking they were included in the analysis for the meal period in this thesis.

The need to intubate the esophagus through the nose is not ideal. Most patients found the study uncomfortable. However, almost all the patients described the test as bearable and only 5 patients said they would not repeat the test if it was necessary. Ninety-two percent of patients were able to eat the stipulated two meals. Overall the test was well tolerated and most patients carried out near normal lifestyles during the period of study. When the importance of an accurate diary was stressed to the patients at the start of the study the compliance was high during the day but relatively poor at night.

CHAPTER 5: MANUAL VERIFICATION OF THE COMPUTER ANALYSIS OF 24-HOUR ESOPHAGEAL MANOMETRY⁴

5.1 BACKGROUND

Prior to clinical application, it was necessary to validate the software program used for automated analysis. The aim of this study was to compare the automated computer analysis of ambulatory esophageal manometry with the accepted gold standard of manual analysis.

5.2 METHODS

The 24-hour ambulatory motility recordings from two normal volunteers (subject 1 and subject 2) and three patients (subjects 3-5) were used for manual and computer analysis. The patients were chosen for their variety of esophageal motor patterns to represent the spectrum of esophageal motility disorders that are likely to be encountered in clinical practice: subject 3 had high amplitude contractions, subject 4 had a hypomotile esophagus and subject 5 showed features of a non-specific esophageal motor disorder with an increased prevalence of multi-peaked contractions and simultaneous waves.

5.2.1 Ambulatory Manometry

After standard stationary esophageal manometry ¹⁷⁸ the subjects underwent 24-hour ambulatory motility monitoring according to the protocols outlined in chapter 4. The recordings were uploaded onto an IBM compatible personal computer and the software described in the previous chapters was used to automatically analyze each of the recordings.

The comparison between manual and computer analysis was divided into three parts: 1) Contraction recognition, i.e., which pressure rises were considered to be valid

⁴ This study was published in *Biomedical Instrumentation and Technology*, 1993;27:49-55

esophageal contractions, 2) Measurement of the contraction parameters of amplitude and duration, 3) Characterization of the propagation of the contraction sequence down the esophagus as either simultaneous (occurring in two different channels at the same time) or peristaltic (contractions in two channels separated by a certain time interval).

5.2.2 Manual Analysis

Since twenty-four hours of recording provides approximately 1000 contractions for each of the three levels of the esophagus, only a representative subset of these contractions were chosen for manual analysis. Six 10 minute periods were randomly chosen from each 24 hour recording: two from each of the upright, supine, and meal periods. This provided a total of 1407 contractions for characterization. Three hundred and eighty eight of these contractions were randomly selected for the measurements of duration and amplitude. Randomization was performed with the aid of a computer program. The tracings of the data for these periods were then printed out and a copy from each subject was given to 4 physicians experienced in esophageal motility studies. The tracings were analyzed separately by each physician with regard to the progression of the contractions from one channel to the next (peristaltic or simultaneous), and for amplitude and duration of each contraction. Amplitude was measured as the distance from the baseline to the peak of the contraction. Duration was measured as the time from the major upstroke of the contraction to the time the pressure returned to baseline. If the pressure wave did not return to baseline because of superimposed respiratory fluctuations the major downslope of the contraction was extrapolated to baseline as suggested by previous studies.³⁴ The results of the manual measurements were pooled and the means of the amplitudes and duration for each contraction were used for comparison with computer analysis. In order to assess the intra-observer variation, the duration of the same contractions was measured by each expert on separate occasions, 4 days apart. The progression characteristics of the contractions was ultimately decided by committee based on the individual expert's results.

5.2.3 Computer Analysis

Contraction recognition was based on an algorithm which defined a contraction

as a rise in pressure of greater than a certain value for a specified period of time (see chapter 3). Such a threshold is necessary because of the background pressure fluctuations that occur with respiration. The sensitivity of the program in recognizing true contractions, i.e., contractions recognized by manual analysis, was assessed by using 5 different threshold criteria for amplitude and duration; 10 mmHg and 1.0 seconds, 10 mmHg and 1.5 seconds, 15 mmHg and 1.0 seconds, 15 mmHg and 1.5 seconds, and 20 mmHg and 1.0 seconds. In order to increase the sensitivity, and decrease the false positive contraction recognition by the computer, the program was modified as previously discussed. An algorithm based on simultaneity and rate of rise in pressure (dP/dt) was developed for detection of coughs and sneezes. Low amplitude contractions (i.e., not meeting both duration and amplitude criteria) were recognized by relating small changes in pressure with valid contractions in either of the other two channels as described previously. The sensitivity and false positive rate of the modified program was assessed for the threshold of 15 mmHg and 1 second.

The baseline from which contractions parameters were measured was set every 60 seconds according to the mode value for that time period. The amplitude of contractions was measured from peak to baseline while the duration was measured as the time during which the pressure was above the threshold (Figure 3.4).

Contractions occurring in sequence in two channels were defined as simultaneous if the speed of propagation exceeded 20 cm/sec, and peristaltic if the propagation speed was less than 20 cm/sec, as previously described. Contraction onset and contraction peak were each used as points with which to measure the speed of propagation to compare with manual analysis.

5.2.4 Statistics

A commercially available computer program (SAS, SAS institute, Cary, North Carolina) was used for statistical analyses. Pearson's correlation co-efficient was used for amplitude and duration comparison, and Wilcoxon signed rank test was used for comparing accuracy of peak vs onset for propagation analysis.

5.3 RESULTS

The sensitivity of contraction recognition and the false positive computer detection of contractions is shown in Table 5.1. The threshold of 15 mmHg and 1 second was found to give the best sensitivity while resulting in an acceptable number of false positives. Deficiencies in sensitivity were due to low amplitude contractions that were unable to fulfill the amplitude and duration criteria, while the false positive contractions resulted from recognition of pressure increases from coughs and sneezes as esophageal contractions, and from the recognition of multi peaked and repetitive contractions as separate and distinct contractions when manual analysis considered these part of the same contraction complex. To overcome these shortcomings the program was modified. Application of the modified program to the threshold of 15 mmHg and 1 second increased the sensitivity from 88 to 93.8% while reducing the number of false positives from 23.4 to only 9.2 for the period considered. The latter represents approximately 1 percent of all computer recognized contractions.

Table 5.1: Sensitivity of computer analysis for contraction recognition in each subject using different thresholds. The number of false positive contractions detected by the computer is also represented (in parentheses).

SUBJECT [# of evaluated contractions]	10mmHg 1.0 s	10mmHg 1.5 s	15mmHg 1.0 s	15mmHg 1.5 s	20mmHg 1.0 s	15mmHg 1.0 s + Algorithm
1 [237]	98.7% (26)	96% (13)	95% (19)	91% (12)	88% (9)	95% (2)
2 [340]	97.9% (54)	92% (40)	91.8% (19)	88.5% (12)	84.4% (12)	97% (3)
3 [351]	98% (72)	88% (40)	91% (21)	87% (16)	80% (5)	95% (10)
4 [218]	94% (63)	92% (54)	76% (15)	71% (8)	66% (3)	89% (11)
5 [261]	96.4% (88)	92% (54)	86.1% (43)	75.2% (25)	67.2% (33)	94.2% (20)
Average [1407]	97% (60.6)	92% (40.2)	88% (23.4)	82.5% (14.6)	77.1% (12.4)	94% (9.2)

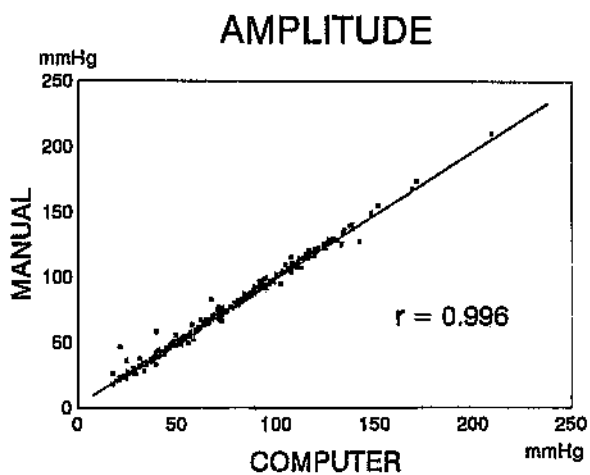


Figure 5.1 Correlation of the computer results for amplitude.

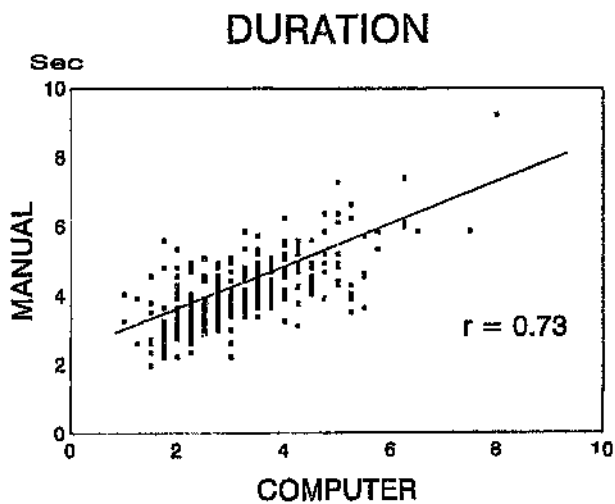


Figure 5.2 Correlation of manual and computer results for duration.

Drift from the ambulatory catheter did not exceed 4 mmHg in any pressure channel for the duration of the study. Comparison of computer calculated and manually measured amplitude showed an excellent correlation ($r=0.996$) while the correlation was less good for duration ($r=0.73$) (Figure 5.1, 5.2). Correlation for duration between experts was similar to this, ($r=0.73-0.77$) as was the correlation for duration measurements of the same expert on the same contractions performed 4 days apart ($r=0.79-0.88$). Comparison of each expert with each other and with computer analysis is depicted in Table 5.2.

Computer analysis of wave propagation was more accurate when contraction peaks were used than when measurements were made relative to contraction onset (Figure 5.3). Overall the accuracy of propagation classification was 93.3% when using contraction peaks and 84.3% when using contraction onset ($p<0.05$). This pattern was similar for each of the subject analyses.

Table 5.2: Correlation coefficients for comparison between experts, and between experts and the computer for contraction duration.

	EXPERT 1	EXPERT 2	EXPERT 3	EXPERT 4	AVERAGE
EXPERT 2	0.73				
EXPERT 3	0.75	0.73			
EXPERT 4	0.77	0.73	0.76		
COMPUTER	0.71	0.65	0.62	0.66	0.73

5.4 DISCUSSION

Validation of an automated computer analysis program is essential prior to its use in either the research or clinical setting.^{161,206,207} The ideal computer program for automatic analysis of ambulatory esophageal motility requires three distinct features. First, the program should recognize what constitutes a contraction as recognized manually, so that any measurements are performed only on those intraesophageal pressure

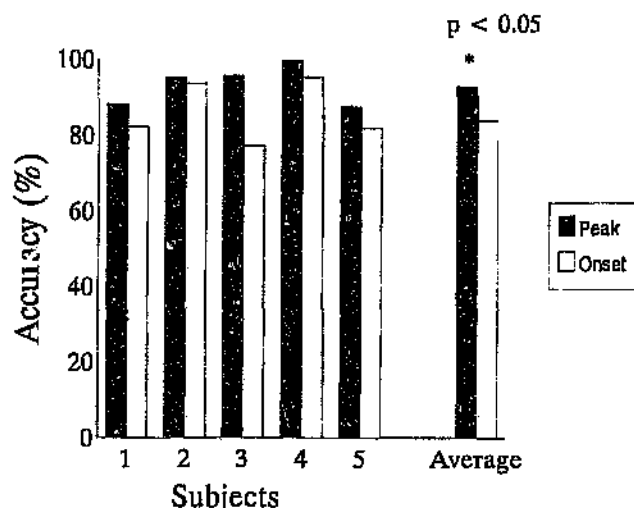


Figure 5.3 Comparison of accuracies of propagation characteristics based on peak and on onset for the five subjects studied.

increases that are due to esophageal contractions. Second, the program should be able to measure characteristics such as amplitude and duration as accurately as manual analysis. Finally, the program should be able to classify the relationship of the esophageal contractions as either peristaltic or simultaneous. These features are not only essential to describe the manometric function of the esophagus but are the basis for the established classification of esophageal motor disorders. This study compared the accuracy of the automated analysis to the gold standard of manual analysis. To minimize the inter-individual variation in the manual analysis of esophageal motility²³⁰, the standard was based on the results obtained from 4 different physicians experienced in esophageal manometry. Because of the background "noise" of respiratory variations (see chapter 3) a threshold for recognition of increases in intrathoracic pressures due to esophageal contractions needed to be defined. The threshold needed to be set high enough to avoid recognition of respiratory fluctuation as contractions (i.e., minimize false positives), but low enough to detect as many low amplitude esophageal contractions as possible (i.e., have high sensitivity). The latter was especially important in patients with low amplitude contractions (as occurs in severe gastro-esophageal reflux disease) which explains the

inclusion of subject 4 in this study.¹²⁷ While specificity cannot be meaningfully described in terms of a percentage (there are infinite true negatives, i.e., "a no contraction" recognized by computer, and "a no contraction" recognized manually), a false positive rate was chosen as an indication of computer recognition of contractions which were not true contractions as described by manual analysis. The decrease in the false positive rate of the modified program was due to the recognition of multi peaked and repetitive contractions which were previously recognized as multiple separate esophageal contractions by the early versions of the program, and which are considered by manual analysis to be part of the same contraction complex. The increased sensitivity of the modified program was a consequence of the ability of the program to recognize low amplitude contractions that did not meet both amplitude and duration criteria by relating these small pressure changes to valid contractions in the other 2 channels (Figure 3.10).

The threshold of 15 mmHg for a duration of 1 second was found to be the most accurate for all subjects studied. For the subject with high amplitude contractions and for the 2 normal volunteers a higher threshold could be used as nearly all of the contractions were greater than 30 mmHg in amplitude. In these subjects a higher threshold did not decrease the sensitivity but did decrease the false positive rate. The threshold of 15 mmHg and 1 second is the best compromise in order to have a standard threshold to be used for normal subjects for construction of a database with which to compare patients.

As could be expected, the correlation of the manual with computer analysis for amplitude of contractions was excellent. A defined baseline with which to measure the peak of the wave allows this, and the peak of the contraction is easily recognized by the computer. Measurements of duration are, however, more complex. The duration cannot always be measured relative to baseline because of the respiratory fluctuations. Furthermore, contractions are described by a variety of wave forms with varying upslopes which makes it difficult to know when the esophageal contraction actually begins and ends. Consequently, for contraction analysis, the duration was defined as the time the contraction amplitude was above our chosen threshold (> 15 mmHg and > 1 second). Comparison of the duration measured in this way with manual analysis demonstrated that the correlation was as good as computer programs that measure only the 10 swallows of stationary motility.¹⁸² The difficulty in measuring duration is well demonstrated by the

correlation co-efficients for the comparison between the single experts, as seen in table 5.2, as well as for the same expert when the same contractions were measured blindly a few days later. The computer analysis does have the added advantage, however, of eliminating the interindividual variation since the same algorithm is always used.

Of interest, measurements relative to contraction peak were shown to be more accurate for characterization of propagation than wave onset. This is contrary to the physiological finding that movement of the bolus coincides with the onset of the contraction (i.e., the contraction upstroke) and not the contraction peak. The reason for the increased accuracy for peak to peak measurements is the imprecision in identifying the onset of the contraction. Compounding this problem is the fact that preceding the contraction an intra-bolus pressure is often seen (especially during meals), which sometimes exceeds the threshold of 15 mmHg in separate channels. In this situation the onset of the contraction is recognized as the start of the bolus pressure and not the start of the contraction.

In this study we evaluated and validated the software program designed for analysis of continuous intraesophageal motility monitoring. The software was found to provide an accurate automated analysis of this very large body of data.

5.5 CRITICAL EVALUATION AND COMMENT

The validation of a software program against manual analysis for the large number of contractions recorded by ambulatory esophageal motility monitoring is arduous, but essential. In the present era of rapidly advancing computerization, a greater number of techniques are becoming available for research and diagnostic purposes. It is imperative that the accuracy of such systems be evaluated before they are put into clinical practice. I am indebted to those physicians who made time to help with the validation study.¹⁷¹

CHAPTER 6. ASSESSMENT OF ESOPHAGEAL MOTOR FUNCTION DURING MEALS

6.1 MONITORING PRESSURES DURING EATING

This chapter outlines aspects of ambulatory manometry from the meal periods that should be borne in mind when interpreting the recordings. Direct comparisons between stationary manometry and ambulatory manometry in terms of amplitudes and durations of contractions cannot be made because of the differences that occur during eating in a physiologic environment.

The nature of the food swallowed and the interval between swallows have a profound effect on the measurements of contractions. Posture, bolus size, and temperature and consistency of the swallowed food have all been shown to affect the amplitude and propagation speed of recorded contractions.^{35,136,137,139,140,142-145,210,231} Keren,¹³⁸ found that the velocity of propagation is significantly slower and the amplitudes of contractions are higher with soft food than with water boluses. Dooley has noted that boluses with high viscosities cause an increase in contraction duration.²³² In a separate study he found that the esophagus responds to increments in consistency (solid boluses) by increasing the contraction amplitude.¹⁴¹

There are neuromuscular mechanisms that alter the esophageal contraction characteristics when swallowing occurs with different intervals. It was mentioned in the introduction that "deglutitive inhibition" was recognized almost a century ago by Meltzer.³ This phenomenon refers to the inhibition of transmission of an esophageal contraction wave when a second swallow follows the first after a short interval. If a glass of water is drunk rapidly, the pharyngeal contractions are not followed by esophageal body contractions until the end of the train of swallows, at which time a normal peristaltic wave progresses through the esophageal body. An example during ambulatory monitoring is shown in chapter 8, figure 8.4. On the other hand it has been noted when a wave of contractions closely follows a previous wave, but at an interval long enough to overcome the effect of deglutitive inhibition, that the second wave will

be characterized by contractions of lower amplitudes and shorter durations. This was termed the refractory period of the esophagus by Ingelfinger²¹ and further evaluated later

For these reasons, the esophageal motor pattern seen during eating as recorded with ambulatory manometry does not seem as organized as the motility recorded during stationary manometry, which is performed under strictly controlled conditions. An example of a recording of a patient in the supine position, swallowing water at regular

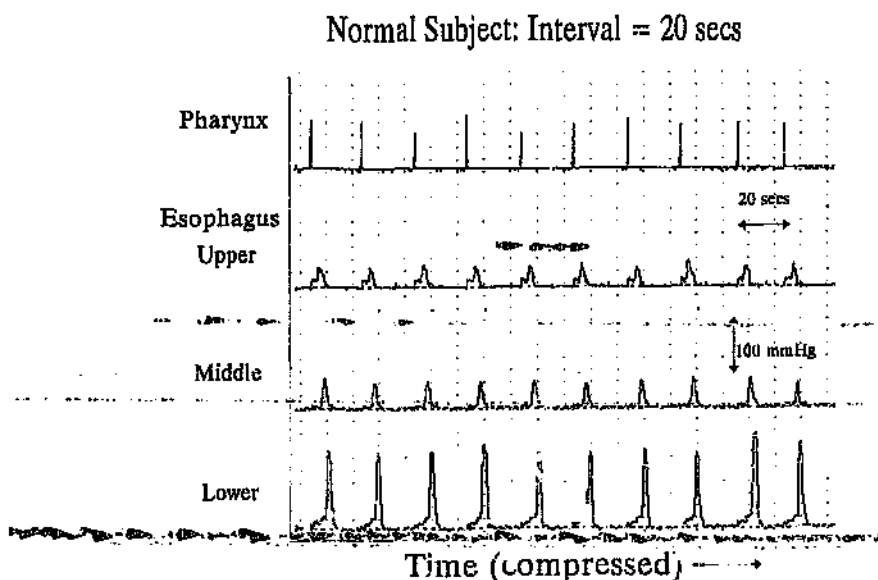


Figure 6.1 An example of the recording of esophageal pressures in a normal subject when the interval between swallows is 20 seconds.

intervals of 20 seconds, is shown in figure 6.1 and is compared to an example of the recording of the same subject with intervals of 5 seconds between swallows (figure 6.2). When there is a long interval between swallows there is no effect of deglutitive inhibition and the esophageal muscle has completely "recovered" from the previous wave of contractions so that the muscle refractory period is not seen.

Normal Subject: Interval = 5 secs

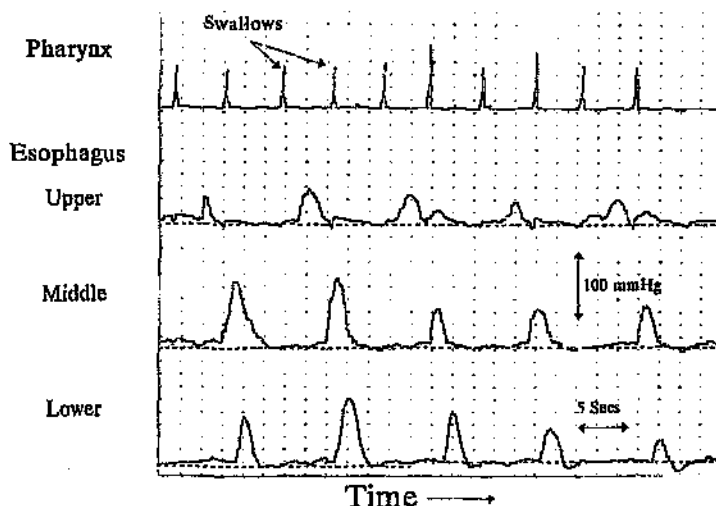


Figure 6.2 An example of a recording of esophageal pressures in a normal subject when the interval between swallows is 5 seconds.

Normal Subject: Meal

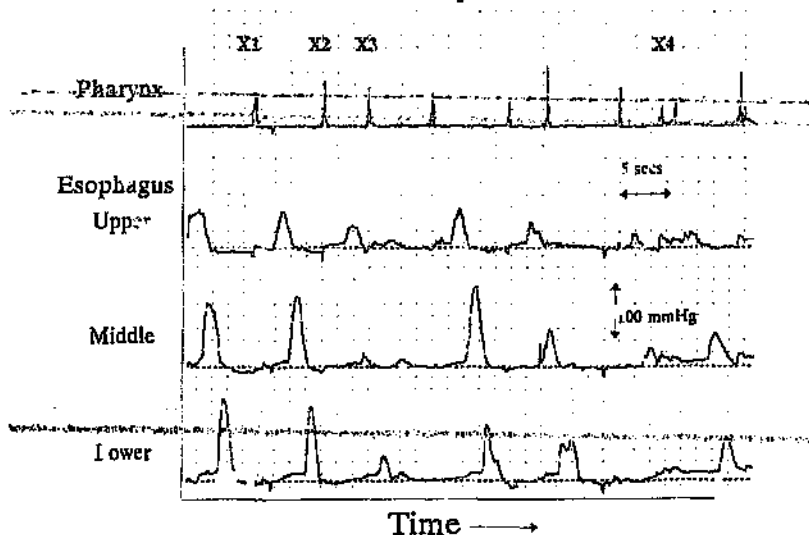


Figure 6.3 An example of a recording of esophageal pressures in a normal subject during the eating of a meal. Note the variation in the amplitudes of contractions.

Figure 6.3 is an example of a recording of pressures in the same subject as in figures 6.1 and 6.2 during a normal meal. Only some of the contractions are transmitted from the pharynx to the esophageal body (deglutitive inhibition) and the amplitudes of some of the contractions are depressed (muscle refractory effect). X1 is a normal wave, X2 shows evidence of the muscle refractory period with decreased amplitudes of contractions. This effect is exaggerated in X3 so that almost no esophageal pressures are generated. The esophagus has recovered by the following swallow. X4 is an example of deglutitive inhibition. There is a pair of swallows with a short interval and the esophageal peristaltic wave only follows the second swallow.

The results of the ambulatory manometry, therefore, can be expected to be significantly different from stationary manometry, especially with respect to some of the measured parameters, such as contraction amplitude. Direct comparisons of measured values should not, therefore, be made between stationary and ambulatory manometry in this thesis. Rather, the value of ambulatory manometry should be looked on as its ability to monitor pressures when the esophagus is functioning i.e., during normal eating. Comparisons of the ambulatory manometric parameters in this thesis are made between groups of patients and between patients and normals for the physiologic settings of meals, the upright interprandial period, and the supine period.

CHAPTER 7: NORMAL CIRCADIAN ESOPHAGEAL BODY FUNCTION

7.1 INTRODUCTION

Prior to interpreting ambulatory recordings from symptomatic patients it is necessary to establish normal values with which to compare patient data. In this study the previously validated software program was utilized to study 25 normal asymptomatic volunteers in order to establish normal esophageal motor function over a circadian cycle.

7.2 METHODS

Twenty five healthy volunteers (mean age 30, range 22-48) were studied. Study protocols were approved by the institutional review board of the University of Southern California. All subjects completed a questionnaire to exclude any foregut symptoms or previous upper abdominal surgery, and all underwent video esophagrams to exclude any anatomical abnormality. Stationary and ambulatory manometry were performed after an overnight fast as previously described in chapter 4. Simultaneous 24-hour pH studies were done to exclude the presence of increased esophageal acid exposure.

7.2.1 Data Analysis

The subjects returned to the laboratory after 24 hours and the catheters were removed and recalibrated. If the drift of a transducer exceeded 6 mmHg the records were excluded. The datalogger was downloaded onto a personal computer and the data was analyzed with the previously mentioned software program.¹⁷¹ The threshold for contraction recognition was set at 15 mmHg for a duration of 1 second. Contraction amplitude was measured from the baseline to the contraction peak and duration was measured at the threshold of 15 mmHg as previously discussed. Contraction morphology and wave analysis was performed as described in detail in chapter 3. Peristaltic waves were classified as "effective" if the amplitude of contractions in the upper, middle and lower esophagus were greater than 20, 25 and 30 mmHg,

respectively.^{127,158} Waves with interrupted or dropped contractions, or simultaneous contractions were classified as "ineffective".

7.2.2 Statistics

Results are expressed as medians, and the 5th and 95th percentiles were used to define upper and lower limits of normal. The Wilcoxon test and Friedman two way anova test were used for comparison where appropriate. Statistical analysis was performed with the aid of a computer program (SPSS for Windows v6.1.3, Chicago, Illinois). Significance was estimated at the 0.05 level.

7.3 RESULTS

The contraction characteristics are shown in tables 7.1 and the prevalence of wave forms in table 7.2. The circadian record showed a variability in frequency and amplitude with different physiologic states (see chapter 3, figure 3.2). The frequency of contractions was lowest during sleep, increased when awake, and was highest during meals. Contraction amplitude increased when the esophagus was used during eating. Similarly, the prevalence of peristaltic waves varied according to different physiologic states, i.e., meals, upright and awake, and during sleep. Of importance was the ability of the esophagus to increase the prevalence of peristaltic waves during meals. The increased amplitude and prevalence of peristalsis accounted for the increase in efficacy during eating. When compared to stationary manometry the normal range for contraction amplitude was less using ambulatory manometry (Figure 7.1).

Table 7.1 Normal ranges for contractions characteristics (Medians with 5th and 95th percentiles). (Level 1 = 15cm, Level 2 = 10cm, and Level 3 = 5cm above LES)

PARAMETER	LEVEL	MEAL	UPRIGHT	SUPINE	SIGNIF.**
AMPLITUDE	1	43 (33-62)	31 (25-49)	34 (21-50)	p<0.001
	2	53 (31-82)	39 (30-60)	46 (28-72)	p<0.001
	3	65 (34-89)	43 (25-59)	52 (29-73)	p<0.001
DURATION	1	2.4 (1.6-3.0)	1.6 (1.4-2.3)	1.9 (1.4-2.5)	p<0.001
	2	2.2 (1.5-3.2)	2.0 (1.5-2.3)	2.3 (1.9-3.1)	p<0.001
	3	2.2 (1.5-3.1)	2.0 (1.4-2.5)	2.7 (1.7-3.5)	p<0.001
%MULTIPEAKED (morphology)	1	1.0 (0-4.3)	0.2 (0-0.6)	0.0 (0-1.9)	p=0.02
	2	0.0 (0-2.2)	0.2 (0-1.4)	0.0 (0-5.4)	NS
	3	0.0 (0-2.7)	0.4 (0-2.7)	1.1 (0-5.4)	p=0.006
FREQUENCY (Contract./min)	1	2.4 (1.5-3.7)	1.0 (0.7-1.7)	0.2 (0.1-0.4)	p<0.001
	2	2.5 (1.6-3.5)	1.1 (0.7-1.9)	0.3 (0.2-0.6)	p<0.001
	3	2.5 (1.5-3.6)	1.1 (0.7-2.0)	0.3 (0.1-0.6)	p<0.001
%ISOLATED (not part of a wave)	1	4.0 (0.7-16.8)	4.1 (1.7-12.2)	7.8 (2.6-28.8)	p=0.003
	2	2.6 (0.0-6.8)	3.6 (0.3-7.5)	8.9 (1.1-22)	p<0.001
	3	2.9 (0.1-8.3)	4.7 (1.2-11.5)	13.2 (5.0-39.1)	p<0.001

** Friedman 2-way anova test.

Table 7.2 Normal Ranges for wave analysis (Medians with 5th and 95th percentiles)

PARAMETER	PERIOD	VALUE	SIGNIFICANCE
% PERISTALTIC	Meal	88 (81-97)	p=0.007*
	Upright	84 (59-94)	p=0.002**
	Supine	71 (51-93)	
% SIMULTANEOUS	Meal	11 (3-19)	p=0.0007*
	Upright	16 (6-41)	p=0.0002**
	Supine	29 (6-48)	
% EFFECTIVE	Meal	54 (36-72)	p=0.0001*
	Upright	32 (14-60)	p=NS**
	Supine	32 (8-53)	
% INEFFECTIVE	Meal	32 (12-44)	p=0.0013*
	Upright	37 (16-62)	p=0.0001**
	Supine	58 (32-83)	

* = Meal vs Upright, ** = Upright vs Supine

7.4 DISCUSSION

Studies on normal ambulatory esophageal motor function over a circadian cycle are limited. Previous reports used water perfused catheters, used catheters with only 2 solid state pressure transducers allowing monitoring of only part of the esophageal body, or were based on intermittent monitoring.^{156,207,233,234} The current study measured pressures continuously from three levels of the esophagus, which improved the quality of the recording. This is important as many esophageal diseases may be segmental.²⁰⁵

The contraction amplitudes measured in this study are similar to other reports,^{155,156,235-237} but the durations were less because of the different reference point used to measure duration. The 15 mmHg threshold was previously shown to be more accurate than measurement at the baseline, because of the artefact induced by respiratory fluctuations.¹⁷¹ Multi-peaked contractions were uncommon and tended to occur at night.

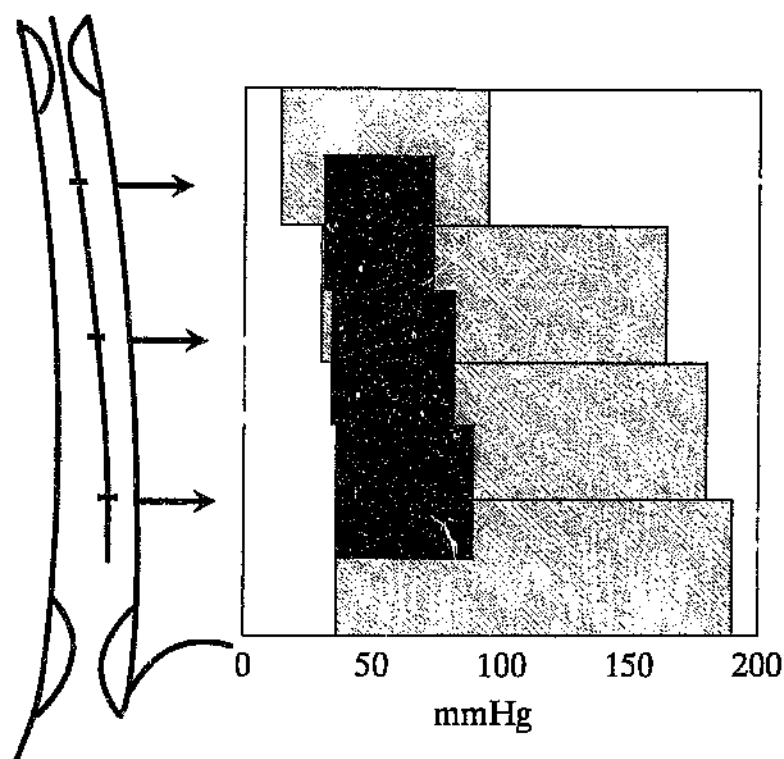


Figure 7.1 The normal ranges of contraction amplitude from ambulatory manometry (black) versus stationary manometry (grey). The shaded areas represent the 5th and 95th percentiles.

Richter also noted that multi-peaked contractions were uncommon on stationary manometry and suggested that their presence should raise the possibility of a motility disorder.³⁴

Ambulatory manometry has been criticized because of the interindividual variation of the contraction characteristics. Most have accepted stationary manometry as a reliable tool. In this regard this study has shown that there is less inter-individual variation for ambulatory manometry than stationary manometry as evidenced by the comparison of normal ranges for contraction amplitude (figure 7.1). This is a result of the larger number of contractions analyzed and shows that monitoring for prolonged periods enhances the assessment of esophageal motor function.

The initial problem with ambulatory manometry was the acquisition of large

amounts of data without a means for effective analysis. Consequently the benefit of monitoring over a circadian cycle during different physiologic states was lost. This has been rectified with the use of the software program utilized in this study. Unique to this software was the sensitivity of detecting low amplitude contractions, and the ability to relate contractions in three levels of the esophagus in terms of waves. This enabled more accurate analysis of contractions and wave forms.¹⁷¹

The observation of an increased efficacy of waves during meals reflects the culmination of previous observations.^{206,237,238} It is known that there is a higher proportion of ineffective waves, i.e., dropped, interrupted, or simultaneous waves, for "dry" as opposed to "wet" swallows on stationary manometry.^{34,144,210} It has also been shown that there is a difference in contraction characteristics depending on the size, temperature, and viscosity of the swallowed bolus; the larger, warmer, and more viscous the swallowed bolus, the greater the contraction amplitude.^{35,136,158-143,145,232} This may be secondary to bolus feedback either at the level of the pharynx where peristalsis is initiated, or by local reflexes during bolus transport.

There are problems associated with monitoring of esophageal pressures during meals as mentioned in the previous chapter. An increased swallowing frequency affects contraction amplitude and the prevalence of peristaltic waves due to deglutitive inhibition and the muscle refractory period.^{5,145} This is prevented during stationary manometry by limiting swallows to every thirty seconds. An unrestricted swallowing frequency makes interpretation of the ambulatory recordings more complex, but gives a physiologic assessment of motor function at a time when the esophagus is being used.

Esophageal contractions are disorganized at night when subjects are sleeping.¹⁵⁶ During this period we recorded a higher prevalence of simultaneous waves and isolated contractions. Castiglione *et al* showed that nocturnal esophageal motor activity is dependent of the stage of sleep.²¹⁵ Overnight esophageal motility monitored with simultaneous electroencephalography detected an increased frequency of spontaneous activity during stage IV or REM (rapid eye movement) sleep. Others have recorded, during the night, bursts of simultaneous contractions associated with phase III of the migrating motor complex.²³⁹ This indicates that resting esophageal body activity can be influenced by the central nervous system and emphasizes caution in performing

ambulatory manometry when the patient is taking central nervous system depressants such as benzodiazepines.¹⁹⁵ It has been noted that the manometric findings are also affected by body position in that contractions amplitudes and durations are greater in the supine versus the upright position which also explains some of the differences between the upright and supine contraction characteristics in this study.¹³⁷ This study provides normal ranges for contraction characteristics for three levels of the esophagus as well as the normal ranges for prevalence of various wave forms during different physiologic states. Further, it emphasizes the importance of assessing the esophagus when it is performing its function, i.e., during eating.

7.5 CRITICAL EVALUATION AND COMMENT

A new concept evolves from the data above; that not all contraction waves need to be "effective" to adequately propel food into the stomach in the upright asymptomatic individual. While one may be tempted to change the thresholds to conform with the conception that "nearly all" contraction waves are "near perfect" in asymptomatic individuals, this would merely camouflage the data. The fact remains that during meals up to 44% of contraction waves may be ineffective in normal asymptomatic subjects, whereas in the supine period up to 83% is normal. While these numbers have confused some of the critics in the laboratory at USC, they remain valid normal values with which to compare abnormal, or symptomatic patients, as is seen in the following chapters.

CHAPTER 8: ASSESSMENT OF ESOPHAGEAL MOTOR FUNCTION IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE (GERD)

8.1 BENEFITS OF MEASURING PRESSURES SIMULTANEOUSLY WITH pH MONITORING

Additional information is offered by simultaneous recording of pressures during ambulatory pH monitoring which help to interpret the pH study. These are 1) the relationship of respiratory symptoms such as coughing to reflux episodes, 2) interpretation of the effect of "napping" on reflux, 3) identification of periods of drinking acidic liquids as an artefactual cause of reflux. While a formal study on these aspects has not been performed in this thesis, examples of these are included here because awareness of such patterns is important in the interpretation of simultaneous studies, and because they open areas for further research in the future. The main objective of this chapter is presented in section 8.2.

8.1.1 The temporal relationship between coughing and reflux

There is an increasing awareness of the relationship between reflux disease and respiratory symptoms such as asthma and chronic cough.²⁴⁰⁻²⁴³ The detection of an association of acid reflux and respiratory symptoms during standard pH testing depends on the patients documentation of symptoms, from which a correlation with the pH record is made. The limitations of this method are related to the compliance of patients in reporting all symptoms, and to the inability to relate coughing as a cause or effect of the reflux event. In chapter 3 it was demonstrated that coughing episodes have a characteristic morphology as recorded by the ambulatory manometry catheter. The simultaneous, isobaric pressure increases have a steep upslope (dp/dt) which can be recognized visually and by the computer (figure 3.5). This provides a means of relating the coughing to the drop in intraesophageal pH with precision.

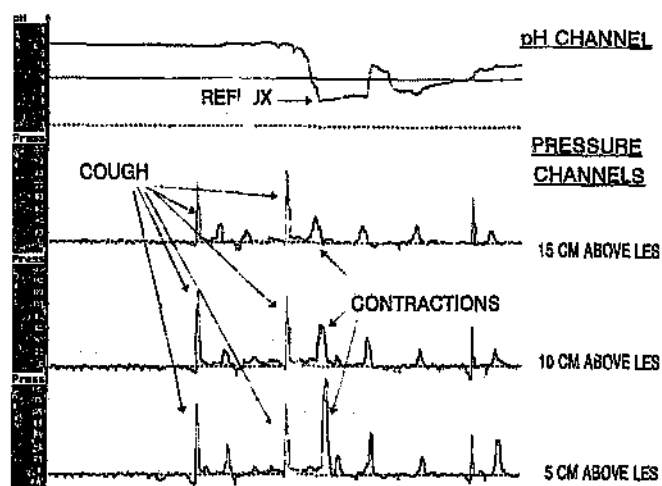


Figure 8.1 An example of a simultaneous pH and manometry record showing coughing preceding a reflux episode.

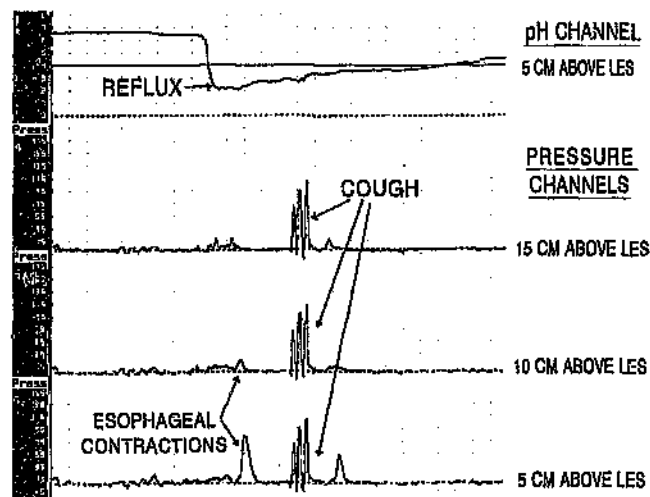


Figure 8.2 An example of the simultaneous record showing coughing following the onset of a reflux episode.

Figure 8.1 shows an episode of coughing preceding a reflux event. In this situation the reflux may have been precipitated by the increase in intra-abdominal pressure caused by coughing. The coughing episode was not caused by the reflux episode. On the other hand when the coughing follows a reflux episode, the reflux may

have precipitated the coughing (figure 8.2).

8.1.2 Interpreting the effect of "napping" on esophageal acid exposure.

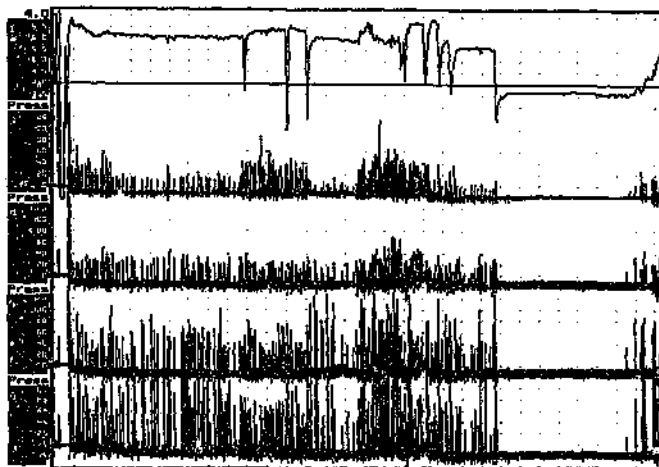


Figure 8.3 A compressed recording showing a post-prandial reflux episode. The addition of manometry shows that the long episode is related to the patient falling asleep after lunch.

During sleep esophageal motility is quiescent because of a decreased swallowing rate. This has important implications on acid clearance in that it provides an explanation for the longer reflux episodes that occur at night (Chapter 11). It was noted in chapter 4 that many patients "doze" during the post-prandial period after lunch. This is important as reflux is more common in the post-prandial period.²⁴⁴⁻²⁴⁶ The addition of ambulatory manometry provides a mechanism to identify sleep periods because of the remarkable decrease in esophageal activity. Figure 8.3 shows a compressed record of the simultaneous study. Seen in isolation, the pH record (top channel) reveals a long reflux episode (± 70 minutes) in the afternoon, soon after lunch. The meal period is characterized by the period of increased esophageal activity. The ambulatory manometry record shows that this post-prandial episode is related to sleep when the activity of the esophagus is dramatically decreased. This was later confirmed by direct questioning of the patient who remembered falling asleep in an armchair after lunch. The long episode is consequently a result of poor arousal by the reflux event with no

initiation of swallowing to clear the reflux. It is not related to poor esophageal body function *per se*.

8.1.3 Artefactual reflux

It was discussed in chapter 4.7 that some soda beverages such as Coca-Cola have an acidic pH. Drinking these liquids causes a drop in intraesophageal pH which could be interpreted as a reflux event if the patient does not follow dietary instructions. An example of this is shown in figure 8.4. Seen in isolation, the pH record would be interpreted as a reflux episode. Even the addition of esophageal manometry (lower three channels) does not dispute this as the contractions of the esophageal body appear to be a normal clearing peristaltic wave in response to the reflux event. The addition of the pharyngeal channel, however, shows that this is not a reflux event at all. Rather, the rapid swallowing indicates drinking. The drop in esophageal pH occurs immediately

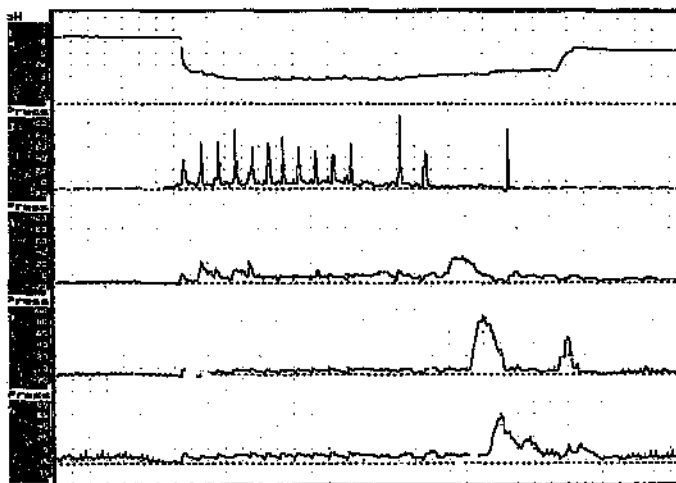


Figure 8.4 An example of how drinking acid drinks can cause a drop in esophageal pH which, in the absence of simultaneous manometry, would be construed as reflux.

after the first swallow. This is confirmed by the slight elevation in the baseline seen in the esophageal channels, as liquid fills the lumen. The end of the train of swallows is followed by a peristaltic wave, providing, in this instance, a good example of deglutitive inhibition in the physiological setting.

8.2 ESOPHAGEAL MOTOR DYSFUNCTION IN PATIENTS WITH GERD

8.2.1 Background

The clearance of gastroesophageal reflux is dependant on gravity, salivation, and on the motor function of the esophageal body.^{247,248} Defective esophageal body function has been found in some patients with GERD and it is thought that this defect contributes to further exposure of the esophageal mucosa to gastric juice, resulting in a vicious cycle.^{126,249} The association between compromised esophageal body function and gastroesophageal reflux disease has been based on findings from provocative testing and results of stationary manometry. There are only few reports on esophageal function using prolonged monitoring in patients with GERD, and it is unclear what abnormalities occur in the physiologic setting of ambulatory monitoring. In this chapter the ambulatory system was applied to a group of patients with proven GERD to elucidate the motor abnormalities associated with this disease.

8.2.2 Methods

Forty-five patients (mean age 55, range 22-88) with GERD proven by pH monitoring were studied. All patients underwent video esophagrams and endoscopy to establish the presence of mucosal injury which was classified according to table 8.1. Patients with grade 0 and I were categorized as "no mucosal injury", and grades II and III were categorized as "mucosal injury". Stationary manometry and ambulatory simultaneous pH and motility monitoring were performed on all subjects according to the protocols previously outlined. Patient data was compared to historical normal values for stationary manometry.^{35,178} A defective sphincter was defined when one or more of the following were present: 1) an abdominal length of less than 1 cm, 2) a total length of less than 2 cm and, 3) a resting pressure of less than 6 mmHg.¹⁷⁸ Defective motility on stationary manometry was defined as abnormally low contractions in the distal esophagus (less than 30 mmHg) or an increase in the prevalence of interrupted or dropped peristalsis (greater than 10% of ten swallows).¹²⁹ This was based on the 5th

percentile of the normal volunteers and supported by studies using manofluorography.^{35,127}

Table 8.1. Endoscopic classification of mucosal injury

Grade of Injury	Endoscopic Findings
Grade 0	Normal
Grade I	Erythema
Grade II	Linear ulcerations
Grade III	Confluent ulcerations, "Cobblestoning"

The ambulatory data from the two groups of patients were compared to the results from the 25 healthy volunteers (see in chapter 7). Defective motility was defined on ambulatory manometry when the percentage of ineffective contractions exceeded the 95th percentile of the normal volunteers, i.e., greater than 44% during the meal periods. Definitions of ineffective waves are discussed in chapter 3 and include simultaneous waves, or dropped or interrupted peristaltic waves.

8.2.2.1 Statistics

Standard non-parametric tests were used. The Mann-Whitney U test and the Wilcoxon matched-pairs signed rank test were used to compare medians and the Fisher exact test was used to compare proportions. Unless otherwise stated the data are presented as means $\pm$ standard error of the mean.

8.2.3 Results

There was no difference in age or sex between the two groups of reflux patients. Table 8.2 shows the stationary manometric data for the two groups and from normal volunteers for comparison. Thirteen of twenty-six (50%) patients with no injury and eight of nineteen (74%) patients with mucosal injury had a defective lower esophageal sphincter. Four of twenty six patients (15%) with no injury and 8/19 (42%) with mucosal injury had defective motility on stationary manometry.

The esophageal acid exposure was greater in patients with mucosal injury than in those with no injury in terms of percent of the time the esophagus was exposed to a pH of less than 4 ($10.3 \pm 1.03\%$, no injury, vs $22.23 \pm 3.13\%$, injury, $p < 0.001$) and in terms of the DeMeester score (34.7 ± 3.32 vs 85.25 ± 11.42 , $p < 0.001$).¹⁷²

The results of the ambulatory manometry are shown in table 8.3. Ambulatory manometry demonstrated that contraction amplitude decreased with increasing severity of injury in the middle and lower esophagus while contractions in the upper esophagus were similar for all groups of subjects (figure 8.5). The ability to increase the amplitude of contractions in the lower esophagus during meals was profoundly compromised in patients with mucosal injury compared to normal subjects and patients with no injury (Figure 8.6). Of interest were the similar amplitudes of contractions in the interprandial periods of all patient groups.

Table 8.2 Stationary manometric data for normal subjects and patients with GERD.

PARAMETER	NORMALS	NO INJURY	INJURY
LES			
Total Length (cm)	3.65 ± 0.1	$2.53 \pm 0.19^*$	$2.53 \pm 0.28^*$
Abd. Length (cm)	2.14 ± 0.1	$1.13 \pm 0.13^*$	$0.82 \pm 0.13^*$
Pressure (mmHg)	14.84 ± 0.5	$8.84 \pm 0.8^*$	$6.67 \pm 1.13^{* \#}$
BODY			
<u>Amplitude (mmHg)</u>			
Level I	91 ± 3.3	83 ± 5.8	$75 \pm 6.8^*$
Level II	45 ± 2.1	$32 \pm 2.5^*$	$24 \pm 3.7^{* \#}$
Level III	80 ± 3.3	$63 \pm 6.6^*$	$43 \pm 6.7^{* \#}$
Level IV	95 ± 3.5	$85 \pm 8.9^*$	$42 \pm 5.6^{* \#}$
Level V	103 ± 5.5	$53 \pm 9.4^*$	$37 \pm 5.7^{* \#}$

* $p < 0.05$ vs normal, # $p < 0.05$ vs No Injury

Twelve of the 45 patients (26%) had defective motility on stationary manometry. Five of these twelve (42%) showed improvement of contractility during meals to within the normal range on the ambulatory study. On the other hand, 21 patients (46%) had defective motility during meals on ambulatory manometry. These included twelve of nineteen (63%) with mucosal injury and nine of twenty-six (35%) with no injury). Only 7 of these patients were suspected of having poor motility based on stationary manometry alone.

Two patients with non-cardiac chest-pain were noted to have abnormal morphology and progression of contractions similar to those seen in DES, but only during episodes of reflux (figure 8.7). This "reflux-induced spasm" was abolished after Nissen fundoplication with concomitant resolution of the chest-pain.

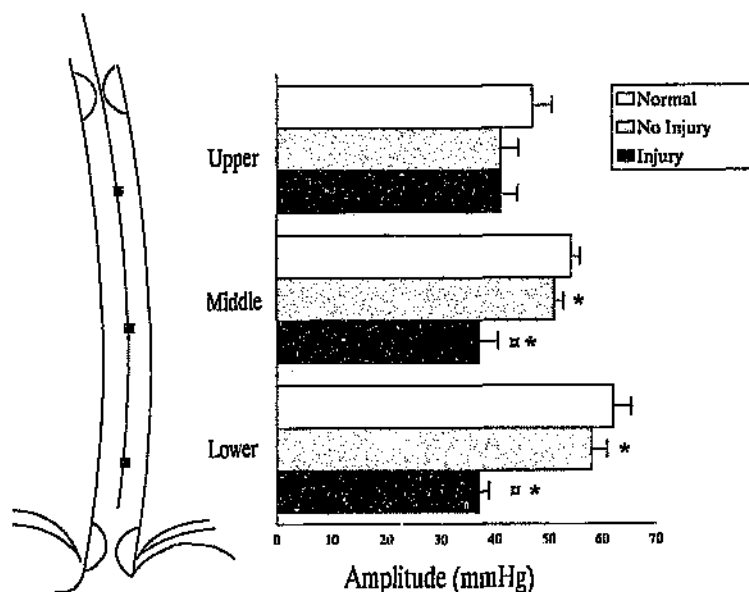


Figure 8.5 The amplitudes of contractions for the upper, middle, and lower esophagus for normal subjects and patients with GERD during mealtimes.

Table 8.3. Ambulatory motility characteristics of normal subjects and patients with GERD.

PARAMETER	NORMALS (n=25)	NO INJURY (n=26)	INJURY (n=19)
AMPLITUDE (mmHg)			
<u>Upright</u>			
Channel 1 #	34±2	33±2	31±2
Channel 2	40±2	40±2	32±3*, ^o
Channel 3	42±2	45±4	32±2*, ^o
<u>Meal</u>			
Channel 1	47±2	41±3	41±4
Channel 2	54±3	51±4	37±4*, ^o
Channel 3	62±4	58±6*	37±3*, ^o
<u>Supine</u>			
Channel 1	35±2	33±2	27±2
Channel 2	47±3	47±3	32±3*, ^o
Channel 3	51±3	54±5	32±3*, ^o
MULTIPEAKED % (Distal Esophagus)			
Upright	0.4±0.2	0.6±0.1	0.7±0.1*
Meal	0.7±0.3	0.7±0.3	2.2±0.6*, ^o
Supine	1.7±0.5	1.2±0.3	1.9±0.4
PERISTALTIC WAVES.(%)			
Upright	82±2.3	75±1.8	72±2.8*
Meal	89±1.0	84±1.6	79±2.7
Supine	71±2.6	59±2.0	69±3.3
EFFECTIVE (%)			
Upright	35±3.2	30±3.1	18±2.8*, ^o
Meal	53±2.6	41±3.3*	29±4.3*, ^o
Supine	31±3.0	25±2.4*	15±2.4*, ^o
INEFFECTIVE (%)			
Upright	40±2.9	52±2.7*	60±3.0*, ^o
Meal	30±1.9	43±2.4*	52±4.5*, ^o
Supine	57±3.0	68±2.3*	67±3.2*

Channel 1, 2, and 3 are 15, 10, and 5 cm above the LES respectively. (Channel 3 = distal)

* = p<0.01 vs normals, ^o = p<0.01 vs no injury.

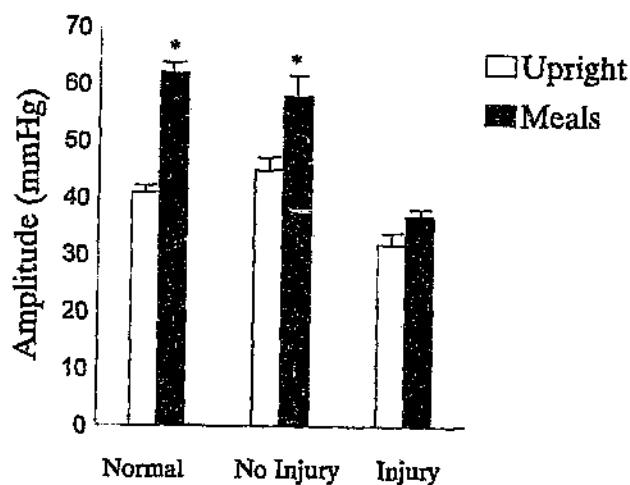


Figure 8.6 The mean amplitude of contractions for the upright and meal periods in normal subjects and patients with GERD. * $p < 0.05$ vs upright.

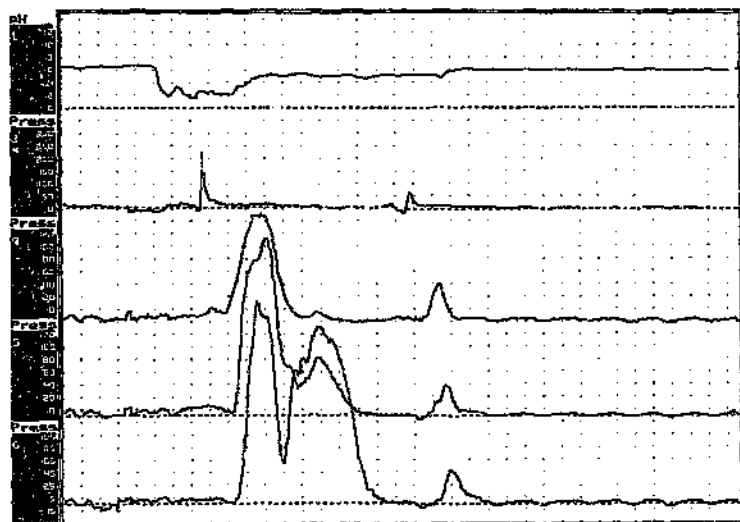


Figure 8.7 An example of a recording demonstrating the reflux induced "spasm" seen in two patients in this study.

8.2.4 Discussion

The association of GERD and motility abnormalities was first made by Booth when he reported an increased acid clearance time in patients with symptomatic GERD compared to normal subjects.²⁵⁰ Stanciu and Bennett later recognized that not all patients with GERD had poor motility with respect to clearance times.²⁵¹ Olsen and Schlegel later recognized an increasing prevalence of poor esophageal body motility with increasing severity of mucosal injury.¹²³ This was confirmed by Kahrilas who showed that 25% of patients with mild esophagitis and 50 % of patients with severe esophagitis had defective body motility.¹²⁷ In the present study the results from stationary manometry are in keeping with earlier reports. The finding of an increasing prevalence of a defective sphincter and an increased esophageal acid exposure in patients with mucosal injury has also been previously reported and serves to underscore the importance of an incompetent lower esophageal sphincter in this disease.²⁵²

Previous studies on esophageal motor function in patients with GERD have predominantly been performed in the laboratory environment using stationary manometry. Esophageal motor function in the setting of ambulatory monitoring is unclear. Stein used an intermittent ambulatory device with two pressure transducers to monitor esophageal motor function in patients with GERD and noted an increased prevalence of low amplitude (<30 mmHg) contractions in the lower esophagus in patients with severe mucosal injury.¹²⁴ Timmer found no difference in motility characteristics in patients with no injury compared to normal volunteers, but this study did not examine manometric function during meals.¹⁵⁵ In a separate study of eleven patients there was a trend toward lower contraction amplitudes in the distal esophagus in patients with esophagitis, but this did not reach statistical significance.²⁵³ It was previously demonstrated in chapter 7 that the esophageal response to eating in normal subjects is an increase in the amplitude and prevalence of effective peristaltic waves. The present study showed that this normal response was significantly depressed in patients with mucosal injury. Since optimal esophageal function occurs when it is being used, i.e., during eating, it is probably most accurate to assess function in this physiologic situation. When assessing esophageal function during meals fourteen patients overall were found to have a severe motility defect not found on stationary

manometry. On the other hand, five of the twelve patients with low amplitude contractions on stationary manometry improved to normal during meals suggesting a significant functional reserve not apparent on stationary manometry.

Other motor abnormalities have been associated with GERD such as acid induced spasm and nutcracker esophagus.²⁵⁴⁻²⁵⁶ As a group, the patients with esophagitis had an increased prevalence of multi peaked contractions in keeping with studies that have suggested that mucosal irritation with acid can induce non-specific abnormalities.^{124,257} These multi peaked contractions were peristaltic with respect to contraction upslope, and did not exceed 10 % in any patient, and consequently were unlikely to have any functional effect. Only 2 patients were seen to have simultaneous, multi peaked waves after the onset of the drop in intraluminal pH (figure 8.7). This picture of "acid induced" spasm was not the predominant motor pattern, and the overall manometric picture was not consistent with diffuse esophageal spasm. Interestingly, anti-reflux surgery resulted in resolution of both reflux, "spasm" and chest-pain.

The predominant defect seen in the patients with GERD was hypomotility characterized by a progressive decrease in amplitude and efficacy of contractions with mucosal damage. The reasons for this are unclear, but it is possible that the inflammation of esophagitis interferes with normal afferent feedback which occurs with the passage of a food bolus. An alternative explanation is continued reflux across a defective lower esophageal sphincter results in mural damage which directly affects the contractility of the esophageal muscle. The fact that changes were more marked in the lower esophagus supports the hypothesis that the defect is secondary to mucosal damage and is not the primary problem in this disease.

There are important surgical implications of these findings. The presence of defective body motility should caution the surgeon against performing a full fundoplication as this may result in an outflow obstruction in the face of poor body motility.^{258,259} Certainly post-operative dysphagia is a recognized complication following fundoplication. In a recent series in our laboratory (unpublished data) the average post-operative resting sphincter/fundoplication pressure was 17 mmHg, but reached 28 mmHg in some patients. It stands to reason that esophageal contraction pressures greater than this would be required to effectively transport a bolus through the

reconstructed valve. In a previous study at USC, it was shown that although the amplitude of distal esophageal contractions improved in patients with mild abnormalities following fundoplication, this did not occur when the mean amplitudes were below 30 mmHg.¹²⁶ For these reasons it is felt to be prudent to avoid a full fundoplication in patients with a severe hypomotility disorder. Evidence on ineffective motility during meals cannot be predicted by stationary manometry alone. Rather, manometric assessment in the physiologic environment of ambulatory manometry should be performed.

8.3 CRITICAL EVALUATION AND COMMENT

The rationale at USC for performing a partial fundoplication in patients with compromised motility was based on experience and extrapolation from available data. Some authors believe that a full fundoplication can be done on all patients as long as the fundoplication is "floppy".²⁶⁰ No randomized studies have yet been performed comparing a full fundoplication to a partial fundoplication in patients with defective contractility. Furthermore, no retrospective analysis of post-operative outcome was possible at USC since the finding of hypomotility always mandated the performance of a partial fundoplication. Because of the sensitivity of ambulatory manometry in detecting motor abnormalities during meals, patients with any suspicion of a motor disorder on history or on stationary manometry are now routinely evaluated with ambulatory manometry prior to surgical intervention. If defective contractility is found, a partial fundoplication is performed. The evolving data suggests that this is in fact a practical method of avoiding post-operative dysphagia in patients undergoing anti-reflux surgery. The new technology consequently contributes significantly to patient management in this regard.

CHAPTER 9: CIRCADIAN ESOPHAGEAL MOTOR FUNCTION IN PATIENTS WITH TREATED AND UNTREATED ACHALASIA

9.1 BACKGROUND

Achalasia has been defined as a motility disorder of the esophagus characterized by an incompletely relaxing lower esophageal sphincter (LES) and an aperistaltic esophageal body.^{37,53,261,262} The definition is based on stationary manometric findings although the diagnosis is often suggested or confirmed on videoesophagography which demonstrates a dilated aperistaltic esophagus with a "bird-beak" deformity at the distal end.^{37,263,264} A number of other manometric features have been described. The resting pressure of the sphincter may be normal or high.²⁶⁴ The intraluminal pressure of the esophageal body may be increased above gastric baseline despite being contained in the relatively negative pressure environment of the thorax. This is presumed to be secondary to swallowed substances which are propelled into the dilated esophageal body which has a closed distal end. Secondary to the non-relaxation of the LES, the esophageal body becomes a "common cavity", in which pressure exerted at one location of the lumen is transmitted to another. This accounts for the "simultaneous" nature of contraction waves in achalasia. By definition the presence of peristaltic progression of a contraction wave on stationary manometry is not compatible with the diagnosis of achalasia.

In this study, ambulatory manometry was used to study the circadian motor patterns in patients with classic achalasia. The characteristic ambulatory manometric patterns are described and the influence of surgical myotomy on these patterns is discussed.

9.2 METHODS

Twenty six patients with a stationary manometric diagnosis of classic achalasia were studied. All patients presented with the primary symptom of dysphagia or were

referred to the center with the diagnosis of achalasia. All patients had barium videoesophagrams, stationary manometry and ambulatory esophageal manometry performed. Nine patients had undergone previous balloon dilatation and twelve had no previous therapy. Nine of these patients then underwent surgical myotomy and volunteered for post-operative studies at the first anniversary of their operation. A further 5 patients had ambulatory manometry after a LES myotomy had been performed but on whom no pre-operative ambulatory manometry was available. The effect of a myotomy on esophageal motor function was assessed by examining the pre and post-operative ambulatory studies on nine patients who volunteered for post-operative evaluation.

9.2.1 Stationary and Ambulatory Manometry

Stationary and ambulatory manometry were performed according to the protocols in chapter 4. The ambulatory catheter was placed so that the transducers were at 5, 10, 15, and 25 cm above the lower esophageal sphincter. This ensured that the uppermost transducer was in the pharynx so that pharyngeal swallows could be flagged. Data was analyzed as previously described. Repetitive contractions were defined as non-swallow induced contractions occurring within 2 seconds of a swallow induced contraction (see appendix E). The swallow-induced contraction wave with the repetitive contractions following it were considered part of a single repetitive contraction complex. Effective waves were defined as peristaltic, with contractions meeting amplitudes greater than 20, 25, 30 mmHg for the three levels of the esophagus as previously discussed. Ineffective waves were defined as either simultaneous, or incomplete (dropped or interrupted) waves.¹⁵⁸ The normal subjects studied in chapter 7 were used to compare the results of the achalasia patients.²⁶⁵

The increase in baseline pressure during meal periods was used as an indicator of esophageal pressurization. The baseline for this calculation was measured with respect to the pre-prandial esophageal baseline. A mean of the baseline pressure reached for the two meals in each subject was used.

9.2.2 Statistics

Statistical analysis was performed with the aid of a computer program (SPSS for Windows v6.1.3, Chicago, Illinois). The Wilcoxon matched-pairs signed rank test was used to compare pre-operative and post-operative data. The Mann-Whitney U test and Kruskal-Wallis tests were used to compare differences between the different groups.

9.3 RESULTS

On stationary manometry all patients met the manometric criteria of "classic achalasia". All had an aperistaltic esophageal body and an incompletely relaxing LES. Videoesophagography confirmed the diagnosis. In untreated patients a dilated lower esophagus with a "bird-beak" narrowing of the LES was seen in all patients.

Patients who had previously undergone balloon dilatation presented with persistent or recurrent dysphagia as the primary symptom, and were considered to have failed dilatation. Stationary manometry results for the LES for the three groups of patients are shown in table 9.1 and contrasted with normal values. Patients studied after myotomy had a significantly lower LES pressure than patients with no treatment ($p < 0.05$).

All patients exhibited characteristic low amplitude simultaneous contractions in the interprandial period. Figure 9.1 shows the isobaric low amplitude pressure responses of the esophageal body (lower three channels) to a pharyngeal swallow (top channel). The meal periods in untreated patients and in patients with failed dilatation were characterized by an increase in esophageal baseline pressure (figure 9.2), and simultaneous contractions which were symmetrical and of identical morphology in different channels, i.e., so-called "isobaric waves". These contractions were frequently repetitive after a single swallow but this occurred in association with an increase in the esophageal baseline pressure (figure 9.3). As shown in figure 9.2, a delay in return to baseline pressure was seen in the untreated group. An increase in baseline pressure during meals was also seen in the failed dilatation group in concordance with the manometric results of a high resting pressure and incomplete relaxation of the sphincter. The amplitudes of contractions of the lower esophagus for the three groups of patients in

the different physiologic settings are shown in figure 9.4. The number of repetitive contractions occurring during the meal periods are shown in figure 9.5.

Table 9.1: Comparison of the LES features by stationary manometry.

TREATMENT GROUP	TOTAL LENGTH	ABDOMINAL LENGTH	LES RESTING PRESSURE
NORMALS ³⁵ (n=136)	3.6±0.06	2.1±0.06	14.8±0.5
NO TREATMENT (n=11)	3.46±0.22	2.25±0.18	28.35±3.58
DILATATION (n=9)	2.6±0.31	1.29±0.24	24.49±2.79
MYOTOMY (n=14)	2.94±0.23	1.84±0.23	8.79±1.21*

* p<0.05 vs no treatment

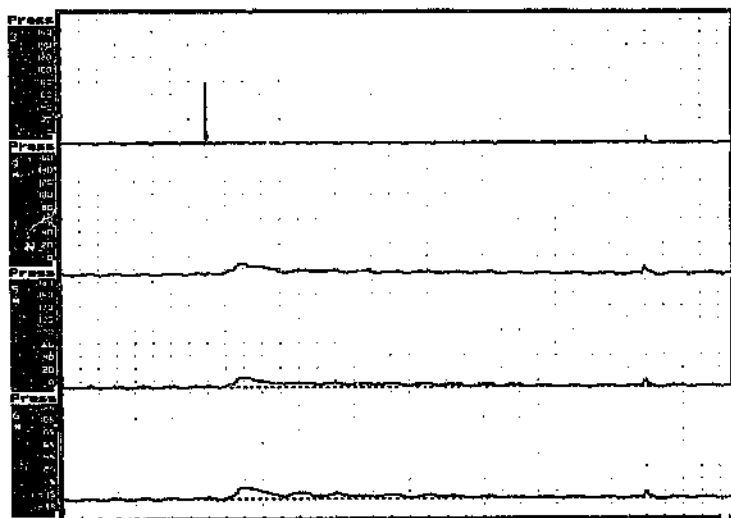


Figure 9.1 An example of the typical low amplitude isobaric esophageal pressure response after a pharyngeal swallow. Time on abscissa = 2 secs between dots.

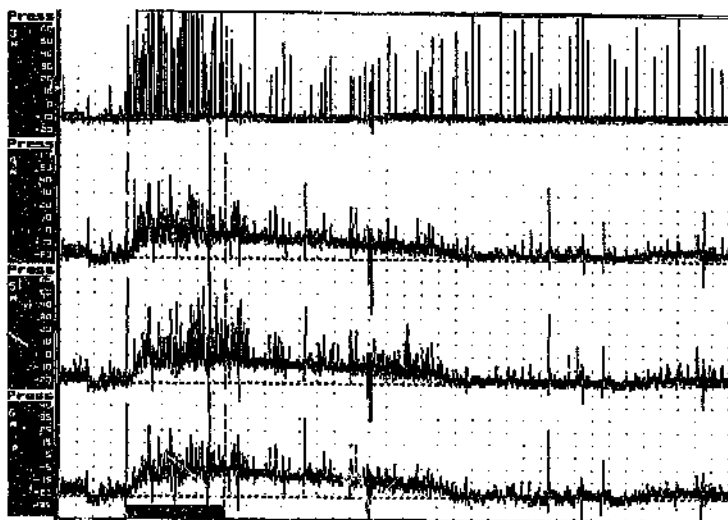


Figure 9.2 An example of a compressed record (80 minutes) showing an elevation in the baseline pressure that occurs with eating. The black bar in the bottom channel indicates the meal period.

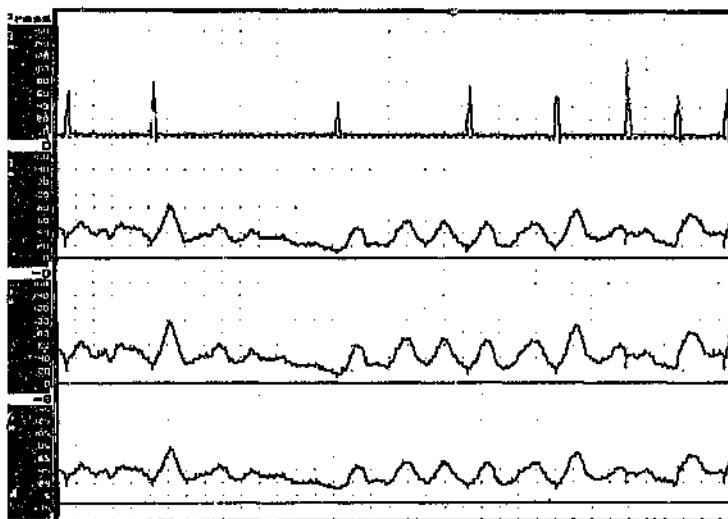


Figure 9.3 An example of the repetitive low amplitude isobaric contractions seen in the esophagus during meals. Note the elevation in baseline pressure. Time = 2 secs between dots.

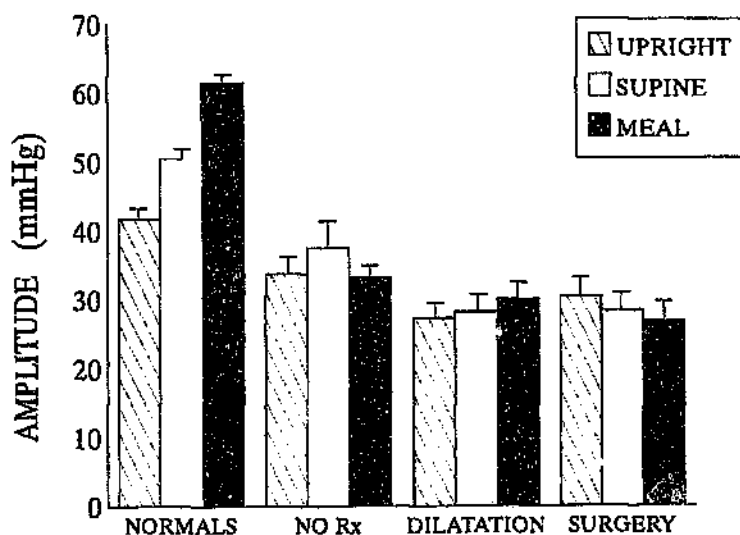
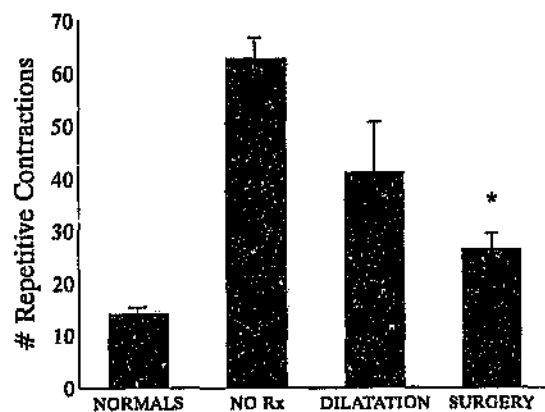


Figure 9.4 The mean contraction amplitude for the lower esophagus for the different physiologic periods for normals and the three patient groups.



* $p=0.019$ vs no treatment

Figure 9.5 A graphic representation of the mean number of repetitive contractions in the lower esophagus during meals.

The pre-operative and post-operative LES resting pressures and the mealtime baseline pressures for the nine patients with pre-operative and postoperative studies are shown in figure 9.6. The amplitudes of contractions during the meals for the upper, middle, and lower esophagus are shown in figure 9.7. The prevalence of incomplete and complete peristalsis, and the prevalence of effective waves before and after myotomy for each subject is shown in table 9.2. Figure 9.8 shows an example of an incomplete peristaltic wave following myotomy. Overall an increase in peristalsis (complete plus incomplete) was seen after myotomy (medians: 14% pre-op vs 48% post-op, $p=0.028$), however, there was no significant increase in efficacy. In one patient a significant return of complete and effective peristalsis was noted post-operatively. This patient was noted on ambulatory manometry to have some pre-operative peristaltic contractions but otherwise had all the typical features of achalasia: aperistalsis on stationary manometry with an incompletely relaxing lower esophageal sphincter, a dilated lower esophagus with a "bird-beak" LES on videoesophagography and an increase in mealtime baseline with repetitive contractions on ambulatory manometry. Post-operatively a decrease in esophageal diameter with free flow of barium into the stomach was seen associated with peristaltic waves. An example of the pre-operative and postoperative ambulatory manometry in this patient is shown in figure 9.9. In one other patient a slight improvement in complete peristalsis and efficacy was seen after myotomy. This patient was noted to have a higher contraction amplitude than the others, although all contractions maintained an isobaric pattern, and on stationary manometry was felt to have a "vigorous" component.

In none of the 26 patients studied besides the 2 mentioned above was the prevalence of complete peristalsis or efficacy greater than 4%.

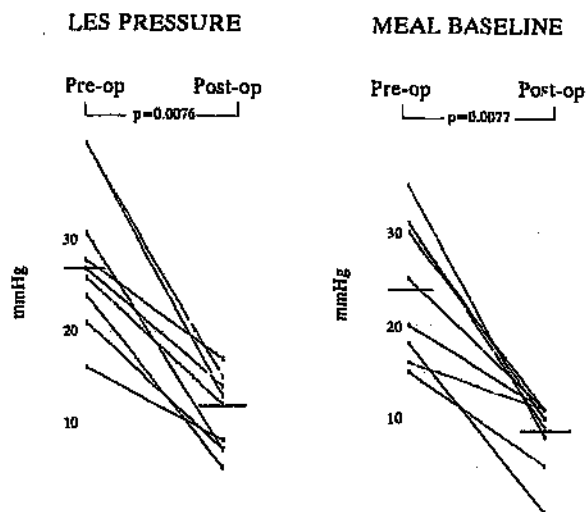


Figure 9.6 The pre and postoperative LES resting pressures and the mealtime baseline pressures for the nine patients studied before and after myotomy.

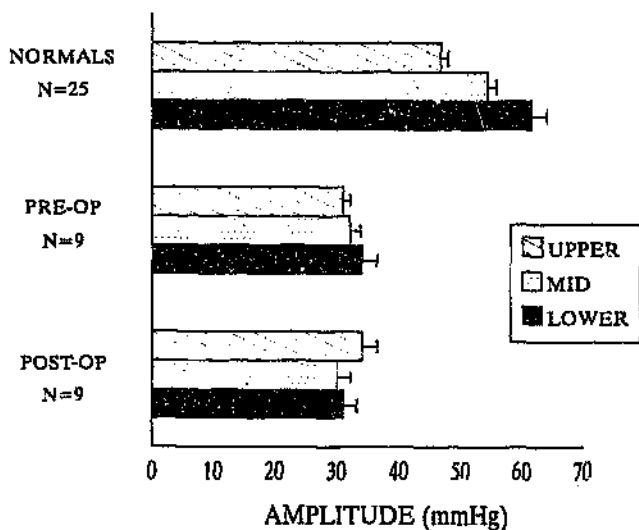


Figure 9.7 The mean amplitudes of contractions during the meal period for the upper, middle and lower esophagus for normals and achalasia patients before and after surgery.

Table 9.2: Ambulatory manometry wave analysis of meal periods before and after surgical myotomy in individual patients. The numbers are given as a percentage of all recognized waves.

PAT.	<u>INCOMPL</u> <u>PERIS</u> PRE-OP %	<u>INCOMPL</u> <u>PERIS</u> POST-OP %	<u>COMP.</u> <u>PERIS</u> PRE-OP %	<u>COMP.</u> <u>PERIS</u> POST-OP %	<u>EFFICACY</u> PRE-OP %	<u>EFFICACY</u> POST-OP %
1.	4	48	1	0	0	0
2.	19	6	1	1	0	0
3.	12	11	0	0	0	0
4.	5	9	0	2	0	0
5.	14	59	0	10	0	2
6.	10	42	3	5	1	3
7.	17	51	2	4	0	2
8.	28	58	9	20	5	13
9.	42	80	21	44	18	<u>38</u> *
Ave.	17	40	4	10	3	6.6

* lower limit of normal = 35% (5th percentile of 25 normal volunteers)²⁶⁵

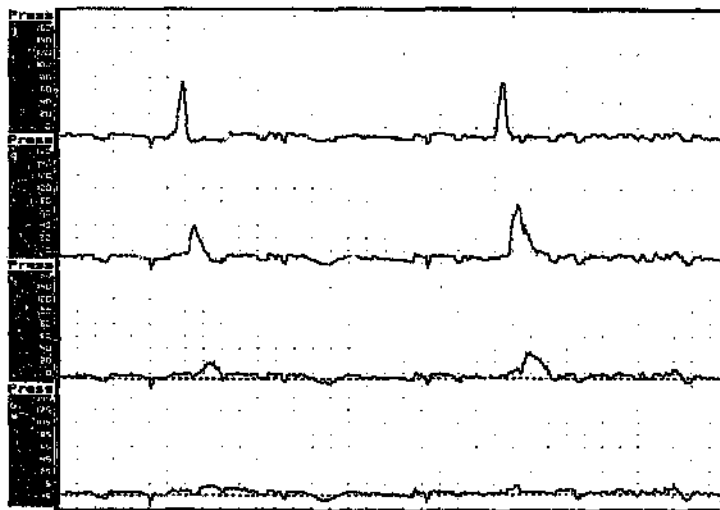


Figure 9.8 An example of the return of incomplete peristalsis that was seen occasionally after myotomy. Note that the peristaltic wave does not reach the lower esophagus.

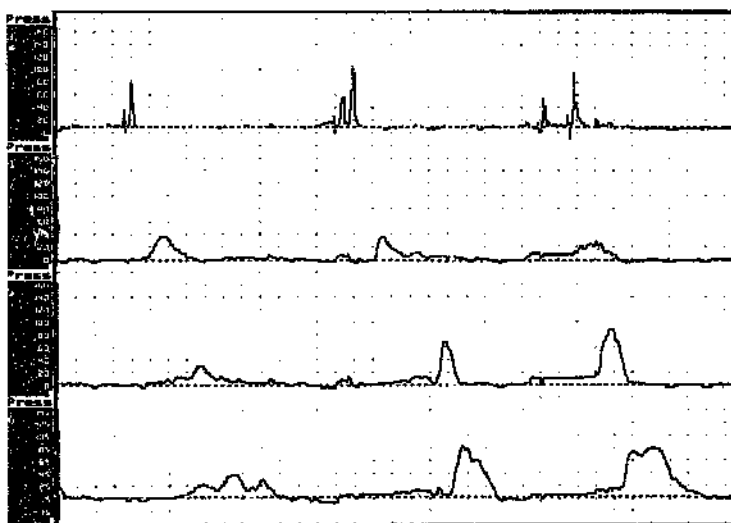
**A****B**

Figure 9.9 An example of the recording from a patient before myotomy (A) showing no peristalsis and, (B), after myotomy with return of some peristaltic waves. Complete peristalsis as seen in B was unusual. More frequently incomplete peristalsis seen only in the upper esophagus was observed after surgical myotomy.

9.4 DISCUSSION

The diagnosis of classic achalasia is made by the finding of an aperistaltic esophageal body with an incompletely relaxing lower esophageal sphincter as measured with stationary manometry. In this study the esophageal body function of all patients with a stationary manometric diagnosis of achalasia was assessed over a complete circadian cycle using the new technology of ambulatory manometry. No comparison should be made regarding treatment with dilatation and myotomy since only patients with persistent dysphagia and presumed unsuccessful dilatation were referred for further study. The sphincter data in table 9.1 is in concordance with previous studies that have shown that myotomy reliably reduces the LES pressure which enables gravity assisted passage of food into the stomach despite the absence of peristalsis.

The increase in baseline pressures during meals is typical of achalasia and corresponds to the retention of food in the esophageal body as discussed in previous reports.²⁶⁶ This increase in pressure was minimal in patients who had undergone myotomy but was present in patients who had undergone previous unsuccessful dilatation. The relationship between the resting pressure of the sphincter preoperatively and the increase in mealtime baseline pressure (figure 9.6) is possibly related to the non-relaxing nature of the LES; a certain "head" of pressure is needed in order to enable passage of food into the stomach.

The high prevalence of repetitive contractions during meals appears related to the increase in esophageal pressurization, although this has not previously been described. In this study pharyngeal contractions were flagged by a pharyngeal transducer which allowed accurate documentation of swallows and enabled analysis of contractions which did not follow pharyngeal contractions. These isobaric repetitive contractions indicate that the esophageal body is not a flaccid tube, but that some contractile activity is occurring. These contractions cannot be explained in terms of a bolus of food being propelled into the esophagus by the pharynx since the repetitive contractions occurred in the absence of further swallowing. It is possible that the distended esophagus predisposes to muscular irritability with local reflexes stimulating contractions. This is in keeping with a denervation hypersensitivity which is the basis for the mecholyt test.

The decrease in these repetitive contractions after myotomy may be related to the decrease in esophageal pressurization as was seen during the meal periods.

The similar amplitudes of contractions in the three levels of the esophagus and the similar amplitudes in the different groups of patients studied reflects the common cavity phenomenon. Whereas normal subjects increase the amplitude of contractions in the lower esophagus the isobaric pressure changes in achalasia showed the same amplitude at all levels of the common chamber.

Recent publications have suggested that "vigorous" achalasia should be abandoned as a distinct clinical disorder because of similar findings on further study to classic achalasia and similar outcomes after treatment.^{58,267-270} Although the findings of higher amplitude contractions may not define a separate clinical entity, they may be an indicator of earlier disease, reflecting preservation of some contractile activity. In this study the two patients who had return of effective peristalsis had higher amplitudes of contractions during meals than those that had no return of function. This is in keeping with the finding that patients with vigorous achalasia have less esophageal dilatation than those with classic achalasia.⁵⁸

The results of the computerized analysis of the ambulatory recordings showed that in all groups occasional peristalsis was observed. When using new technology it is important to understand its limitations. The algorithms for computer automated analysis of esophageal contractions were written to recognize normal contraction morphology with the exception of a feature of recognizing multi peaked and repetitive contractions.¹⁷¹ The increases in intraluminal pressure in achalasia are associated with the common cavity effect, and often have a bizarre morphology. The automated program, in an attempt to recognize "contractions", can produce numbers suggestive of normal peristalsis but which are artefactual. This stresses the importance of visualizing the contractions and the results of the automated analysis on screen. Software programs that do not have this facility are likely to result in accepted numbers that have not been authenticated visually. Although this is a limitation of currently available software programs, new technology in the field of neural networking holds promise for recognition of more complex contraction morphology.²⁷¹ Despite the software limitations, true peristaltic progression of contractions was occasionally observed in

untreated patients. Complete peristalsis, however, was uncommon. Incomplete peristalsis was more frequent as seen in figure 9.8. Peristaltic progression from the upper-most channel to the second channel may be understood in terms of possible preservation of the upper striated muscle from the disease process of achalasia. This explains, in part, the higher prevalence of partial peristalsis observed in the patients post-surgery. The myotomized lower esophagus relieves the outlet obstruction, the esophagus becomes less distended during meals, and the common cavity phenomenon is minimized. Consequently contractions are only seen in the upper esophagus and the overall prevalence of partial peristalsis is greater in the absence of the common cavity phenomenon.

It is probably more important when analyzing peristalsis to analyze the prevalence of complete and effective peristalsis as this gives functional meaning to the pressure observations. In this study the prevalence of complete and effective peristalsis was negligible in all the groups of patients, including the post-operative group. The two exceptions to this showed an improvement in efficacy to 13 and 38% respectively. These two patients may have had an earlier form of the disease.

The finding of a return of normal effective peristalsis in one patient supports the theory that the sphincter dysfunction is primary and that the loss of peristalsis is secondary to esophageal distention. In this patient only the lower esophagus was dilated on videoesophagography. During the barium study, partial peristalsis could be observed in the upper esophagus, but this disappeared as the wave reached the distended lower end. It is of interest that the pre-operative increase in mealtime baseline (18 mmHg) was not as marked as in the other patients. This is in keeping with Bielefeldt and colleagues who noted a return of some peristalsis after myotomy in those in patients with a minimal increase in resting esophageal pressures on pre-operative stationary manometry.²⁷²

Although indentations of the luminal image of barium suggesting "tertiary" contractions were seen in many patients, the contractions did not appear to be organized as has been suggested by Zaninotto *et al.*²⁷³ They have suggested that the esophagus retains its peristaltic ability in many patients with achalasia but that the dilatation of the esophagus precludes luminal occlusion which is necessary to detect pressure changes with a manometry catheter.

There are now many emerging reports on post-dilatation and post-operative return of peristalsis.²⁷²⁻²⁷⁹ Closer examination of these reports reveal that peristalsis returning to the whole length of the esophagus (complete peristalsis) is very uncommon. In the few reports where the data is available, the patients with significant return of peristalsis had a minimally dilated esophagus at the outset or only a marginally increased esophageal resting pressure pre-operatively.^{272,273,279} This could be explained in terms of an early stage of disease as discussed above. As in this study significant return of functional peristalsis in terms of "efficacy" is very unusual. The growing body of data that suggests return of function by quoting only partial peristalsis should be regarded with caution. This view is consistent with the morphologic studies of Goldblum and colleagues on resected esophageal specimens from patients with achalasia.²⁸⁰ Their finding of a loss of ganglia together with muscular degeneration and fibrosis in the dilated lower and mid-esophagus suggests permanent loss of function. Some ganglia were found in the upper, less-dilated portion of the esophagus.

If the outflow obstruction of the LES is relieved at an early stage before significant esophageal dilatation has occurred, it is possible that loss of esophageal body function can be diminished. While long-term follow-up is needed, the advent of ambulatory manometry has provided a more detailed means of examining esophageal motor function in this disease. Possibly the presence of some peristalsis pre-operatively is predictive of return of function post-operatively as was indicated in the two patients in this study.

Ambulatory manometry is more sensitive in detecting some normal motor activity in patients with achalasia and suggests that the presence of occasional peristalsis does not preclude the diagnosis. Rather, the typical motor patterns as described above help clarify the confusion that may arise occasionally from the limited number of swallows performed during stationary manometry. The increase in esophageal baseline during meals associated with repetitive isobaric contractions is diagnostic and reflects the outflow obstruction and esophageal distention associated with the disease. Once significant esophageal distention has occurred return of function after treatment is unlikely.

CHAPTER 10: THE HYPERTENSIVE LOWER ESOPHAGEAL SPHINCTER: A MARKER OF A MORE SEVERE MOTILITY DISTURBANCE

10.1 BACKGROUND

The diagnosis of a hypertensive lower esophageal sphincter (HTLES) is made when the lower esophageal sphincter (LES) pressure on manometry is abnormally high but relaxes normally on swallowing. The original description by Code²⁸¹ included a group of patients with diffuse esophageal spasm but more recently patients with diffuse spasm have been excluded from the diagnosis.^{282,283} The finding of an isolated HTLES is uncommon, occurring with a prevalence of 2.3 to 4.8% of manometries performed.^{256,282,284,285} Patients usually complain of dysphagia or chest pain and with the exception of the high pressure sphincter have normal manometric findings. The clinical significance of the disorder has been questioned since the manometry findings do not appear to provide an explanation for the symptomatology.^{282,283,286}

More detailed study of the LES has shown that the apparent relaxation of the LES may not be as complete as seen in normal subjects.²⁸⁴ Some authors have shown that the post-relaxation contraction is abnormally high and have called this entity a hypertensive hypercontracting sphincter.²⁸⁷⁻²⁸⁹ Other investigators have found a shortened duration of relaxation and have attributed symptoms to this manometric finding.²⁸⁵ In the current study we have assessed the esophageal body function in patients with a hypertensive lower esophageal sphincter with ambulatory esophageal manometry in an effort to explain the complaint of dysphagia commonly encountered in these patients.

10.2 METHODS

10.2.1 Patient Population

Over a three year period thirteen patients diagnosed with a hypertensive lower esophageal sphincter at the esophageal motility laboratory at the University of Southern

California underwent ambulatory manometry. The diagnosis was made on the basis of a resting pressure of the lower esophageal sphincter of greater than the 95th percentile of previously published normal volunteers, and normal relaxation on manometry. All patients had a video-esophagram and endoscopy to exclude a structural abnormality such as stricture or carcinoma. All underwent stationary manometry and simultaneous ambulatory pharyngo-esophageal manometry and pH monitoring. Patients with a diagnosis of diffuse esophageal spasm or achalasia on stationary manometry were excluded.

Twenty normal asymptomatic volunteers were used as controls. Normal subjects were screened by questionnaire to exclude foregut symptomatology and by videoesophagram to exclude any structural abnormalities as previously described.

10.2.2 Motility and pH studies

Stationary manometry was performed according to the protocol previously discussed. Standard diagnostic categories were made according to table 4.1 in chapter 4. The resting pressure of the lower esophageal sphincter was calculated as a mean of five pull-throughs with the side hole oriented radially so that the asymmetry of the sphincter was taken into account. The resting pressure of the sphincter was measured at mid-inspiration at the respiratory inversion point.¹⁷⁸ Relaxation was assessed with the side holes of the catheter located just above the respiratory inversion point to avoid possible artefact from descent of the catheter into the stomach on swallowing.^{199,200} The completeness of relaxation was measured from the baseline and expressed as a percentage of the resting pressure. The function of the esophageal body was assessed by 10 wet swallows performed every 30 seconds as previously described.

Ambulatory manometry and the analysis of recordings were performed as described in chapters 4 and 5. The amount of esophageal acid exposure ($\text{pH} < 4$) was quantitated using a composite scoring system.¹⁷³ A patient was considered to have increased esophageal exposure to gastric juice if the composite score for $\text{pH} < 4$ exceeded the 95th percentile of 50 normal healthy volunteers, i.e., a score value of 14.7.¹⁸⁵

An assessment of the outflow resistance through the relaxed lower esophageal

sphincter was based on measuring the intrabolus or "ramp" pressure measured in the lower esophagus during mealtimes. The pressure was measured at a point on the contraction wave just prior to the upslope and was related to esophageal baseline pressure (Figure 10.1). The intraesophageal pressure dynamics as measured by a transducer in the lower esophagus during a contraction wave are shown in figure 10.2. "A" represents the resting intra-esophageal pressure, which is recording only the background respiratory fluctuations. "B" shows the peristaltic wave progressing down the esophageal body. The intraluminal pressure recorded by the transducer is a function of the oncoming wave and the outflow resistance at the LES. In the normal situation the LES relaxation provides minimal resistance. If incomplete anatomical relaxation occurs the resistance to outflow increases and the transducer records a higher "ramp" or intrabolus pressure. When the contraction wave reaches "C", the transducer records the contraction at that level. At "D", the wave has moved distally and the luminal pressure again falls to baseline.

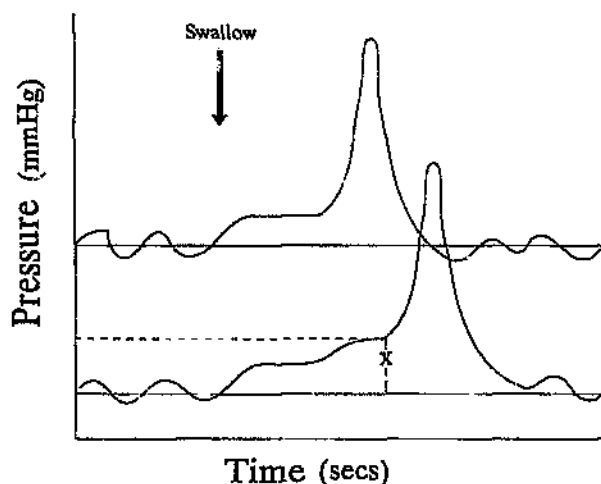


Figure 10.1 Graphical representation of the measurement of the intrabolus pressure (X) during the meal periods

10.2.3 Statistics

Statistical analysis was performed with the aid of a computer program (SPSS for

Windows v6.1.3, Chicago, Illinois). The Mann-Whitney U test was used to compare differences for ambulatory data. Significance was estimated at the 0.05 level. The amplitudes of contractions were related to the intrabolus pressures by using the Pearson correlation analysis.

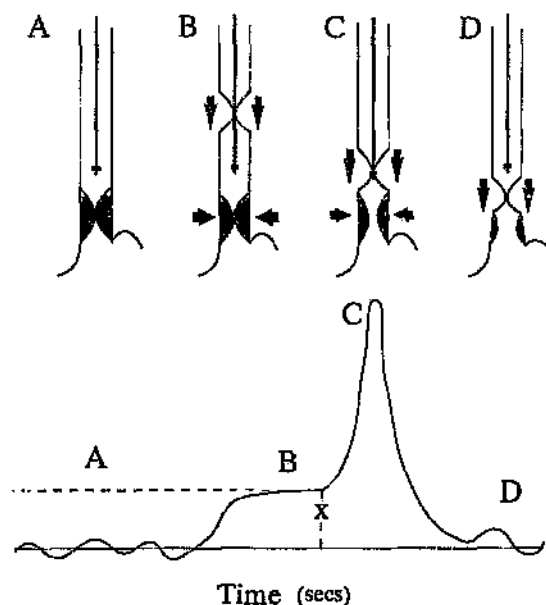


Figure 10.2 The pressure dynamics in the lower esophagus during a peristaltic contraction wave. See text for description.

10.3 RESULTS

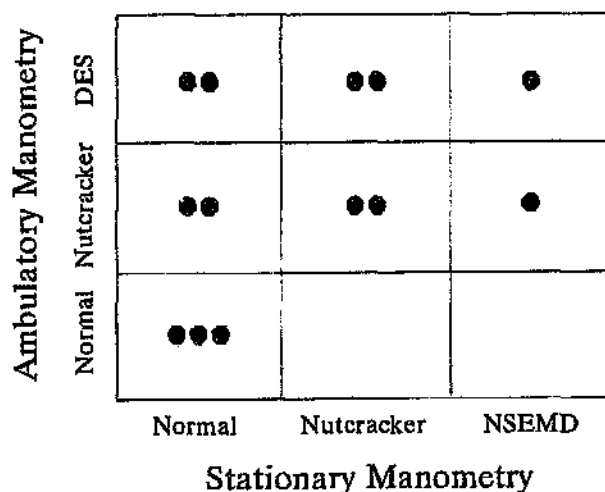
Thirteen patients (six men, seven women) met the criteria for HTLES. The median age was 50 years (range 42-85). Ten patients presented with dysphagia, one with a sensation of tightness in the throat only, and two with chestpain and heartburn with no dysphagia. Five patients with dysphagia also complained of heartburn, and three of them had chestpain.

The manometric data for the LES is shown in table 10.1 with previously published values of normal subjects from our laboratory for reference.³⁵

Table 10.1. Lower esophageal sphincter characteristics of normal subjects and patients with HTLES

GROUP	%RELAXATION	TOTAL LENGTH	ABDOMINAL LENGTH	LES RESTING PRESSURE
NORMALS ³⁵ (n=136)	93.1±1.6	3.6±0.06	2.1±0.06	14.8±0.5
HTLES (n=13)	94.6±1.7	3.54±0.19	2.05±0.24	29.04±0.56

The ambulatory manometric data for the patients with HTLES and the 20 normal subjects are shown in table 10.2. The results of ambulatory manometry reclassified eight of the thirteen patients (62%), (Figure 10.3).

**Figure 10.3** The diagnoses of the thirteen patients as assessed with stationary and ambulatory manometry.

Four patients had abnormal exposure to pH < 4 as measured by the DeMeester score (Scores, 15, 26, 40, 46). However only one patient had an increase in upright reflux. All subjects had a long nighttime reflux event which contributed significantly to

the overall exposure.

Table 10.2. Ambulatory motility characteristics of normal subjects and patients with HTLES

PARAMETER	NORMALS	HTLES	SIGNIFICANCE
AMPLITUDE (mmHg)			
<u>Upright</u>			
Channel 1*	35±3	42±5	NS
Channel 2	40±2	58±7	p=0.006
Channel 3	43±3	69±6	p=0.001
<u>Meal</u>			
Channel 1	49±3	50±4	NS
Channel 2	57±4	71±7	NS
Channel 3	68±4	85±8	p=0.039
<u>Supine</u>			
Channel 1	40±3	35±3	NS
Channel 2	50±3	61±9	NS
Channel 3	53±3	66±7	NS
DURATION (seconds)			
<u>Meals</u>			
Channel 1	2.41±0.13	2.28±0.17	NS
Channel 2	2.28±0.15	2.71±0.15	p=0.04
Channel 3	2.38±0.11	2.98±0.21	p=0.01
PERISTALTIC WAVES.(%)			
Upright	81±2.7	60±4.2	p=0.0002
Meal	88±1.4	78±3.8	NS
Supine	68±2.5	51±5.3	p=0.015
EFFICACY (%)			
Upright	36±4.0	30±5.3	NS
Meal	56±2.7	53±6.3	NS
Supine	32±3.2	15±3.4	p=0.003

* Channel 1, 2, and 3 are 15, 10, and 5 cm above the LES respectively. (Channel 3 = distal)

The mean intrabolus pressures for the normal subjects and the patients with HTLES during meals are shown in figure 10.4. No intrabolus pressures were detectable in either patients or normal subjects in the interprandial periods. An example of the

intrabolus pressures in a patient with HTLES during a meal and between meals is shown in figure 10.5.

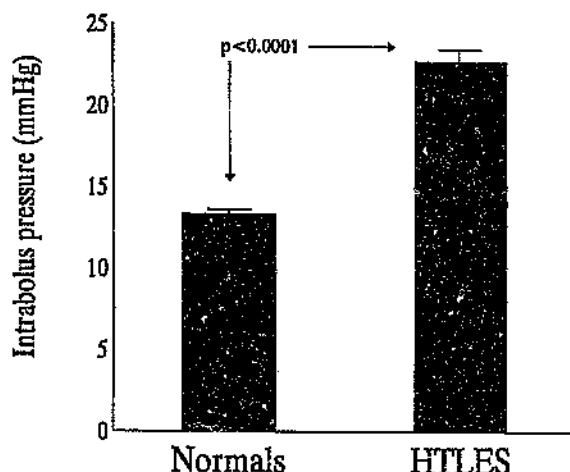


Figure 10.4 The mean $\pm$ standard error for the intrabolus pressures in normal subjects and patients with HTLES.

10.4 DISCUSSION

The diagnosis of a hypertensive lower esophageal sphincter poses an enigma since the functional abnormalities in relation to the symptoms have remained elusive. The thirteen patients with hypertensive lower esophageal in the current study included patients with high amplitude contractions, the so-called nutcracker esophagus, since these patients retain normal peristaltic wave progression of contractions and consequently do not have a motility abnormality that can easily explain the symptom of dysphagia.

When monitored for prolonged periods of time 5/13 (38%) of the patients had motility abnormalities significant enough to diagnose diffuse esophageal spasm that was not apparent on stationary manometry. Since the ambulatory study provides information from more than 1000 contraction waves occurring over a full circadian cycle, its

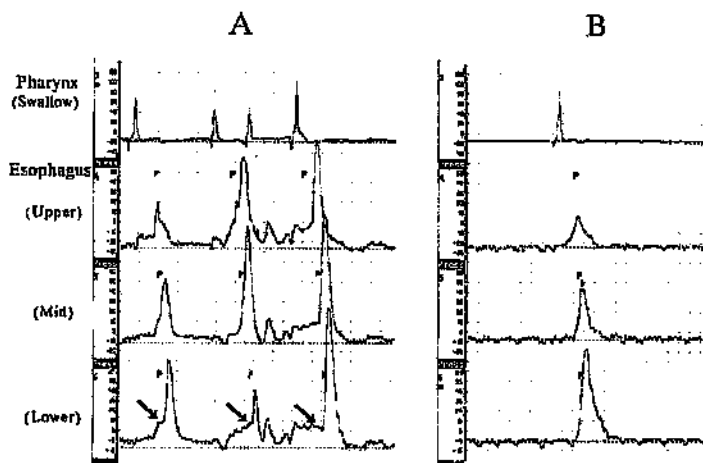


Figure 10.5 An example of the ambulatory recording of a patient with HTLES during a meal (A) and during the interprandial period (B). Note the prominent intrabolus pressures in A (Arrows).

diagnostic accuracy exceeds that which can be achieved from the 10 swallows obtained on stationary manometry. On the basis of these findings a HTLES occurs uncommonly in isolation and is usually associated with a more diffuse esophageal body disorder.

The presence of an intrabolus pressure was referred to as the "second positive deflection" on stationary manometry by Vantrappen in 1967.²⁹⁰ More recently, Ren and colleagues used simultaneous manofluorography to study the dynamics of a bolus as it traverses the esophageal body, and noted that the intrabolus pressure is a complex of forces from above produced by the squeeze of an oncoming peristaltic wave, the compliance of the esophageal segment surrounding the bolus, and the resistance to outflow. The resulting pressure in the bolus is a sum of these forces. An increase in the outflow resistance provided by increasing the intra-abdominal pressure elevated the intrabolus pressure in normal volunteers.²⁹¹ This effect was also noted by Vantrappen when a large bore catheter partially obstructed the LES.²⁹⁰ Consequently, it appears that the magnitude of the intrabolus pressure can be used as a measure of outflow resistance.

Cook has defined the pharyngo-esophageal pressure dynamics in patients with cricopharyngeal dysphagia.^{292,293} He noted that patients with evidence of an increased outflow resistance from incomplete radiologic relaxation of the cricopharyngeus, or a

cricopharyngeal bar, showed a profound "ramp" pressure in the pharynx prior to the pharyngeal contraction. This correlated with the symptom of transfer dysphagia. Of importance was the finding that manometric relaxation still occurred despite inadequate anatomic relaxation, in which case the only manometric abnormality was an increased "ramp" pressure.

In the present study the intrabolus pressure was used to measure outflow resistance during eating. Although on stationary manometry the relaxation was normal, the significantly increased bolus pressure recorded in patients with a HTLES supports the concept of an increased outflow resistance. This provides a pathophysiologic explanation for the patients symptoms who otherwise have normal findings. While it could be argued that the increased intrabolus pressure was a result of a greater pump pressure from the oncoming esophageal contraction, this was unlikely since the amplitudes of contractions in the patients with HTLES were not significantly different from the normal subjects at a level 5 cm above the pressure transducer used to record intrabolus pressure, i.e., 10 cm above the LES. Neither was there a correlation between the intrabolus pressure and the contraction amplitude at this level. The other possible contributing factor is poor compliance of the lower esophageal muscle secondary to muscle hypertrophy as has been found in patients with DES and nutcracker esophagus.

The associated higher contraction amplitude in the lowest segment of the esophagus (5 cm above the LES) in patients with HTLES suggests a possible feedback mechanism whereby the increased outflow resistance results in an increase in the force of propulsive contractions. This hypothesis which was originally suggested by Kaye²⁹⁴ and reinforced later by Freidin²⁸³, explains why the lower esophageal muscle hypertrophies in animal models with controlled outflow obstruction.²⁹⁵ It also provides an explanation, in part, for the successful treatment of many of these patients with pneumatic dilatation or LES myotomy.^{285,296}

A high pH score was found in four of the thirteen patients in keeping with previous reports.²⁵⁶ In one of these the score was only 15.2 (normal < 14.8). Two others had abnormal scores because of a single long nocturnal episode suggesting that failed clearance rather than "sphincter incompetence" was responsible.

The common finding of nutcracker esophagus and DES on ambulatory manometry in patients with HTLES suggests a common etiology of these disorders. It has been postulated that they may be part of a spectrum of motor disorders and there have been reports of one HTLES progressing to DES or achalasia.^{52,70,71,74,78,104,106,107,297}, the finding of HTLES seems to be a marker of a more significant motor disorder than is suspected on stationary manometry. Measurement of the intrabolus pressure during meals also provides information of the outflow resistance and provides a explanation for the symptomatology in these patients for the first time.

10.5 CRITICAL EVALUATION AND COMMENT.

It could be argued that the assessment of intrabolus pressures is inaccurate since patients were not eating a standardized meal with standardized bite sizes. Standardization may prove to be the most accurate means of quantifying this measurement in the future. In the present study the identification of the increased intrabolus pressures was made retrospectively, but the measurements of intrabolus pressures were made in the same way for both patients and normal subjects and consequently the comparisons are valid.

CHAPTER 11: AMBULATORY ESOPHAGEAL MANOMETRY IN PATIENTS WITH CLASSIC DIFFUSE ESOPHAGEAL SPASM

11.1 BACKGROUND

Diffuse esophageal spasm is defined by an increased prevalence of simultaneous contractions on stationary manometry, with preservation of a degree of normal peristalsis, in patients presenting with dysphagia and/or chestpain.⁶⁸ Associated abnormalities such as high amplitude, long duration and multi-peaked contractions have been described, but these are not consistent findings.^{52,60,62,63,66,75} There is also a marked overlap with the manometric features of many of the named motor disorders and non-specific motor disorders as previously discussed. An explanation for the confusion in this area is the episodic nature of spastic abnormalities and the limited number of swallow responses recorded during standard stationary manometry. In an effort to understand these disorders better, the ambulatory manometric system was applied to 14 patients with classical diffuse esophageal spasm, and are presented in this chapter. The results of the ambulatory studies from patients with classic motor disorders are then applied to a group of patients with unclear diagnoses and discussed in the next chapter.

11.2 METHODS

During a three year period 14 patients with diffuse esophageal spasm were studied. All patients presented with symptoms of dysphagia and/or chest pain and completed a questionnaire regarding the severity of their symptoms according to table 11.1. One patient was unable to eat at all and was fed via gastrostomy tube. Meal periods for this patient, therefore, could not be assessed on ambulatory manometry. Patients had endoscopy and video esophagography followed by stationary manometry and ambulatory simultaneous pH and motility monitoring as described in chapter 4. All patients had greater than 20% simultaneous waves in at least the distal 2/5 of the esophagus on 10 wet swallows according to the accepted definition of DES at USC.⁶⁷

The results of stationary manometry were compared to historical normals from the laboratory at USC.

Abnormalities on ambulatory manometry were defined when values exceeded the 95th percentile of 25 normal subjects. The prevalence of high amplitude contractions, defined as greater than 150 mmHg, was used to provide an indication of the episodic nature of these contractions. The intrabolus pressures of peristaltic waves were measured as described in the previous chapter.

Table 11.1. Severity scoring of patients symptoms.

SYMPTOM		GRADE
DYSPHAGIA	1	Occasional with course foods (meat sandwich, hard roll) lasting for a few seconds
	2	Requiring clearing with liquids
	3	Severe - semi-liquid diet or history of meat impaction
	4	For liquids
CHEST PAIN	1	Minimal or occasional episodes
	2	Moderate, Reason for visit
	3	Severe, interfering with daily activities
REGURGITATION	1	Mild, after straining and/or after large meals
	2	Moderate - predictable with position change, straining or lying down
	3	Severe - constant regurgitation, presence of aspiration
HEARTBURN	1	Minimal, identifiable symptoms, occasional episodes, no prior medical visit
	2	Moderate - primary reason for visit
	3	Severe - constant marked disability in activities of daily life

11.2.1 Statistics

Statistical analysis was performed with the aid of a computer program (SPSS for Windows v6.1.3, Chicago, Illinois). The Mann Whitney U test was used to compare differences between medians for the two non-parametric data sets. Significance was estimated at the 0.05 level. Data is expressed as means $\pm$ standard error of the mean.

11.3 RESULTS

Fourteen patients (six males, eight females) with a mean age 73 years (range 46-90) were studied. The severity of symptoms is shown in table 11.2. All patients complained of grade 2 or greater dysphagia, five patients with grade 2 or greater chest pain, and five with grade 2 or greater heartburn.

Table 11.2. Severity scores for the patients with DES

Symptoms (DES pts, n=14)	Dysphagia	Chest Pain	Heartburn	Regurgitation
Mean score $\pm$ SEM	2.57 $\pm$ 0.2	1.07 $\pm$ 0.3	0.86 $\pm$ 0.3	2.1 $\pm$ 0.3

Table 11.3. Stationary manometric data

PARAMETER	NORMALS	DES	SIGNIFICANCE
LES			
Total Length (cm)	3.65 $\pm$ 0.1	3.6 $\pm$ 0.24	NS
Abd. Length (cm)	2.14 $\pm$ 0.1	2.01 $\pm$ 0.2	NS
Pressure (mmHg)	14.84 $\pm$ 0.5	23.4 $\pm$ 2.8	p=0.0004
BODY			
<u>Amplitude (mmHg)</u>			
Level I	91 $\pm$ 3.3	75 $\pm$ 9.3	NS
Level II	45 $\pm$ 2.1	41 $\pm$ 8.3	NS
Level III	80 $\pm$ 3.3	99 $\pm$ 18.0	NS
Level IV	95 $\pm$ 3.5	95 $\pm$ 16.6	NS
Level ,	103 $\pm$ 5.5	106 $\pm$ 21.1	NS

Videosesophagography demonstrated abnormalities ranging from "corkscrew esophagus" to mild tertiary contractions with retrograde escape of barium. The stationary manometry results are shown in table 10.3. Only two patients had borderline competency of the LES by virtue of a short abdominal length in each patient. Only one

patient had an abnormal pH study with an esophageal acid exposure of 8.3% the total time (DeMeester Score 25.2).

The results of the ambulatory manometry study are shown in table 11.4. All patients exhibited episodes of high amplitude, long duration, and multi peaked contractions (figure 11.1). The meal periods were characterized by repetitive simultaneous contractions not related to swallowing. The episodic nature of high amplitude contractions was reflected by the greater prevalence of contractions of more than 150 mmHg. All patients but one with grade 2 or 3 chest pain, and none of the patients who had no chest pain had an increased prevalence of contractions greater than 150 mmHg. Of note, the overall amplitude or duration of contractions for the patients with DES was not significantly different to the normal subjects during mealtimes. However, abnormally high intrabolus pressures were detected in 10 of eleven patients (Figure 11.2). In three patients intrabolus pressures could not be measured because the prevalence of simultaneous contractions during meals was too high. Eight of thirteen patients (62%) had an increased prevalence of multi peaked contractions. Overall, the prevalence of multi peaked contractions increased from the upright to the meal period (2.3% to $4.4 \pm 1.2\%$, $p < 0.01$). In addition, the prevalence of isolated contractions in the lower esophagus (i.e., not related to contractions in the other levels) was greater for the DES patients in the upright and meal periods (5.6 ± 1 vs 14.8 ± 3.4 normal vs DES, Upright, $p < 0.01$; 3.5 ± 0.6 vs 9.0 ± 2.8 , Meal, $p < 0.01$). The inability to increase the peristaltic nature of contraction waves during meals is depicted in figure 11.3. As a consequence, the prevalence of ineffective contractions remained high during meals (Table 11.4).

Six patients had greater than 50% simultaneous waves during meals. Of these, all but one underwent esophageal myotomy or have been offered the option of myotomy. Only one of the patients with less than 50% simultaneous waves required myotomy for relief of symptoms.

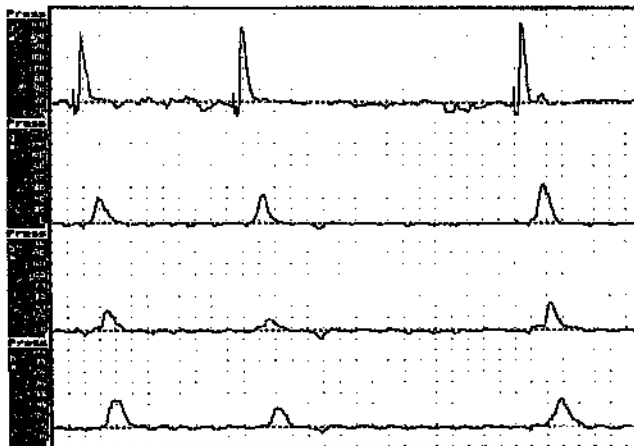
Table 11.4. Ambulatory motility characteristics of normal subjects and patients with DES.

PARAMETER	NORMALS (n=25)	DES (n=14)**	SIGNIF (p value)
AMPLITUDE (mmHg)			
<u>Upright</u>			
Channel 1 #	34±2	42±5	NS
Channel 2	40±2	62±7	0.015
Channel 3	42±2	68±7	0.002
<u>Meal</u>			
Channel 1	47±2	52±6	NS
Channel 2	54±3	64±8	NS
Channel 3	62±4	68±8	NS
<u>Supine</u>			
Channel 1	35±2	41±4	NS
Channel 2	47±3	69±11	0.03
Channel 3	51±3	73±8	0.01
% CONTRACTIONS > 150mmHg (lower esophagus)			
<u>Upright</u>	0.7±0.2	14.1±3.6	0.0001
<u>Meal</u>	1.9±0.7	15.9±3.9	<0.0001
<u>Supine</u>	2.4±1.0	15.4±4.5	0.0001
DURATION (secs)			
<u>Meal</u>			
Channel 1	2.3±0.1	2.1±0.2	NS
Channel 2	2.2±0.1	2.8±0.4	NS
Channel 3	2.3±0.1	3.0±0.4	NS
MULTIPEAKED % (Distal Esophagus)			
Upright	0.4±0.2	2.3±0.4	0.001
Meal	0.7±0.3	4.4±1.2	<0.0001
Supine	1.7±0.5	1.7±0.7	0.075
PERISTALTIC WAVES.(%)			
Upright	82±2.3	46±3.5	<0.0001
Meal	89±1.0	51±5.0	<0.0001
Supine	71±2.6	50±3.9	<0.0001
INEFFECTIVE (%)			
Upright	40±2.9	84±2.9	<0.0001
Meal	30±1.9	80±4.6	<0.0001
Supine	57±3.0	86±2.3	<0.0001

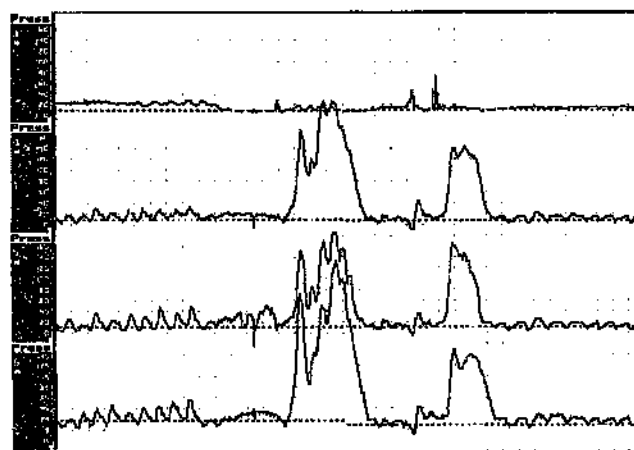
Channel 1, 2, and 3 are 15, 10, and 5 cm above the LES respectively.

** Values for meal periods are for 13 patients.

Figure 11.1. An example of the recording from a normal volunteer, A, and from one of the patients, B, showing the characteristic spastic contractions of the esophageal body. The channels reflect recordings from the pharynx and the upper, middle and lower esophagus from above, down. The contractions in the patient with DES show typical multi-peaked contractions of high amplitude (greater than 200 mmHg), and long duration (greater than 8 seconds). The time interval between dots on the abscissa is 2 seconds.



A: Normal Subject



B: Patient with DES

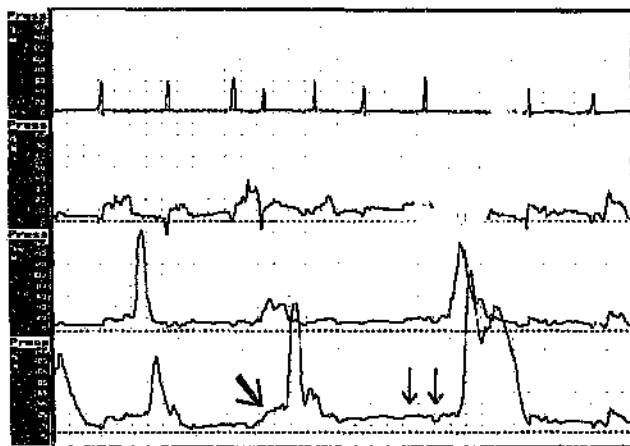


Figure 11.2 Example of the increased intrabulbar pressure in the lower esophagus in a patient with DES (heart rate). Note also the esophageal pressurization between swallows (double arrow)

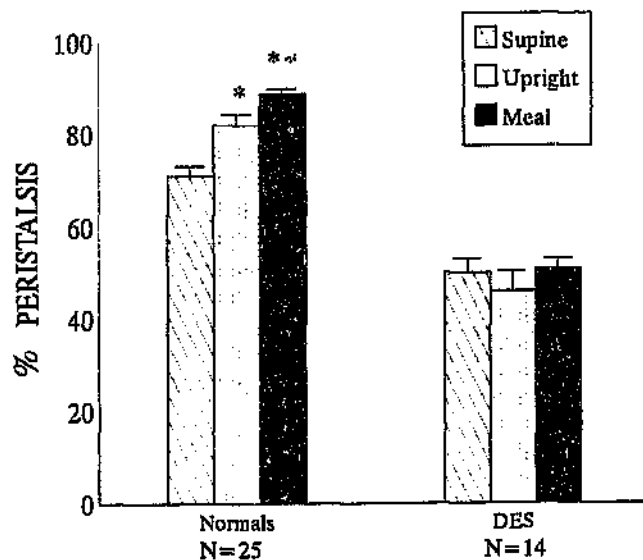


Figure 11.3 The prevalence of peristalsis during the different periods in normal subjects and DES patients. * = $p < 0.05$ vs Supine, ** = $p < 0.05$ vs Upright

11.4 DISCUSSION

There is currently no precise definition of DES. The most consistently used definition is an increase in simultaneous contractions with preservation of a degree of normal peristalsis in a patient with chest pain and/or dysphagia.⁶⁸ The threshold of increased simultaneous waves required to make the diagnosis is controversial. In our laboratory more than 20 percent of the 10 wet swallows on stationary manometry are required to be simultaneous before the diagnosis can be made. The argument for this threshold is that the diagnostic criteria should err in favor of specificity, especially if these patients are to be considered for surgical therapy.

The higher resting pressure of the sphincter in this report is in keeping with previous observations, and with the finding of only one patient with an abnormal esophageal acid exposure.^{298,299} It is interesting that five patients complained of heartburn while none had an increased esophageal acid exposure. It is possible that these patients have a heightened sensitivity of the esophagus and that disorganized esophageal contractions were experienced as heartburn.

When monitored for prolonged periods the patients exhibited similar characteristics to those on stationary manometry, and no patient was reclassified as having another manometric disorder. Two patients, however, were noted to have an elevation of the baseline pressure during meals suggesting esophageal pressurization as in achalasia. These patients did have intermittent peristalsis and typical high amplitude, multi-peaked spastic contractions which defined the disorder as DES rather than achalasia. This finding does, however, lend support to the hypothesis that these disorders may be related.^{71,78} In all patients, the "spastic" element of intermittent high amplitude, multi-peaked contractions, was more evident with prolonged monitoring, but overall the simultaneous nature of the contractions, i.e., the hallmark of DES, was consistently increased. Although, the amplitudes of contractions overall were not different in DES patients compared to the normal subjects, a finding in keeping with previous work,²⁹⁸ the episodic nature of high amplitude contractions was reflected by the increased prevalence of contractions greater than 150mmHg.

No, previously described, however, was the inability of the patients to improve the

prevalence of peristalsis or increase the amplitude of contractions during meals, as is typical for normal subjects. Rather, in 8 of 13 patients (62%) the efficacy of contraction waves deteriorated during eating. This is in concordance with the description of swallow independent contractions in DES patients³⁰⁰, and with work that has shown that manometry during eating increases the diagnostic yield in these patients.^{211,301} Sifrim *et al*³⁰² have also noted that the presence of a balloon in the esophagus, even under low pressure, stimulates repetitive secondary contractions in patients with DES. In effect the esophagus appears to be hypersensitive to the presence of a bolus perhaps secondary to a defect in the normal inhibitory mechanisms.³⁰³ It is conceivable that in this situation the simultaneous waves impede propagation of the bolus, the uncleared bolus stimulates more simultaneous waves, and a vicious cycle results.

The interesting finding of an increased intrabolus pressure in 10 of 11 patients suggests significant resistance to outflow in these patients. This may be secondary to decreased compliance of the lower esophagus or an inability of the lower esophageal sphincter to relax *anatomically* even if manometric relaxation has been recorded (see chapter 10). This is in keeping with others who have noted inadequate or short duration relaxation of the LES in many patients with DES.^{298,299} It could be argued that the LES dysfunction is primary and that the body abnormalities are secondary to the increased outflow resistance.²⁹⁴ Support for this is given by animal studies in which a loose band surgically placed around the LES of the cat resulted in high amplitude disorganized contractions.⁷⁹ In this thesis further evidence is provided to support the outflow obstruction theory, by the finding of an increased prevalence of simultaneous waves and high amplitude contractions in patients with a stationary manometric diagnosis of hypertensive lower esophageal sphincter. The HTLES may represent an early stage of the disease process. Long-term follow up using ambulatory manometry will answer this question. The high ramp pressures do, however, give a further argument for extending the myotomy across the sphincter in patients undergoing long esophageal myotomy for DES.

In summary, the ambulatory manometric characteristics in these patients are

- 1) An increased prevalence of simultaneous waves in all periods, meals, upright awake, and supine. This is associated with an inability to improve the prevalence

of peristaltic waves, and consequently wave efficacy, during the meals periods.

- 2) An increased amplitude of contractions in the upright and supine periods, but normal amplitudes during meals.
- 3) An increase in episodic high amplitude contractions (>150 mmHg) and multi peaked contractions.
- 4) An increase in the intrabolus pressure in the lower esophagus, indicating increased compliance or incomplete LES relaxation resulting in increased outflow resistance.

Surgical therapy in this disease is directed toward improving the symptom of dysphagia and the ability to eat. The symptom of pain is less often relieved by myotomy.^{67,304,305} The ability of a bolus to move through the esophagus is normally dependent on the effect of gravity and on propulsive esophageal contractions. Effective propulsion is a function of contraction amplitude and peristaltic progression.¹⁵⁸ In DES, the bolus transport is impeded by the functional obstruction resulting from simultaneous contractions and decreased muscle compliance. A long esophageal myotomy reduces the simultaneous contractions and improves the compliance of the esophagus, but at the expense of abolishing normal peristalsis and reducing contraction amplitude.⁶⁷ In order for a long myotomy to relieve dysphagia, the degree of functional obstruction causing dysphagia needs to outweigh the existing propulsive activity since after the long myotomy, bolus transport will be gravity dependent. Consequently, it is difficult for the surgeon to decide when to perform a myotomy. In the present study an effort was made to estimate the severity of the disorder by dividing patients into those with greater than and those with less than 50% simultaneous waves during meals. Of those with more than 50% simultaneous waves the intractability of symptoms, and failure to respond to medical therapy, had encouraged the decision for surgical treatment. In those with less than 50% simultaneous contractions only one patient had symptoms severe enough to warrant surgery. This may be the threshold at which the gain realized by the loss of the simultaneous wave forms exceeds the detriment incurred from the loss of the peristaltic waves. This is currently under prospective evaluation with ambulatory manometry at USC.

11.5 CRITICAL EVALUATION AND COMMENT

Classic diffuse esophageal spasm is uncommon, and only 14 patients were diagnosed on the stationary manometry over a three year period. Variants, i.e., an increased prevalence of simultaneous contractions but insufficient to classify as DES, are included in the following chapters, as are patients who were diagnosed as DES only by ambulatory manometry.

The higher severity scores for dysphagia compared to chestpain is probably related to a referral bias and not to the nature of symptoms in patients with DES in general.

The algorithms for detection of multi peaked contractions are discussed in appendix E. Contractions with three or more peaks meeting the algorithm criteria are uncommon in normal subjects, with the upper limit of normal in the lower esophagus during meals being 2.2 %. The algorithm for triple or more peaks detects only the extreme and obvious multi peaked contractions and therefore probably underestimates the prevalence of bizarre shaped contractions. Nonetheless the same algorithm was used for normals and patients and consequently comparison between them is valid.

The obvious question is one of outcome after surgical therapy. This is presently being studied at USC and is beyond the scope of this thesis, but it is felt that the insight provided by ambulatory manometry will prove to be useful in selecting patients for surgical therapy and evaluating them post-operatively.

CHAPTER 12 THE VALUE OF AMBULATORY MANOMETRY IN PATIENTS WITH UNCLEAR DIAGNOSES

12.1 BACKGROUND

The episodic nature of esophageal motor disorders and the limitations of stationary manometry do not always enable classification of the manometric recording into one of the named esophageal motor disorders. This has resulted in a number of sub-classifications and the large subgroup of patients with non-specific esophageal motor disorders (NSEMD). The diagnostic difficulties may, at least in part, account for the less than satisfying results of surgical or medical therapy of functional disorders of the esophagus. The underlying esophageal body abnormality responsible for dysphagia or chest pain frequently cannot be determined on stationary manometry.⁹¹ To do so, requires assessment of the physiology of esophageal function and identification of abnormalities associated with the complaint rather than categorization of motor disorders based on the morphology of esophageal contractions.

The ability to monitor the esophagus throughout different physiological circumstances has enabled the study of motor function during symptoms and during eating. The previous chapters have discussed the pathophysiological insight that ambulatory manometry has provided in patients with named motor disorders. The predominant motor abnormality in patients with GERD is hypomotility and an inability, in some, to organize contractions during eating. Patients with achalasia have a typical mealtime pattern and may exhibit occasional peristaltic activity outside of meals. Diffuse esophageal spasm is characterized by an increased prevalence of simultaneous wave forms and intermittent "spastic" activity of high amplitude, long duration, multi-peaked contractions. The symptom of pain appears to be related to these episodic phenomena and the ability of the esophagus to generate high contraction amplitudes, while dysphagia is related to the prevalence of simultaneity which causes a functional impedance to the passage of a bolus during eating. A previous chapter has shown that many patients with a hypertensive lower esophageal sphincter (HTLES) exhibit a motor

pattern consistent with a more severe abnormality than is appreciated on stationary manometry. Furthermore, the increased ramp, or intrabolus pressure, provides a means of manometrically assessing the resistance to the outflow of the lower esophagus during normal esophageal function.

In this study ambulatory manometry was performed on a group of patients with non-organic dysphagia and/or chest pain with an unknown or unclear diagnosis after standard investigation, in an attempt to find a functional reason for the patients symptoms. A new classification system based on the functional disorder is proposed as a means to direct therapy.

12.2 METHODS

During a three year period 40 patients were investigated in the esophageal laboratory at USC for symptoms of dysphagia and/or chest pain which was felt to be functional in nature but in whom no specific diagnosis could be made. There were 21 females and 19 males, (mean age 53 years, range 25-85). Patients had been studied by videoesophagography, endoscopy, stationary manometry and 24-hour pH monitoring. Excluded from this group were patients with achalasia, diffuse esophageal spasm, connective tissue diseases, severe hypomotility, and patients with GERD. Patients with GERD were excluded because reflux induced injury is often associated with the symptom of dysphagia even in the absence of motor abnormalities.¹²⁹ Patients with high amplitude contractions with normal progression (the "nutcracker esophagus") were included because of the controversial cause of symptoms in these patients.⁹⁰ Endoscopy excluded any obstructive lesion as a cause of dysphagia. Stationary manometry was performed as described in chapter 4 and diagnostic classifications were made according to table 4.1.

The ambulatory manometric results for the meal periods provided a means to classify patients into the following groups:

- 1) No abnormalities - NORMAL
- 2) Increased prevalence of ineffective waves resulting from low amplitude or incomplete peristalsis

- 3) Increased intrabolus pressures indicating outflow obstruction
- 4) Increased prevalence of simultaneous waves

These groups were classified to provide a functional assessment in an effort to explain the patients symptoms. Dysphagia can be explained in terms of inadequate propulsion, functional obstruction at the level of the LES, and a functional obstruction from esophageal body spasm, for groups 2, 3, and 4 respectively.

12.3 RESULTS

Forty patients, mean age 53 years (range 25-85) were studied. Four of these had no dysphagia. Two of these patients had chestpain and no dysphagia and ambulatory manometry was consistent with a diagnosis of nutcracker esophagus, i.e., high amplitude contractions with normal peristaltic progression, but with no evidence of an increased intrabolus pressure. Another patient with the complaint of chestpain without dysphagia was normal on ambulatory manometry but the patient experienced no pain during the study. The last of these patients had nutcracker esophagus and normal intrabolus pressures. On ambulatory monitoring, the patient was noted to have high amplitude contractions of normal progression, but had episodes of reflux induced "spasm" which correlated with the patients symptoms (an example of this phenomenon is shown in another patient in chapter 8, figure 8.7).

The thirty six patients with dysphagia were reclassified into the functional categories as shown in figure 12.1. Five of these patients (14%) had no abnormalities on ambulatory manometry and no cause for their symptoms could be ascertained. In one patient with intermittent dysphagia an increased intrabolus pressure was the only abnormality found after all investigations. Expectant therapy was advised but the dysphagia progressed and seven months later stationary manometry revealed severe deterioration of function with hypomotility as well as increased simultaneous waves consistent with DES.

Ambulatory Manometry	↑ Simultaneous Waves (body)			
	↑ Intraabdominal Pressure (LES)			
	Hypomotility			
	Normal			
		Normal	NSEMD	Nutcracker

Stationary Manometry

Figure 12.1 Classification of patients with non-obstructive dysphagia based on the functional defect.

12.4 DISCUSSION

This study applies the results of ambulatory manometry to patients with dysphagia and/or chest pain in whom no clear diagnosis was possible on standard investigations. The patients were classified according to functional abnormalities on the basis of the ambulatory manometry results, in an attempt to provide an explanation for the patients symptoms. Previous attempts at functional classification systems have been based on stationary manometry and, although innovative, suffer the same limitations prescribed by performance of only 10 swallows.^{33,121}

Non-obstructive dysphagia, the symptom associated with impedance of the normal progression of a food bolus into the stomach, can be conceived to result from three functional defects. Firstly, low amplitude contractions, incomplete (failed) peristalsis, or the non-transmission of pharyngeal swallows to the esophageal body result

in failure of the propulsive mechanism of the esophageal body. Second, a defect in the normal progression of peristalsis results in simultaneous waves which impede the bolus in the esophageal body as in diffuse esophageal spasm. Third, an increased resistance to outflow because of incomplete anatomical relaxation of the sphincter results in impedance of the bolus at the LES. Using this classification system the ambulatory esophageal manometry provided a functional basis for dysphagia in all but 5 patients. Viewed in another way, the addition of ambulatory manometry provided an explanation for dysphagia in 31 of 36 patients (86%), in whom no diagnosis before ambulatory manometry could be made. The frustration in attributing patients symptoms based on stationary manometry alone is demonstrated by the conclusions of some that the symptoms may not be related at all to esophageal motor disturbances.¹²²

This study substantiates the findings of others that patients with NSEMD have a selective impairment of semisolid emptying when studied with radioscintigraphic techniques.³⁰⁵⁻³⁰⁹ In the present study, ambulatory manometry enabled all of the patients with NSEMD to be classified into one of the functional abnormality groups. It also underscores the importance of circadian monitoring in patients in whom the diagnosis is uncertain after standard investigations, since it provides insight into the pathophysiologic mechanism responsible for the patient's symptoms. Furthermore, since the study can be performed at the same time as pH monitoring, it would be prudent to perform ambulatory manometry in all patients with non-obstructive dysphagia while undergoing pH studies.

Using the criteria described in the previous chapter on DES, 14 of 36 (39%) patients in this group with dysphagia exhibited characteristics of diffuse esophageal spasm. Three of these patients underwent long esophageal myotomy on the basis of the ambulatory manometric results alone. All had a good to excellent symptomatic outcome.

In this study, all patients with chest pain but without dysphagia were found to have nutcracker esophagus on ambulatory manometry, and all had normal intrabolus pressures. On the other hand, all patients with DES on ambulatory manometry had dysphagia. This suggests that patients presenting without dysphagia are unlikely to be diagnosed as DES even after ambulatory manometry. This reinforces the concept that

simultaneous waves impede propagation. The patients with nutcracker esophagus and a delayed esophageal transit recently reported,³¹⁰ may in fact have had diffuse esophageal spasm which would only have been detected on ambulatory studies. In the present study four of the ten patients (40%) with nutcracker esophagus had an abnormal prevalence of simultaneous waves in keeping with the diagnosis of DES. This is consistent with reports of transition from nutcracker esophagus to DES.⁷⁴ The normal intrabolus pressures in the patients without dysphagia, supports the theory that an increased intrabolus pressure is indeed related to an increased outflow resistance.

This classification is currently being applied prospectively at USC, since it provides a rational approach to therapy which is directed at improving the functional defect as seen on ambulatory manometry. It is believed that ambulatory manometry will become a valuable tool to assist with management decisions for this previously enigmatic group of patients.

CHAPTER 13: ASSESSMENT OF ACID CLEARANCE USING SIMULTANEOUS AMBULATORY PHARYNGOESOPHAGEAL MANOMETRY AND pH MONITORING⁵

13.1 BACKGROUND

Esophageal exposure to gastric juice is a function of both the number of reflux episodes and the ability of the esophagus to clear the refluxed material rapidly and restore a normal luminal pH. While much work has been done concerning the barrier function of the lower esophageal sphincter, relatively little is known about the clearance function of the esophageal body. The earliest work was done by Meltzer in the beginning of this century, who made the distinction between primary and secondary peristalsis.^{5,162} The former was initiated by a pharyngeal swallow, and the latter occurred "spontaneously" in the absence of a pharyngeal contraction. Rapid distention of the esophagus with a balloon, or instillation of hydrochloric acid was subsequently shown to initiate secondary peristaltic contractions.³¹¹⁻³¹³ Consequently, secondary peristalsis was assumed to be a mechanism whereby the esophagus cleared refluxed acid.³¹⁴ Subsequently, secondary contractions were found not to be as organized as previously thought.³¹⁵ Helm and Dodds have also emphasized the importance of swallowed saliva in restoring normal luminal pH.^{316,317} These concepts have been based on studies performed in an unphysiologic laboratory environment over short time periods, utilizing a limited number of swallows and provocative maneuvers. The actual response to naturally occurring reflux episodes over a circadian cycle outside of the laboratory is unknown. By using the technology to simultaneously record intraluminal pH and pressures in the ambulatory subject, the mechanisms responsible for clearance of naturally occurring reflux episodes from the esophagus could be studied for the first time.

⁵ This study was published in *Annals of Surgery*, 1993;213,364-370

13.2 PATIENTS AND METHODS

13.2.1 Study Population

Ten normal subjects (median age 34, range 26-38) and fourteen patients (median age 51, range 15-83) with gastroesophageal reflux proven by 24-hour pH monitoring were studied. Normal volunteers were asymptomatic and had a video esophagram to exclude the presence of an anatomic abnormality. All patients had increased esophageal acid exposure by criteria previously described.¹⁸⁵ Normal subjects and patients underwent stationary manometry using the station pull-through technique to identify the position of the lower esophageal sphincter for the placement of the ambulatory pH and motility catheters.

13.2.2 Ambulatory pH and motility monitoring

Simultaneous pH and manometry was performed with a glass Ingold pH probe and a 7 French Sentron Catheter according to the protocols outlined in chapter 4 on all subjects. The 7 French ambulatory motility catheter contained a pharyngeal transducer so that pharyngeal swallows could be flagged.

13.2.3 Analysis

The pH and motility records were analyzed for the upright interprandial and the supine periods. Reflux periods were analyzed separately. The start of a reflux episode occurred when the pH of the esophagus fell to below pH 4 and ended when it returned to 4. Standard criteria for the classification of waves and propagation as outlined previously were used. Swallows were recognized by a rapid rise in the pressure in the pharyngeal channel and were called non-transmitted if they were not followed by a contraction wave in the esophageal body (figure 13.1). Waves were called primary if they followed a pharyngeal swallow and secondary if they occurred unrelated to a pharyngeal swallow (figure 13.2). Clearance of a reflux episode from the esophagus occurred when the pH rose to above 4. The pharyngo-esophageal activity just prior to the return of esophageal pH to normal, i.e., above pH 4, was assumed to be responsible

for this change.

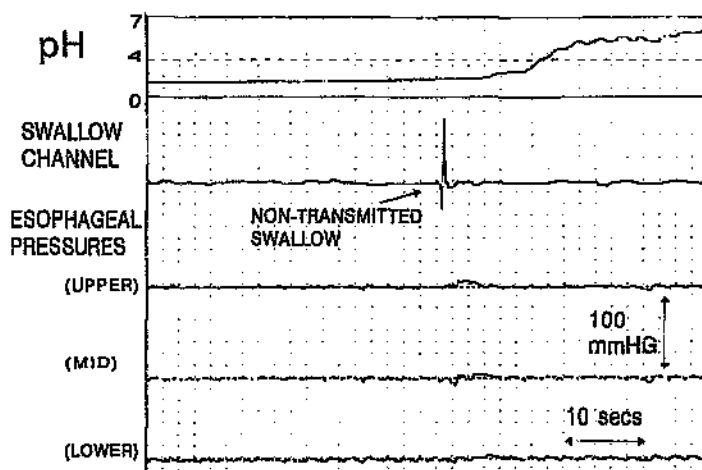


Figure 13.1 An example of the simultaneous recording of pharyngoesophageal motility and esophageal pH showing clearance of the esophagus by a non-transmitted swallow.

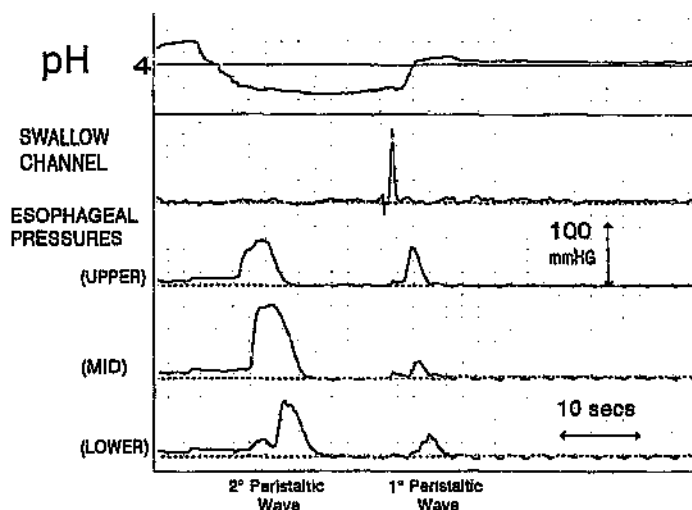


Figure 13.2 An example of the recording demonstrating a secondary peristaltic wave occurring soon after the onset of the reflux episode. A primary peristaltic wave cleared the esophagus of acid.

The frequency of swallows was calculated for the reflux periods during the day and night, and for the non-reflux baseline period during the day. The latter was obtained by calculating the swallowing frequency for six random 10 minute interprandial periods that were not related to reflux episodes. The first two hours were excluded to allow for accommodation to the catheter and to minimize any increased swallowing frequency that may have accompanied the sensation of the tubes in the nasopharynx.

Statistical analysis was performed with the aid of a commercially available software program (SAS 6.04, SAS institute Inc. Cary, NC). The Fisher exact test was used to compare proportions and the Wilcoxon rank sum test was used for comparisons of means.

13.3 RESULTS

A total of 1288 reflux episodes were analyzed. Of these, 173 occurred in normal subjects, 168 during the day and 5 during the night; 1115 occurred in the patients, 840 during the day, and 274 during the night. During reflux episodes, the pharyngeal swallowing frequency increased (figures 13.3, 13.4) and a total of 2781 esophageal contraction waves occurred. Three hundred and four of the waves occurred in the normal subjects; 296 during daytime and 8 during night-time reflux episodes. In patients, 2477 waves occurred, 1615 during daytime and 862 during night-time reflux episodes. During the cumulative reflux period, primary waves, i.e., waves that followed a pharyngeal swallow, predominated, whereas secondary waves i.e., spontaneous waves unrelated to a pharyngeal swallow, were uncommon (figure 13.5). When the secondary wave was peristaltic it almost always occurred as the first motor event of a reflux period, otherwise it occurred in a random order. Only 19% (74/386) of the secondary waves were peristaltic.

Figure 13.6 shows the effectiveness of the various waves in clearing the esophagus of acid in normal subjects and patients. Primary peristalsis was responsible for clearance of the majority of reflux episodes in normal subjects and patients. Overall, 94% of reflux episodes were cleared by a pharyngeal swallow followed by a primary peristaltic wave or a non-transmitted pharyngeal swallow. Secondary peristaltic waves were responsible for clearing only 9 of the 1288 episodes.

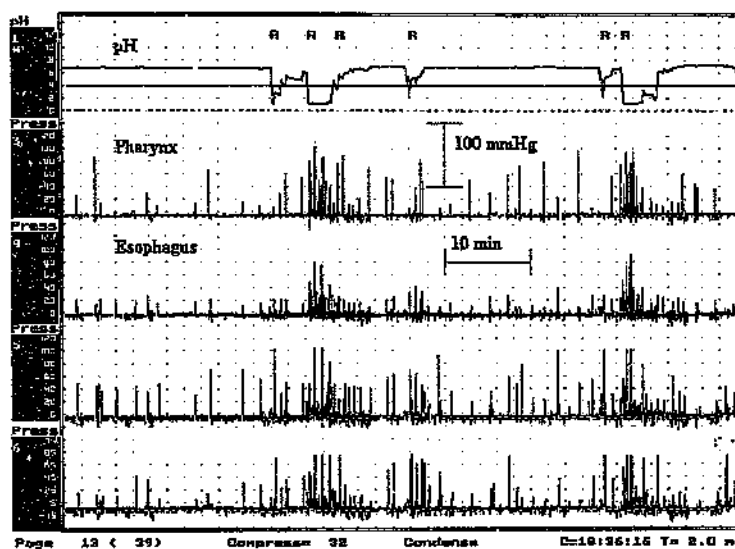


Figure 13.3 An example of the recording which has been compressed to show an 80 minute period. Note the increased frequency of pharyngeal swallows during reflux episodes.

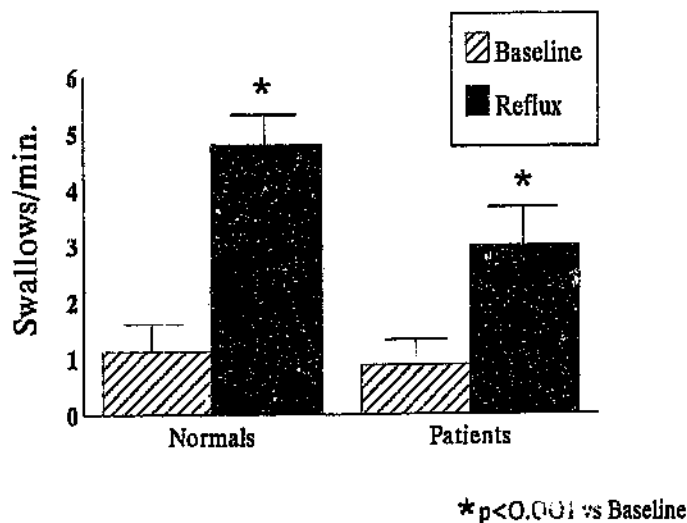


Figure 13.4 The frequency of swallowing during the baseline non-reflux and the reflux periods for normal subjects and patients with reflux disease.

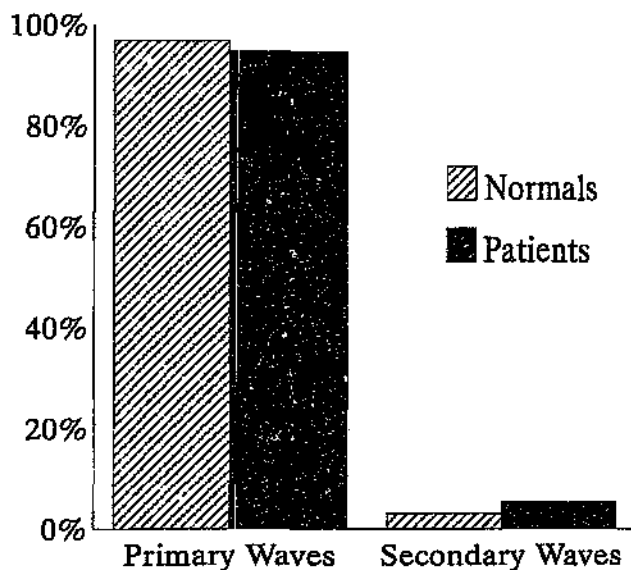


Figure 13.5 The prevalence of types of waves occurring during reflux episodes in normal subjects and patients.

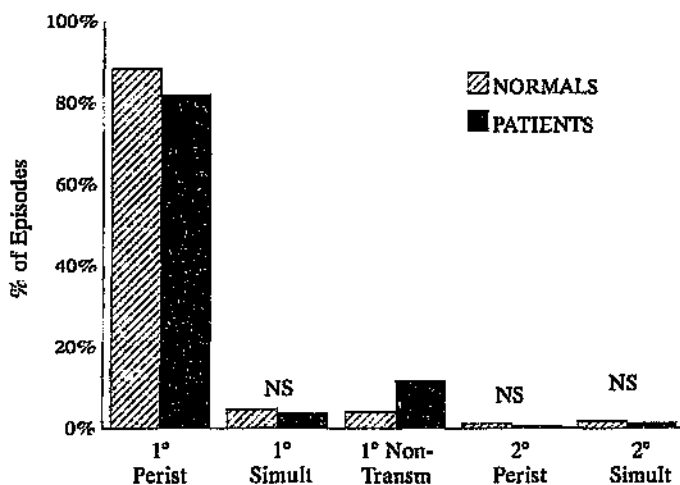


Figure 13.6 The types of contractions that resulted in acid clearance from the esophagus. Most reflux episodes were cleared by a pharyngeal swallow followed by a primary wave.

The effect of gravity on clearance was assessed by comparing, in the patients, night-time with daytime reflux episodes. Normal subjects were excluded because night-time reflux was an uncommon event. Of interest, some reflux episodes were cleared by non-transmitted swallows during the daytime when the patient was upright (figure 13.7).

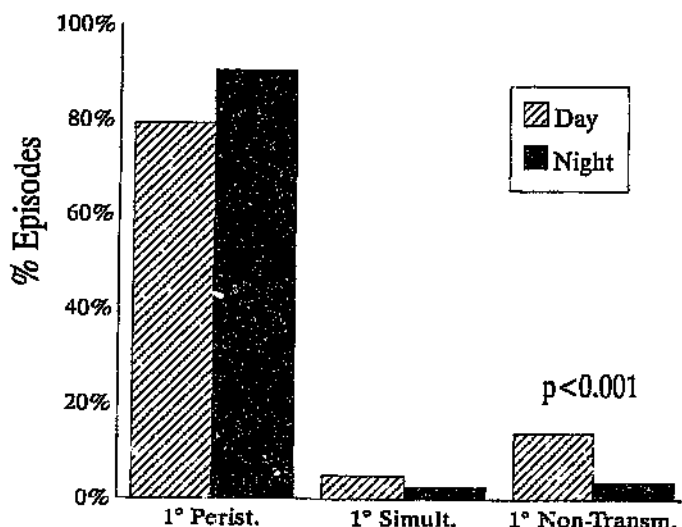


Figure 13.7 Types of contractions responsible for clearing daytime and nighttime reflux episodes in patients with reflux disease.

Night-time reflux episodes were of longer duration and required a greater number of primary waves per episode for clearance (figure 13.8). The swallowing frequency during a night-time reflux episode was lower than a daytime episode, and the response was frequently delayed (figures 13.9, 13.10).

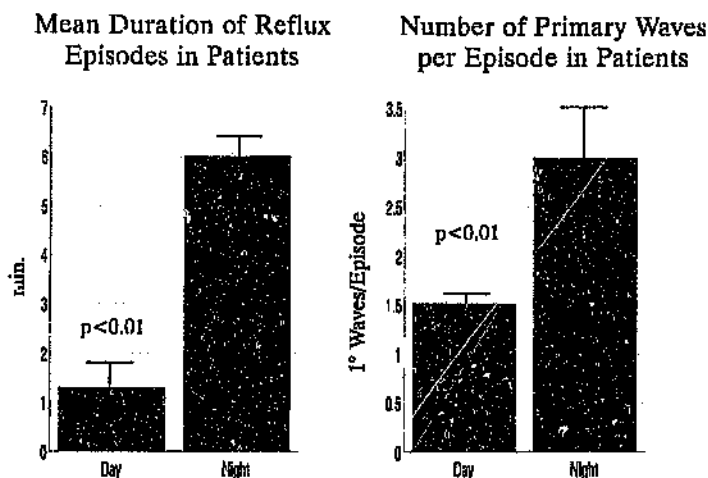


Figure 13.8 The mean duration of reflux episodes and the number of primary waves per reflux episode in patients during the day and during the night

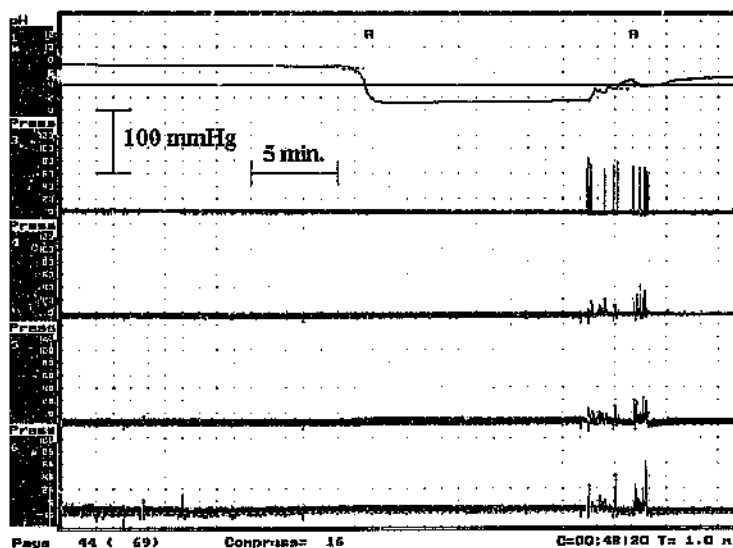


Figure 13.9 An example of a recording showing a reflux episode occurring at night. The swallowing response to reflux is delayed, resulting in a prolonged reflux episode.

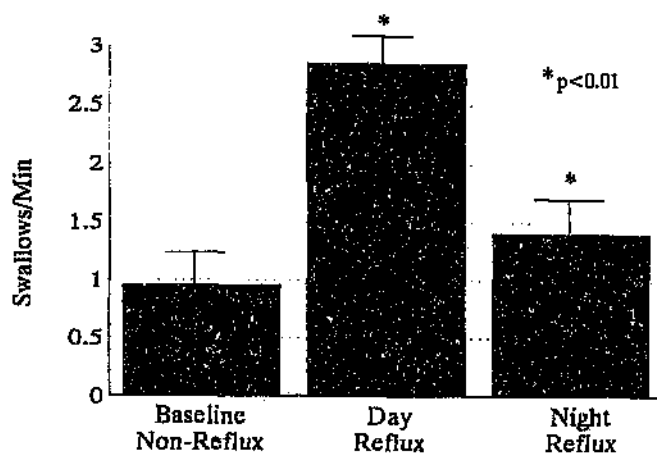


Figure 13.10 The swallowing frequency in patients during the baseline period, and during daytime and nighttime reflux.

13.4 DISCUSSION

Observations that the infusion of acid, or the distention of the esophageal lumen, can stimulate esophageal contractions, have led to the widely-held view that refluxed gastric juice is cleared from the esophagus without the aid of pharyngeal swallows. Contrary to this view, we have found that secondary peristaltic waves are uncommon and do not play an important role in esophageal acid clearance. Even when stimulated, 80% of the secondary waves were simultaneous in character and ineffective in clearing the esophagus of acid. This is in agreement with Paterson and colleagues, who noted that with balloon distention, secondary waves were less often peristaltic than previously thought.³¹³

It is important to make the distinction between chemical and volume esophageal clearance. The former is the restoration of esophageal pH to normal, i.e., to above pH 4, while the latter refers to clearance of a bolus of food or liquid. While peristalsis, whether primary or secondary, may clear the volume of refluxed acid from the esophageal body, pharyngeal swallowing is all-important in chemical clearance. This is due to the neutralizing effect of swallowed saliva, as documented by Helm and

colleagues.^{316,317} The finding in our study that non-transmitted pharyngeal swallows can result in chemical clearance in a significant number of instances supports this view. An example of this is seen in figure 13.1. In this situation, saliva, after being transported from the pharynx into the upper esophagus by a swallow, flows down the esophagus aided by gravity. This is supported by the observation that non-transmitted swallows rarely result in the clearance of night-time reflux episodes, since in the supine position, the movement of saliva down the esophagus is not assisted by gravity. These findings are in concordance with a recent report that patients with xerostomia have longer reflux episodes and more severe esophagitis than patients with normal salivation.³¹⁸

It is interesting that the frequency of swallowing increases during reflux episodes. This may represent a learned, protective mechanism that depends on mucosal sensitivity. Two of our patients failed to increase the swallowing frequency during reflux episodes, and both had severe mucosal damage, which may have destroyed their mucosal sensitivity. Also, sleeping may dull the response of the esophagus to acidification, as seen in figure 13.9. This may explain why there is a lower swallowing frequency during night-time than daytime reflux. Similarly, sleeping also reduces salivation, and this may further contribute to the prolonged duration of night-time reflux episodes. Consequently, night-time reflux is particularly injurious, since the esophagus is less protected by the mechanism of increased swallowing, salivation is reduced, and the beneficial effects of gravity are lost. A common argument against esophageal intubation studies is that the findings can be explained solely by increased swallowing frequency caused by catheter irritation of the pharynx. The observation that swallowing frequency was increased during reflux episodes goes against this argument. Further, others have shown that naso-esophageal intubation increases salivation, but not swallowing, and its effect on salivation lasts for only two to four hours.²²¹ To minimize the effect of the initial increased salivary flow that may be related to catheter irritation, the first two hours of each study were excluded from analysis.

The important clinical implication of these findings is that normal subjects and patients clear the esophagus of refluxed gastric juice using the same mechanism — pharyngeal swallowing, followed by primary esophageal peristalsis. It is unlikely, therefore, that medical therapy, aimed at improving contraction amplitude and

frequency, will improve this protective mechanism. This is probably why prokinetic agents, when used alone, are unable to give satisfactory results in the treatment of patients with gastroesophageal reflux disease. Rather, the focus should be on reducing the number of reflux episodes and the volume of refluxed material. This may be accomplished by surgically reconstructing the barrier between the esophagus and the stomach. The loss of this barrier has been repeatedly identified as a common finding in patients with severe reflux disease. The re-establishment of a high pressure zone with an antireflux procedure has been an effective and lasting long-term therapy for this disease. This should be done, however, before the protective clearance mechanisms of the esophageal body have been lost from repetitive inflammatory injury.

13.5 CRITICAL EVALUATION AND COMMENT

In this chapter only 10 normal subjects were studied with a pharyngeal transducer for flagging swallows. In the following chapter 12 normal subjects were studied. The number of subjects was not changed in this chapter since the study has been published with the data presented above from 10 normal subjects.

CHAPTER 14: MECHANISMS OF ESOPHAGEAL ACID CLEARANCE IN PATIENTS WITH BARRETT'S ESOPHAGUS⁶

14.1 BACKGROUND

The exposure of the esophagus to gastric juice is dependant on the amount refluxed and on the ability of the esophagus to recognize the presence of gastric juice and to clear it with active contractions. The quantity of refluxed juice over time is dependant on the number of reflux episodes and on the volume of each episode. These have been shown to be a function of the competency of the lower esophageal sphincter, and of various gastric factors such as hypersecretion, gastric distention, and a persistent gastric reservoir.^{178,226,319-323}

The duration of contact of gastric juice with the esophageal mucosa depends on the clearance function of the esophageal body. In the past, attention has been focussed on the contribution of salivation and esophageal body function to the clearance ability of the esophagus. Helm has shown that clearance usually takes place in a two-step process.^{317,324} First, a peristaltic wave clears the volume of the refluxed material, and swallowed saliva then neutralizes the remaining acid. The two elements of salivation and motility are consequently both necessary, but depend on the initiation of peristalsis by a swallow. This is an area that has not previously received much attention.

In the previous chapter it was shown that the normal response to naturally occurring reflux episodes is to increase the frequency of swallowing.¹⁷⁰ This acts to clear the esophagus of refluxed gastric contents quickly, so that the contact time of the esophageal mucosa with gastric juice is minimized. Acid clearance in patients with Barrett's esophagus is known to be compromised but the reasons for this are not clear. The aim of this study was to examine for the first time the physiologic esophageal acid clearance mechanisms in patients with Barrett's esophagus using the technique of

⁶ This study was presented at the American Gastroenterology Association in San Francisco, 1996

simultaneous ambulatory pH and pharyngo-esophageal motility monitoring.

14.2 METHODS

Twelve normal volunteers and 14 patients with Barrett's esophagus were studied. Volunteers were screened by questionnaire and were included only if asymptomatic and without a history of previous upper abdominal surgery. They underwent videoesophagography in order to exclude the presence of anatomical abnormalities. Consecutive patients with Barrett's esophagus were selected from a pool of patients presenting to the University of Southern California Swallowing Center with foregut symptomatology. Barrett's esophagus was determined by endoscopically directed biopsy. Only patients with specialized epithelium were included. For the purposes of this study the endoscopically measured length of the Barrett's segment was used to group the patients into those with a shorter columnar segment (SCS, 3-5 cm, nine patients) and those with a longer columnar segment (LCS, 9-13 cm, five patients). There were no patients with columnar segments of between 5 and 9 cm.

After an overnight fast all subjects underwent standard manometry as previously described. Abnormal body motility was defined by the 95th percentile of normal volunteers.^{34,35} Amplitudes of contractions, peristaltic nature, and prevalence of interrupted or dropped contractions were used to determine normal or abnormal motility as these parameters have previously been found to correlate with esophageal volume clearance.¹⁵⁸ After stationary manometry simultaneous ambulatory pH monitoring and pharyngo-esophageal manometry were performed according to the protocols outlined in chapter 4. Ambulatory manometry parameters were defined as abnormal if they fell outside the 5th and 95th percentiles of the 25 normal volunteers discussed in chapter 7.

Measurements of swallowing during reflux episodes were made according to figure 14.1;

- 1) The time from the onset of the reflux episode to the first swallow, (a)
- 2) The duration of the reflux episode (a+b)
- 3) The total number of swallows (X) during the episode.

From this analysis the average swallow frequency for each reflux episode was calculated. The reflux episodes were further categorized as occurring during the day or

during the night. The baseline swallowing frequency was calculated from six randomly chosen 10 minute periods for both the daytime and the nighttime periods that were not within 10 minutes of a reflux episode.

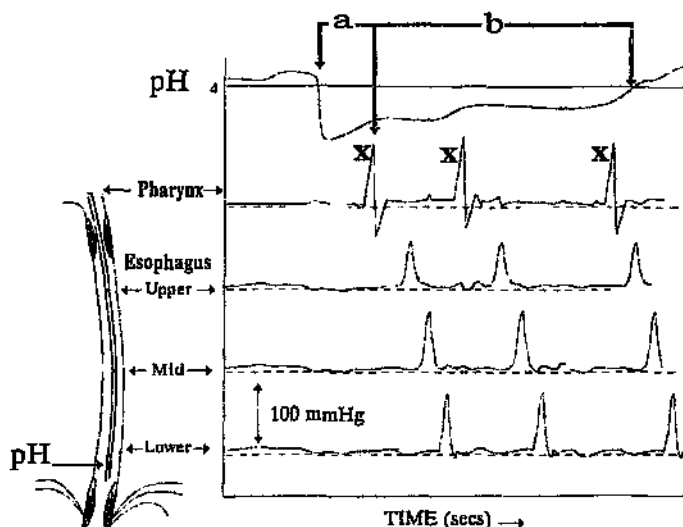


Figure 14.1 Graphical representation of a portion of the ambulatory recording showing the measurements made during reflux episodes. See text for explanation.

14.2.1 Statistics

Data are expressed as means $\pm$ SEM. The Mann-Whitney U test was used to compare differences between groups. Statistical studies were performed with the aid of a computer program (SPSS for windows version 6.01, Chicago, Illinois). Significance was determined at the 5% level (NS denotes not significant).

14.3 RESULTS

Table 14.1 shows the stationary manometric data. As expected, patients with Barrett's esophagus had defective sphincter characteristics and lower contraction amplitudes in the distal esophagus compared to normals. Eight patients, however, had

normal esophageal body characteristics by stationary manometric criteria. Table 14.2 shows the ambulatory manometric results. By ambulatory manometric criteria only 2 patients had normal motility. Strikingly, the Barrett's patients were unable to increase the overall prevalence of effective contraction waves during meal periods when compared to the upright interprandial period as was characteristic of the normal volunteers (normals $39 \pm 3.3\%$ upright vs $58 \pm 3.8\%$ meals, $p=0.015$, Barrett's $26 \pm 4.3\%$ upright, vs $29 \pm 4.0\%$ meals, $p=NS$).

Table 14.1 Lower esophageal sphincter and esophageal body characteristics by stationary manometry.

PARAMETER	NORMALS	BARRETT'S	SIGNIFICANCE
LES			
Overall Length	3.38 ± 0.97	2.43 ± 0.36	$p=0.003$
Abdominal Length	1.91 ± 0.55	0.93 ± 0.11	$p=0.001$
Pressure	16.84 ± 4.86	6.89 ± 1.33	$p=0.001$
Esophageal Body*			
Amplitudes (mmHg)			
Channel 1	90 ± 8	92 ± 14	NS
Channel 2	51 ± 9	42 ± 6	NS
Channel 3	94 ± 8	62 ± 9	$p=0.01$
Channel 4	112 ± 8	56 ± 7	$p=0.001$
Channel 5	99 ± 13	44 ± 3	$p=0.02$

* Channel 1 = proximal, channel 5 = distal

Overall, the Barrett's patients had a greater number of reflux episodes than normal subjects (49.0 ± 5.41 vs 17.75 ± 4.13 , $p=0.0005$), longer reflux episodes than normal subjects (mean duration in minutes 4.35 ± 0.67 vs 0.56 ± 0.12 , $p<0.0001$), and as a consequence, a greater percent time the pH was less than 4 for the 24 hour period ($21 \pm 4.5\%$ vs 1.24 ± 0.33 , $p<0.0001$).

Swallow responses to daytime reflux episodes in patients with Barrett's were compared to responses in normal subjects. Nighttime reflux episodes were compared to daytime episodes in the same patient. This was done because normal subjects had few nocturnal reflux episodes. Baseline swallowing frequency during reflux free periods was the same for normal subjects and patients with Barrett's esophagus (1.12 ± 0.1 VS

1.1±0.07 swallows/min). Patients with Barrett's esophagus had a diminished swallow response to daytime reflux episodes characterized by a longer time to the first swallow, and a lower swallow frequency (Figures 14.2, 14.3). Nighttime reflux episodes in patients with Barrett's esophagus were characterized by a further blunting of the swallow response (frequency: 2.39±0.18 swallows/minute for the day, vs 1.44±0.27 night, $p=0.02$). The number of swallows per reflux episode was increased in patients with Barrett's esophagus (1.7±0.14 vs 3.84±0.5, $p=0.001$).

Table 14.2. Ambulatory motility characteristics of normal subjects and patients with Barrett's esophagus.

PARAMETER	NORMALS	BARRETT'S	SIGNIFICANCE
AMPLITUDE (mmHg)			
<u>Upright</u>			
Channel 1*	34±2	42±5	NS
Channel 2	40±3	36±3	NS
Channel 3	43±4	36±3	NS
<u>Meal</u>			
Channel 1	51±3	55±8	NS
Channel 2	59±5	38±2	$p=0.0008$
Channel 3	72±7	38±3	$p=0.0003$
<u>Supine</u>			
Channel 1	38±4	38±4	NS
Channel 2	47±4	39±5	NS
Channel 3	52±4	36±4	$p=0.022$
PERISTALTIC WAVES (%)			
Upright	81±4.0	71±4.5	NS
Meal	89±1.7	77±4.5	$p=0.03$
Supine	72±2.9	66±3.9	NS
% DROPPED			
Upright	7±2.2	17±3.3	NS
Meal	5±1.2	18±3.5	$p=0.0002$
Supine	10±2.5	15±2.7	$p=0.02$
EFFICACY (%)			
Upright	39±3.3	36±4.3	$p=0.013$
Meal	58±3.8	29±4.0	$p=0.0002$
Supine	33±4.8	21±4.5	NS

* Channel 1, 2, and 3 are 15, 10, and 5 cm above the LES respectively. (Channel 3 = distal)

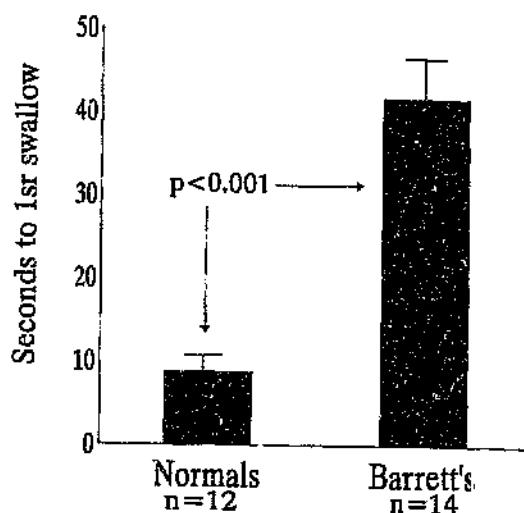


Figure 14.2 The average time (mean $\pm$ SEM) to the first swallow for the normal subjects and patients with Barrett's esophagus.

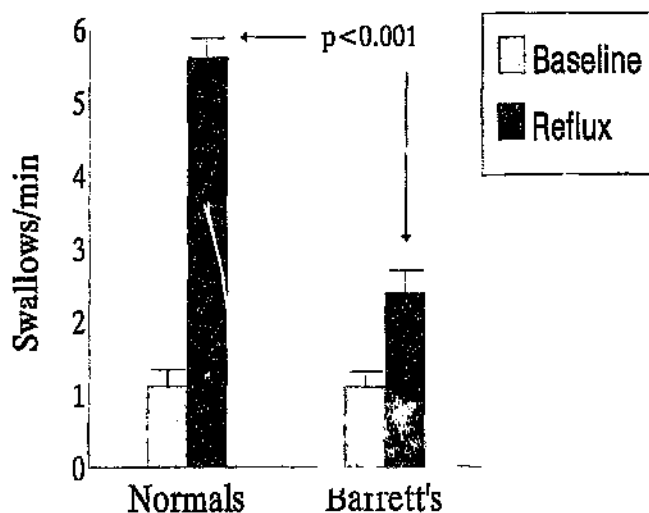


Figure 14.3 The mean $\pm$ SEM of the swallowing frequency during daytime reflux episodes for normal subjects and patients with Barrett's esophagus.

Acid exposure time was greater in patients with LCS than SCS (time below pH 4, 39.2 ± 3.2 % vs 12.3 ± 2.46 , $p=0.005$) despite similar ambulatory motility measurements for amplitude, peristalsis and efficacy (Table 14.3). Patients with LCS had a longer delay from the start of a reflux episode to the first swallow than those with SCS (figure 14.4) and a lower swallowing frequency during reflux episodes (figure 14.5). Despite this, the number of swallows per reflux episode was similar for patients with LCS and SCS (3.14 ± 0.36 vs 5.1 ± 1.1 , NS).

Table 14.3 Ambulatory motility characteristics of patients with SCS and LCS.

PARAMETER	<u>SCS</u>	<u>LCS</u>	SIGNIFICANCE
AMPLITUDE (mmHg)			
<u>Upright</u>			
Channel 1*	42 ± 6	44 ± 9	NS
Channel 2	32 ± 4	36 ± 4	NS
Channel 3	39 ± 4	30 ± 3	NS
<u>Meal</u>			
Channel 1	57 ± 11	52 ± 10	NS
Channel 2	38 ± 2	39 ± 2	NS
Channel 3	42 ± 4	30 ± 3	NS
<u>Supine</u>			
Channel 1	39 ± 5		NS
Channel 2	40 ± 6		NS
Channel 3	41 ± 6		NS
PERISTALTIC WAVES.(%)			
Upright	70 ± 6.6	72 ± 4.9	NS
Meal	72 ± 6.4	86 ± 2.9	NS
Supine	73 ± 5.9	62 ± 3.5	NS
EFFICACY (%)			
Upright	29 ± 5.4	20 ± 7.2	NS
Meal	31 ± 4.6	24 ± 7.7	NS
Supine	26 ± 6.3	11 ± 1.8	NS

* Channel 1, 2, and 3 are 15, 10, and 5 cm above the LES respectively. (Channel 3 = distal)

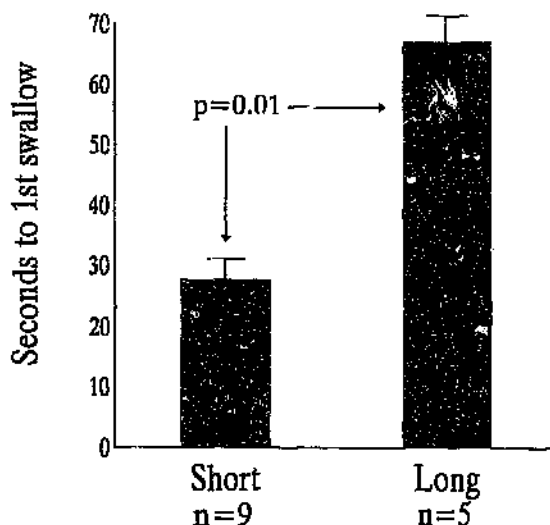


Figure 14.4 The average time (mean $\pm$ SEM) to the first swallow for patients with short (SCL) and long (LCS) columnar segments.

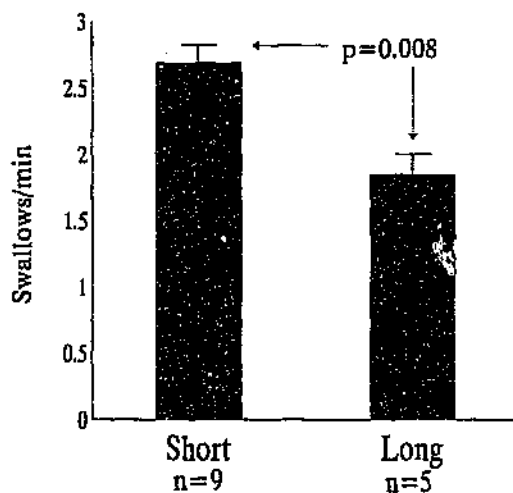


Figure 14.5 The mean $\pm$ SEM swallowing frequency during daytime reflux for patients with short (SCS) and long (LCS) columnar segments.

14.4 DISCUSSION

The overall length, abdominal length, and sphincter pressure were all markedly decreased in Barrett's patients when compared to normal subjects, supporting previous findings, and the paradigm, that lower esophageal sphincter incompetence is the main explanation for the increased episodes of reflux.^{133,321,322} Further, the long duration of the reflux episodes in patients with Barrett's esophagus compared to normal subjects indicates that their clearance function is also deficient and is an important contributor to the increased esophageal exposure to gastric juice.

Kahrilas has made a distinction between chemical and volume clearance.¹⁵⁸ Chemical clearance takes place by initially clearing the volume of the refluxed material and then neutralizing the remaining acid with swallowed saliva.³¹⁷ The neutralizing capacity of swallowed saliva is minimal when compared to the concentration of the refluxed gastric acid. Helm found that an intubated subject producing 1.2 ml of saliva per minute would require 5 minutes to titrate 1 cc of 0.1 N HCl from a pH 1.2 to pH 4.³¹⁶ Saliva, then, can only neutralize small volumes of remaining acid. Consequently deficient esophageal body function results in poor volume clearance resulting in prolonged exposure of the esophagus to refluxed gastric juice.^{124,127,158,249,317,324} On the other hand, inadequate salivation, as is found in xerostomia following radiation, also results in longer reflux episodes and overall greater esophageal acid exposure.³¹⁸ Helm has also shown that continuous aspiration of saliva after acid has been instilled into the esophagus results in prolonged clearance times, despite adequate swallowing.³²⁴ This would indicate that the complete neutralization of the mucosal surface is dependant on salivary function.

In the past most attention has been focussed on the manometric parameters of the esophagus with regard to clearance.^{127,249,325} Booth's original study on clearance found that subjects with poorer motor function of the esophagus required more swallows to clear the esophagus than normal volunteers.²⁵⁰ Patients with Barrett's esophagus, as a group, are known to have poorer esophageal body motility compared to normal volunteers.³²⁶ As a consequence, the number of reflux episodes lasting longer than 5 minutes and the duration of the longest episode exceeds that measured in normal

subjects or patients with esophagitis. In the present study the ambulatory manometry enabled a detailed assessment of esophageal motor function by analyzing more than 1000 contraction waves in a physiologic environment. This has provided insight into the motor function in patients with Barrett's esophagus that was not evident on stationary manometry. It showed that there is a profound defect in the ability of the esophageal contractions to be organized into effective peristaltic wave forms. Normally the amplitude of contractions, and the prevalence of peristaltic waves are increased during meals. This may be due to the stimulus of increased viscosity and volume of the swallowed food.^{138,141,232} Neuronal feedback from mucosal afferents in response to the bolus of food travelling down the esophageal body may be responsible for this phenomenon.¹⁴¹

The contribution of compromised motility to the prolonged reflux episodes is, however, difficult to ascertain. Previous studies using the standard acid clearance test were performed by infusing acid into the esophagus of the supine subject and having the subject swallow at specific intervals. In this situation abnormal motility has been shown to affect clearance times.^{250,251} But whether esophageal motility plays a similar role to clear refluxed juice in the upright position is not known. In this regard, it has been shown that non-transmitted swallows can result in chemical clearance of reflux episodes in the upright position.¹⁷⁰ In the upright position the relaxation of the LES that occurs with swallowing would allow gravity to assist the return of refluxed gastric juice to the stomach without the assistance of the propulsive action of the esophageal body. Swallowed saliva, presumably assisted by gravity, neutralizes remaining acid adherent to the esophageal mucosa. This is in concordance with observations that the upright position is associated with shorter acid clearance times when compared with the supine or head down position³²⁷. Consequently, it is likely that the importance of esophageal body function for clearing acid in the upright individual has been overplayed in that it has been indiscriminately applied to the upright position as well.

The clearance mechanisms involved in restoring esophageal pH to normal after naturally occurring reflux episodes in the upright position has not previously been studied in detail. The new technique of simultaneous ambulatory pH and pharyngo-esophageal manometry has enabled the investigation into the influence of swallowing

frequency on clearance in the upright position. Using this technology we have shown that the normal response to naturally occurring reflux episodes is to increase the frequency of swallowing.³²⁸ Presumably this response is secondary to afferent feedback from receptors in the esophagus which are sensitive to the noxious quality of the refluxed material. This concept is based on observations showing that acid infusion is associated with greater swallowing rates than water infusions.²¹⁴

In the present study we examined three other aspects of the clearance of a reflux episode, i.e., the time to the first swallow after the start of the reflux episode, the frequency of swallowing during the episode, and the number of swallows required for clearance. Patients with Barrett's esophagus exhibited a delayed time to the first swallow compared to normal subjects and an overall decreased frequency of swallowing during the reflux episode. This suggests that the reflex to swallow after esophageal acidification is somewhat depressed in these patients. Rodrigo has described afferent nerve endings that are found at variable depths of the stratified squamous epithelium.³²⁹ When the stratified squamous epithelium has been destroyed by reflux the mucosal afferents are presumably also destroyed. When the epithelial lining is replaced by columnar epithelium the afferent system may not regenerate, or the new epithelial cells may provide a barrier between the lumen of the esophagus and the deeper neuronal afferents.³³⁰ This barrier, or the loss of mucosal afferents, may also account for the decreased subjective pyrosis reported previously in patients with Barrett's esophagus.³³⁰⁻³³² The fact that even patients with Barrett's esophagus with normal motility had a blunted response, underscores the importance of the swallowing mechanism to esophageal acid clearance.

It has been shown that instillation of acid into the esophagus of normal subjects results in increased salivation.³³³ The response, however, occurs only with the conscious experience of heartburn. The normal volunteers in the present study did not experience heartburn and presumably, did not increase salivation. Consequently the increased clearance cannot be explained solely on this basis. Similarly, decreased salivation cannot be entirely excluded as a contributing mechanism to clearance in patients with Barrett's esophagus, since it has been shown that salivary flow may be decreased in patients with severe reflux disease.^{334,335}

Mittal recently showed that reflux can occur from a herniated stomach into the esophagus with the onset of LES relaxation after a swallow.³³⁶ This to-and-fro reflux could also explain, in part, the delayed clearance observed in patients with Barrett's esophagus. It has also been noted that a hiatal hernia may result in compromised body function because the lower esophagus is no longer anchored.³³⁷ A picture consistent with the concept of to-and-fro reflux was occasionally observed in the present study although this was not a common event. Whether the to-and-fro reflux came from the hernia or the stomach proper cannot be ascertained. It seems probable that this would be a more common phenomenon at night when the subject is supine without the effect of gravity. It is possible that this to-and-fro reflux may contribute to reflux episodes of long duration in patients with large hernias, small crural openings, and defective sphincters. It cannot, however, be the only explanation for the decreased time to the first swallow, which is likely to be a more accurate indicator of acid mucosal sensitivity.

We postulated that if acid sensitivity is due to mucosal receptors, then the amount of esophageal mucosal replacement with Barrett's mucosa should be related to the degree of loss of acid sensitivity. For this reason we chose to categorize patients into those with a short columnar segment ($< 5\text{cm}$) and those with a long columnar segment ($> 9\text{cm}$). The LCS patients had a longer time to the first swallow and a lower swallow frequency during reflux. This supports the hypothesis of a progressive destruction of mucosal afferents by the metaplastic process. The ambulatory motility characteristics were similar for the SCS and the LCS although the latter had a tendency toward poorer motility in the lower esophagus.

The swallow response to reflux at night was further depressed in the Barrett's patients. This is in concordance with Orr *et al* who have shown that swallowing during sleep is related to the state of arousal as measured by EEG.²¹⁴ In his studies the arousal response in normal subjects was significantly greater with esophageal infusions of acid than with water infusions. This arousal response has also been shown to be modified by neuroleptic drugs.¹⁹⁵ The insensitivity of patients with Barrett's esophagus to nocturnal reflux results in a mucosal exposure to gastric juice for even longer periods than when awake.

If the swallow response to gastro-esophageal reflux is dependant on acid

sensitive nociceptors, the current ubiquitous use of acid suppression therapy has important implications. The reflux of alkalinized gastric juice would not initiate the normal clearance response. This may result in an even greater exposure time of the esophageal mucosa to gastric juice which may be noxious despite having a more neutral pH.

This study shows for the first time that there is an additional mechanism responsible for the prolonged esophageal acid exposure seen in patients with Barrett's esophagus. In these patients the swallow response to reflux episodes is defective. In addition, the lower esophageal sphincter is mechanically defective which results in more frequent reflux episodes of probably greater volume than normal subjects. The compromise in sphincter and clearance function results in excessive exposure of the mucosa to noxious substances in the refluxed juice. Recent studies have shown that the presence of duodenal juice in the refluxed juice is associated with a greater prevalence and severity of mucosal injury, particularly dysplasia, in patients with Barrett's mucosa.³³⁸ The only sure way of improving the situation would be to correct the defective sphincter. This is the defect that anti-reflux surgery is designed to correct. This would ease the burden on an already defective clearance function. Trying to improve the defective clearance with prokinetic agents in patients with Barrett's esophagus is likely to have little benefit since the problem appears to be one of poor recognition that a reflux episode has occurred.

CHAPTER 15: CONCLUSIONS

Advances in computer technology has stimulated the development of an automated system for monitoring and analyzing intraesophageal pressures and pH for prolonged periods of time. This thesis has described the development of the hardware and software necessary for the task, and the application of the system to normal subjects and to patients with a spectrum of motor disorders.

15.1 HARDWARE AND SOFTWARE DEVELOPMENT

The early bench testing of catheters and recorders, methods of data sampling and data reduction, and a description of the software development used for data analysis constitute the first part of the thesis. The developed system was capable of monitoring pressures from the pharynx and three levels of the esophagus, while simultaneously recording lower esophageal pH, for a full circadian cycle. Subjects were monitored in the physiologic environment of their own homes while performing normal activities of daily living which included eating and sleeping.

15.2 VALIDATION AND ESTABLISHMENT OF NORMAL VALUES

Prior to application to the clinical setting, the system was validated by comparing the automated analysis to the manual analysis by four physicians experienced in manometry. The system was found to be accurate and provided the advantage of objective, rapid, and automated analysis. Normal values were then established by studying 25 healthy volunteers sanctioned by the Institutional Review Board of the University of Southern California. Normal patterns of esophageal function during eating, sleeping and during normal activities of daily living were noted. The motor function of the normal esophagus was shown to improve significantly during eating, and to be relatively quiescent during sleeping. These patterns were shown to be altered early in many disease processes.

15.3 GASTROESOPHAGEAL REFLUX DISEASE

The use of ambulatory manometry in patients with gastroesophageal reflux disease demonstrated that contraction amplitudes in the middle and lower esophagus decreased with increasing severity of mucosal injury. The ability to increase the amplitude of contractions in the lower esophagus during meals was profoundly compromised in patients with mucosal injury compared to normal subjects and patients with no mucosal injury, a finding not predicted by stationary manometry. These patients may require tailoring of anti-reflux surgery to avoid post-operative dysphagia. The ability of ambulatory manometry to assist in this regard is now being prospectively evaluated at USC.

15.4 ACHALASIA

Patients with achalasia were found to exhibit occasional peristaltic contractions when monitored by ambulatory manometry. This phenomenon was uncommon and of little functional significance. A characteristic pattern of an increase in mealtime baseline pressure with repetitive isobaric contractions in the esophageal body was seen in patients with achalasia. Adequate myotomy reduced the mealtime baseline to normal and abolished the repetitive contractions. Postoperative ambulatory manometry could be used as a measure of the relief of outflow obstruction. Return of postoperative peristalsis was uncommon although this appeared to be related to the prevalence of pre-operative mealtime peristalsis.

15.5 HYPERTENSIVE LOWER ESOPHAGEAL SPHINCTER (HTLES)

Sixty two percent of the 13 patients with HTLES were found to have a more severe motor abnormality when studied with ambulatory manometry. This, together with the overlap of motility characteristics of diffuse esophageal spasm (DES) suggests a common etiologic origin between these two disorders. Study of the pressure dynamics during eating enabled quantitation of the intrabolus pressure as a measure of lower esophageal outflow obstruction. The increase in this intrabolus pressure in patients with HTLES has not previously been described and suggests an inadequate anatomic relaxation of the LES. This provides a possible strategy for future therapy in these

patients for the first time.

15.6 DIFFUSE ESOPHAGEAL SPASM

Motor abnormalities in patients with DES were characterized by:

- 1) An increased prevalence of simultaneous waves during all periods (mealtimes, upright awake, and supine). This was associated with an inability to improve the prevalence of peristaltic waves, and consequently wave efficacy, during the meal periods.
- 2) An increased amplitude of contractions in the upright and supine periods, but normal amplitudes during meals.
- 3) An increase in episodic high amplitude contractions (> 150 mmHg) and multi-peaked contractions.
- 4) An increase in the intrabolus pressure in the lower esophagus, indicating increased compliance or incomplete LES relaxation resulting in increased outflow resistance.

Most of these characteristics have been described in part previously, but ambulatory manometry has enabled clarification of these functional defects. It has also provided a guide as to when a long esophageal myotomy may alleviate symptoms in patients with this disease.

15.7 FUNCTIONAL CLASSIFICATION

The information provided by ambulatory manometry made it possible to categorize patients with an unclear diagnosis into a functional abnormality of either the esophageal body or the sphincter. Application of this new classification using ambulatory manometry provided an explanation for dysphagia in 86% of studied patients in whom no explanation was possible on stationary manometry alone. This has enabled therapy to be directed to the functional defect in this enigmatic group of patients. This is currently under prospective study at USC.

15.8 CLEARANCE

The ability to monitor esophageal pH simultaneously with pharyngoesophageal manometry enabled the study of gastroesophageal clearance mechanisms in the

ambulatory subject for the first time. Pharyngeal swallowing was found to be all important in clearing the esophagus of refluxed acid and was related to the state of consciousness at the time of reflux. Secondary peristalsis in the absence of pharyngeal swallowing was very uncommon and did not result in clearance. The frequency of swallowing increased during reflux episodes in both patients and normal subjects but was profoundly compromised in patients with Barrett's esophagus. Patients with Barrett's were also noted to have a delayed onset of the first swallow following the beginning of a reflux episode providing a further mechanism for the long duration of reflux episodes seen in these patients. These findings have important implications for therapy in patients with severe gastroesophageal reflux disease.

15.9 AMBULATORY MANOMETRY IN THE FUTURE: ONGOING RESEARCH

The established system of ambulatory manometry is currently being evaluated prospectively as a tool to direct therapy in patients with GERD, HTLES, and DES. The long-term effects of antireflux surgery and esophageal myotomy on the function of the esophageal body are currently under investigation in the department of Surgery at USC.

The system is available for use by other centers interested in esophageal manometry. The opportunity to study the effect of medications on esophageal body function is apparent but has not, as yet, been undertaken at USC. There are many other avenues open for research in the arena of primary motor disorders as the studies in this thesis have only begun to scratch the surface of this complicated area. It is believed that the ability of ambulatory manometry to evaluate esophageal motor function over a complete circadian cycle will provide the means for understanding the spectrum of disorders of esophageal body function.

CHAPTER 16. APPENDIX

APPENDIX A

SPECIFICATIONS OF THE MICRODIGITRAPPER VER. 5.0

Weight: 416 grams (14.7 oz).

Dimensions: 150 x 72 x 28 mm.

Power: Run by a 9 V alkaline battery and typically consumes 45 mA of current.

Memory: 4 megabytes

Display: 32 character liquid crystal display

Technical Outline

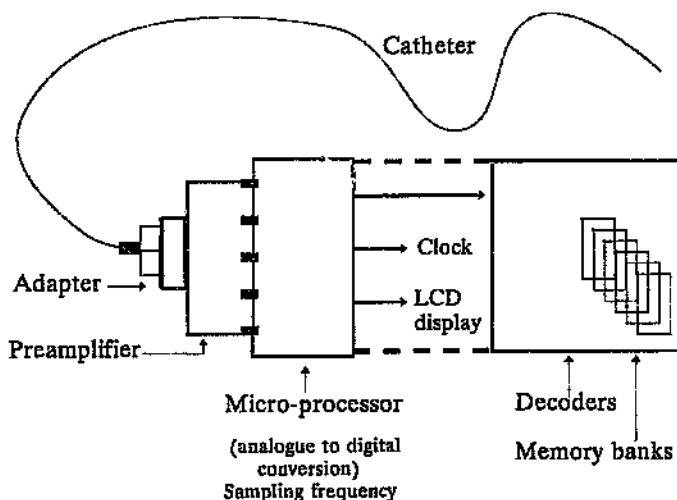


Figure A.1 Diagrammatic representation of the microdigitrapper.

The system contains preamplifiers which amplify and determine the frequency response and impedance of the analogue signal from the transducers (Figure A.1). The

APPENDIX A

Preamplifiers relay the analogue signal to the microprocessor which contains the analogue to digital converter (ADC). This converts the continuous analogue signal into digital data which is transferred to the microprocessor. This enables data reduction by using a decreased frequency sampling as discussed. The signal is then sent to the memory banks where it is stored as a charge. The banks are also associated with an operating system and an internal clock. These are connected to a display so that incoming data for storage can be displayed on the screen of the Microdigitrapper

In the Microdigitrapper ver 5.0, pseudostatic random access memories are used for data storage as these have a very high memory capacity per capsule. The Microdigitrapper can address 128 banks (0-127) each containing 32 kilobytes of memory. It has a total storage capacity of up to 4.194394 megabytes. It is equipped with a single permanent memory capsule of 32 kilobytes. Twenty four kilobytes are used for the operating system and 8 kilobytes are used for the stack pointer and other necessary registers. The memory is mapped into banks where 1 bank equals 32 kbyte and is divided into 128 "pages" where 1 page equals 256 bytes.

APPENDIX B

TECHNICAL SPECIFICATIONS OF THE SOLID STATE CATHETERS

The Konigsberg and the Sentron catheters have a rate-response of greater than 500 mmHg per second which is superior to the infusion systems used for stationary manometry. Table B.1 shows the differences in the technical specifications of the two catheters.

Table B.1 Technical Specifications of the Sentron and Konigsberg catheters.

SPECIFICATION	SENTRON	KONIGSBERG
Diameter	2.7 mm	4.65 mm
Material	Ducor soft polyurethane	Medical grade silicone
Sensor	Piezo-resistor bridge	Micro strain gauge array
Stability	3 mmHg/2 hrs 5 mmHg/24 hrs	< 2.5 mmHg/hour
Temperature shift	< 1 mmHg/°C	< 1 mmHg/°C
Sensitivity	5 μ V/V/mmHg $\pm$ 2 %	5 μ V/V/mmHg $\pm$ 2 %
Pressure operating range	-50 to +450 mmHg	-50 to +450 mmHg
Max allowable pressure	1000 mmHg	1000 mmHg

Tests run in a calibration column showed that both the catheters had negligible drift over 24 hours and that minor drift of up to 5 mmHg could easily be accommodated by utilization of a dynamic baseline in the software program used for analysis (Chapter 3). The Konigsberg catheter did require pre-test soaking in sterile water because the silicone coating of the transducer is hygroscopic. If not saturated with water the baseline can be affected by up to 20 mmHg as the catheter reaches saturation during the study in the lumen of the esophagus. The different signal from the two transducers

APPENDIX B

required different preamplifiers in the Microdigitrapp, so for testing purposes, one microdigitrapp was configured for the Konigsberg and one for the Sentron catheter.

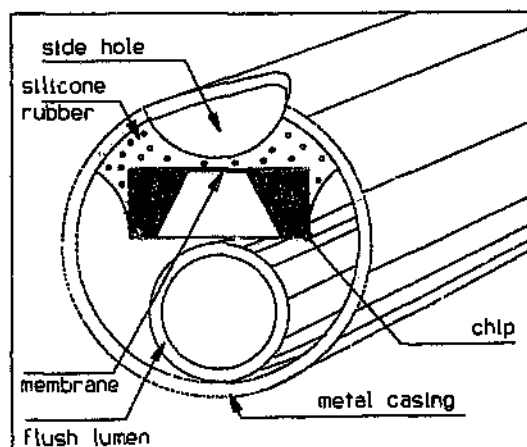


Figure B.1 Diagram of the design of the Sentron catheter.

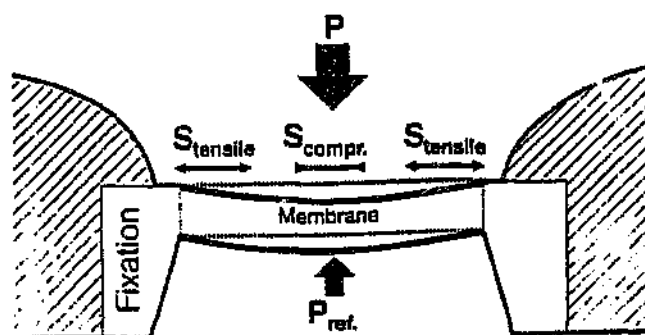


Figure B.2 Cross-section of the Sentron catheter pressure transducer.
P=pressure, S=stress

The design of the sentron catheter is shown in figure B.1 and a cross section of the compressible membrane covering the pressure transducer is shown in figure B.2.

APPENDIX C

MODIFICATIONS OF THE KONIGSBERG CATHETER

Comparison of the Konigsberg catheter with the Sentron catheter revealed two major differences; dimensions of the transducer and catheter, and the recession of the transducer surface from the catheter surface on the Sentron catheter. A modified catheter addressing the latter was then manufactured and tested. Figure C.1 shows how the surface of the transducer was recessed slightly from the surface of the rest of the catheter. However, further studies on normal volunteers showed that the cardiac interference still occurred although this was less common than with the original catheter. The larger surface area of the Konigsberg transducer resulted in detection of the heart beat and aortic pulsations, while the far smaller Sentron transducer did not.

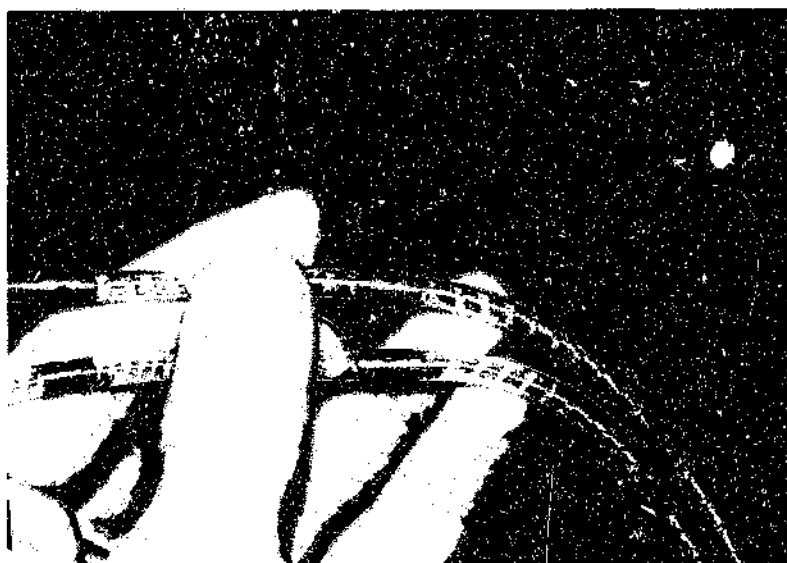


Figure C.1 Photograph to show the recessed silicone membrane covering the transducer on the modified Konigsberg catheter (above) compared to the original catheter (below).

APPENDIX C

Further modifications aimed at reducing the surface area of the Konigsberg transducer were discussed, but the cost of making the changes was very high. Consequently a decision was made to use the Sentron catheter only, accepting the risk of the fragility of the transducers. Use of the Sentron catheter ensured reliable recording of pressures for the 24 hours of the study. Transducer breakage did occasionally occur which necessitated replacement from Amsterdam, The Netherlands, as the catheters were custom manufactured. All of the studies in this project made use of the Sentron catheter and cardiac interference was not subsequently seen.

APPENDIX D**DEFINITIONS OF TERMS****Esophageal level/channel**

The esophagus is spanned by a catheter that measures pressures at three levels of the esophagus. These are referred to as levels and the transducers measuring these pressures are referred to as channels; an upper channel, a middle channel, and a lower channel.

Baseline

The mode value of datapoints calculated for each 60 second sector of the recording.

Threshold

A value which is set by the user which defines the level at which pressure changes should be considered for further evaluation.

Amplitude

The height of the pressure increase in mmHg measured from the baseline.

Duration

The period of time that a pressure increase exceeds the threshold.

Contraction

A pressure increase that is a consequence of esophageal muscle contraction. The pressure increase from an esophageal contraction has a certain morphology which enables computer recognition.

APPENDIX D**Valid contraction**

A pressure increase that exceeds the set threshold value for a determined period of time. The optimum threshold and duration criteria were calculated to be 15 mmHg and 1 second, respectively.

Recognized contraction

By virtue of the temporal relationship of low amplitude contractions to valid contractions in other levels of the esophagus, it was possible to establish computer algorithms to enable recognition of low amplitude contractions by "wave" analysis (see below).

Multipeaked contraction

A contraction that has more than two peaks. Contractions with two peaks are called double-peaked. Secondary peaks are recognized by virtue of the trough before the peak, the amplitude of the peak with respect to the amplitude of the highest peak, and the duration between the trough and the secondary peak (see Appendix E).

Repetitive contraction

A contraction that follows a previous contraction within a short period of time (less than 1 second). These contractions are considered part of the first contraction in that they are not stimulated by a pharyngeal swallow (see text).

Artifact

A pressure increase that exceeds the threshold but not for the required duration to establish it as a contraction, and, has no temporal relationship to valid contractions in the other levels of the esophagus, i.e., a pressure increase which is neither a valid nor a recognized contraction.

APPENDIX D**Cough**

A wave of simultaneous contractions where the amplitudes and durations are the same in all levels i.e., isobaric contractions, and the slope of the contractions (dP/dt) exceeds 100 mmHg/sec.

Isolated contraction

A valid contraction that bears no relation to another contraction in other levels of the esophagus.

Wave

A series, or sequence, of contractions that are recognized in different levels of the esophagus within a certain time frame (defined as 5 seconds between 2 channels which are 5 cm apart). This is an important concept as it enables analysis of peristaltic progression. Contractions only need to be recognized in two levels of the esophagus in order for a wave to be recognized.

Peristaltic wave

A wave in which the progression of contractions is sequential and orderly. The progression of contractions must be less than 20 cm/sec and greater than 1 cm/sec.

Simultaneous wave

A wave in which the contractions occur at the same time at different levels of the esophagus. The progression of contractions is defined as greater than 20 cm/sec.

APPENDIX D**Complete wave**

A wave which has contractions recognized in all three levels of the esophagus.

Interrupted wave

A wave which has two recognized contractions but a "missed" or "skipped" contraction in either the upper or middle esophageal channels.

Dropped wave

A wave in which a contraction is not recognized in the lowest level of the esophagus.

Effective wave

A complete peristaltic wave in which the contractions at each level meet a defined amplitude. These amplitudes were defined as 20, 25, and 30 mmHg for the upper, middle and lower esophageal levels respectively (see text), based on previous work done concerning bolus propagation using manoflourography.

Ineffective wave

A wave which is either simultaneous, interrupted or dropped.

Possibly effective wave

A complete peristaltic wave in which contractions in any of the levels of the esophagus do not meet the criteria for an effective contraction (i.e., less than 20, 25, and 30 mmHg for the three levels of the esophagus). This category was defined because it was unknown how gravity affects bolus movement of food in the upright position (see text).

APPENDIX E

ALGORITHMS FOR MULTYPEAKED AND REPETITIVE CONTRACTIONS

I. Multipeaked contractions

Clouse's definition³³ of a multipeaked contraction was used by Castell¹⁸¹ for the development of a software program for computer analysis of stationary esophageal manometry. A contraction was defined as having multiple peaks when additional peaks had an amplitude of at least 10% of the maximum peak for a period of at least 1 second. This definition was designed to exclude background noise from clinically relevant aberrations in contraction morphology. Multipeaked contractions are usually considered abnormal as they are exceedingly uncommon in normal volunteers. Richter found in a study of 95 normal volunteers that double-peaked waves were seen in approximately 11% of contractions on stationary manometry, but that triple peaked contractions constituted less than 1% of all contractions.³⁴ In the study by Costantini *et al*, no multipeaked contractions were found in 134 normal volunteers.³⁵ Multipeaked contractions have been associated with DES, but do not constitute a criterion for diagnosis.^{69,71,298} Castell notes that multi-peaked contractions may "indicate an underlying motility disorder".³³⁹ Kahrilas and Jacob have noted multipeaked contractions when studying patients with reflux esophagitis and non-reflux related dysphagia with combined synchronous videofluoroscopy and motility, but noted that they were not associated with any clearance dysfunction when they were not simultaneous or of low amplitude.^{127,340} This is probably because the bolus of barium was propagated with the onset of the upslope of the manometric contraction as seen on manofluorography.¹⁵⁸ How this relates to the swallowing of solid food in the upright position is not known.

In order to better understand what is meant by these terms we studied the tracings of these contractions manually. The morphology of multipeaked waves on stationary motility tracings and on printed ambulatory tracings from patients with a high number of bizarre wave forms was examined by four physicians with experience in

APPENDIX E

esophageal manometry. Contractions were chosen at random and the physicians made independent decisions on what constituted multi peaked or repetitive contractions. Based on these contractions, definitions of secondary peaks were made and compared to previous definitions of these forms of contractions.¹⁷¹

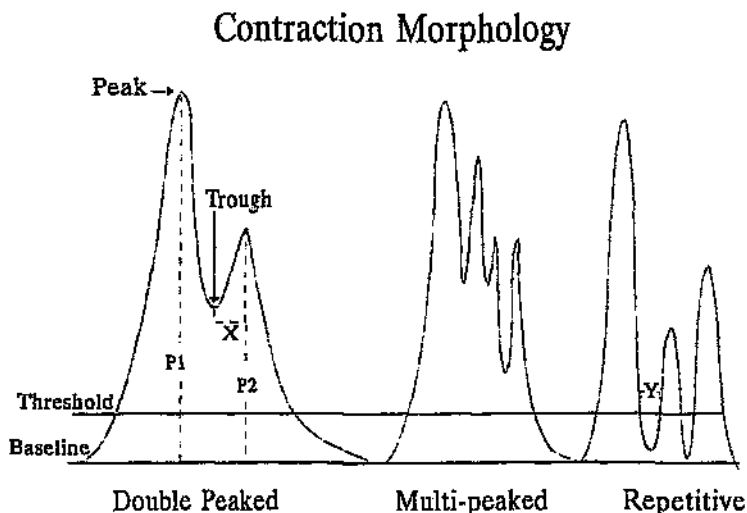


Figure E.1 Graphical representation of multi peaked and repetitive contractions.

The uncertain functional significance of the presence of multiple peaks made it difficult to define parameters for the computer to recognize such wave forms. There were two possible problems with Clouse's definition of multiple peaks as defined above. Firstly, the definition did not take into consideration the trough between peaks and could potentially register small pressure changes ("blips") in the descent of the contraction which were due to background noise (cardiac, respiratory fluctuations etc.) as secondary peaks. Secondly, in our experience, the first peak was not always the highest peak and if a wave had many peaks all with increasing amplitude the wave would not be recognized as a multi-peaked wave.

The computer program written for analysis of the stationary manometry in our laboratory used the concept of a significant trough prior to the onset of a second

APPENDIX E

upslope. This was done to avoid minor changes (eg. 1 mmHg) in the downslope of the contraction as being considered a secondary peak. Using this concept, and the criteria of Clouse and Staiano, a new definition was made. A secondary peak was identified if it had "significant" amplitude, "significant" duration, and occurred after a "significant" trough. These were defined as a trough of $> 10\%$ of the amplitude of the secondary peak, with a secondary peak amplitude of $> 10\%$ of the highest peak ($P2 > 0.1 \times P1$, in figure E.1), and a trough to peak duration (X) of > 0.5 seconds. While these numbers were somewhat arbitrary they were designed to identify bizarre contractions as recognized by physicians with extensive experience with stationary manometry.

II. Repetitive Contractions

Richter³⁴ used Clouse's³³ definition of repetitive contractions to include those contractions which have a peak of greater than 10% of the initial contraction with an interval of more than 1 second from the previous contraction. Lesser intervals were noted as multi peaked contractions although these contraction forms were not clearly defined. Repetitive contractions are those where one contraction follows another in the absence of a second peristaltic wave originating in the pharynx and implies conclusion of one contraction prior to the onset of another. It has been used to describe the "irritability" of the esophagus seen in motility disorders and with reflux episodes. We chose to modify Clouse's definition for the purposes of ambulatory motility to pressure events that met the criteria for valid contractions occurring within a defined period from the conclusion of the previous contraction (Y, in figure E.1). This duration was defined as greater than 0.5 seconds but less than 2 seconds at the threshold. This was based on the fact that for pharyngeal swallows to be transmitted to the lower esophagus, at least 3-5 seconds must elapse between swallows.^{145,341} Deglutitive inhibition will inhibit transmission of the first wave if the swallow interval is less than this. Repetitive contractions therefore do not occur in response to a swallow except by their relationship to the preceding contraction. The distinction between this type of contraction and multi peaked contractions was made as the two types of contractions seemed to occur

APPENDIX E

occasionally in different individuals and under different circumstances. It was decided that a repetitive contraction, even if it had more than one repetition should be analyzed as a single contraction for that wave sequence. This was done to avoid confusion should the circumstance arise of "irritability" of a segment of the esophagus leading to many repetitive contractions. In this situation, if each peak was considered a separate contraction then an unusually high percentage of "isolated" contractions would be found.

APPENDIX F

DIARY FOR 24 HOUR STUDY
USC ESOPHAGEAL FUNCTION LABORATORY

NAME: _____ DATE _____

AGE: _____ WEIGHT _____ HEIGHT _____

We have explained to you the purpose of the diary. It is imperative that you be as accurate as you can with the recording of events such as meals, sleep periods, and symptoms. (eg. heartburn, coughing, sneezing, abdominal or chest pain, belching, difficulty swallowing, regurgitation). We have given you guidelines as to what, and when you should eat, and that you should lie down only at night to sleep. However, if for some reason you need to deviate from the guide lines, (for example, you drink an extra glass of water during the night, you fall asleep after lunch, or you take some tylenol) we ask you please to mark this on your diary as it will aid us in our analysis of your study. Furthermore, if you do not know the exact time of an event (say you forgot to record lunch but it was about 2pm to 2:30 pm) then document that it is an approximate time on your diary. We do realize that it is difficult to keep an accurate diary, but we ask that you try to remember to document as much as you can. No diary is too detailed. Was your watch set with the machine?

Start Time	Finish Time	Event	Comment
<u>example</u> 12:48 pm	1:11pm	Lunch	Potatoes, chicken, bread (difficulty with bread)

* A second page providing space for extra information is provided.

APPENDIX G

QUESTIONNAIRE AFTER 24 HOUR STUDY
USC UNIVERSITY HOSPITAL
ESOPHAGEAL FUNCTION LABORATORY

NAME _____ DATE _____

In order to evaluate patient tolerance to the "tubes" and to help us with the analysis of your study we would like you to fill out the following questionnaire as best you can. We realize that keeping a diary over 24 hours is difficult but we would appreciate it if you could be as accurate as possible with questions regarding meals and sleep patterns.

1. Did you manage to maintain a relatively normal lifestyle during the test?

Yes _____ No _____ If not, why? _____

2. Regarding the diary:

Did you mark down times of meals, sleep, symptoms etc.....

- a) At the time.
- b) A few hours later.
- c) The next morning.

3. Do you have any comments about the diary? _____

3. Did you manage to eat two meals? Yes _____ No _____.

4. How were you able to eat?

- a) Normally
- b) Slightly limited amounts
- c) Very limited amounts
- d) Unable to eat at all

5. Please list any foods that you had difficulty eating.

6. How many tylenol tablets did you need to take?(eg. 2tabs 3x) _____

7. Did you document these times on your diary? Yes _____ No _____

8. Did you eat or drink anything outside of these two meals?

Yes _____ No _____.

If yes, give approximate times and content of these meals/beverages.

APPENDIX G

9. How difficult was it to keep to the menu?
- a) Very easy
 - b) Relatively easy
 - c) Difficult
 - d) Unable to keep to menu.
10. Were you able to record accurate meal times (within 2 minutes) on your diary?
Yes _____ No _____.
11. Did you nap at any time during the study? (Even for 5 minutes)
Yes _____ No _____.
12. If yes, did you document these times on the diary?
Yes _____ No _____.
13. If you did nap could you please list approximate times of your nap/s? _____
14. How would you describe your nights sleep?
- a) Normal
 - b) Slightly restless
 - c) Very restless
 - d) Did not sleep at all.
15. Were you able to record fairly accurately the times of your _____ sleep (within 5 minutes)?
Yes _____ No _____.
16. Did you sleep through the night? Yes _____ No _____.
17. If not, how many times did you wake? _____.
18. If you woke, did you manage to record accurately on your diary (within 2 minutes) the times that you were awake?
Yes _____ No _____.
19. If you woke, did you eat or drink anything at these times?
Yes _____ No _____.
20. If yes, did you record these accurately on your diary?
Yes _____ No _____.

APPENDIX G

21. What was the most difficult time over the last 24 hours?
- a) Eating
 - b) Sleeping
 - c) Travelling
 - d) Being seen by people, family or friends.
 - e) Being restricted to a certain diet and to limited meals.
 - f) Other _____
22. Overall, how would you describe your experience with the "tubes"?
- a) Barely noticed them.
 - b) Uncomfortable but bearable.
 - c) Very difficult to tolerate at times but generally bearable.
 - d) Extremely uncomfortable.
 - e) The worst experience of your life.
23. If you had 3 tubes, do you think that 2 tubes would have been....
- a) a lot easier to tolerate.
 - b) not much different to 3 tubes.
 - c) no different to 3 tubes.
24. If you had 2 tubes, do you think that 1 tube would have been...
- a) a lot easier to tolerate.
 - b) not much different to 2 tubes.
 - c) no different to 2 tubes.
25. Knowing that the test is providing valuable information about your problem, would you have the test if given the choice again. Yes _____ No _____ Possibly _____.
26. Occasionally, because of technical errors in the equipment, the test does not always provide us with all the information we need. Would you do the test again if it needed to be repeated.
- Yes _____ No _____ Possibly _____.
27. Did you smoke or drink any alcohol during the study? Yes ____ No ____
- If yes please give details _____
28. Other comments: _____

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