

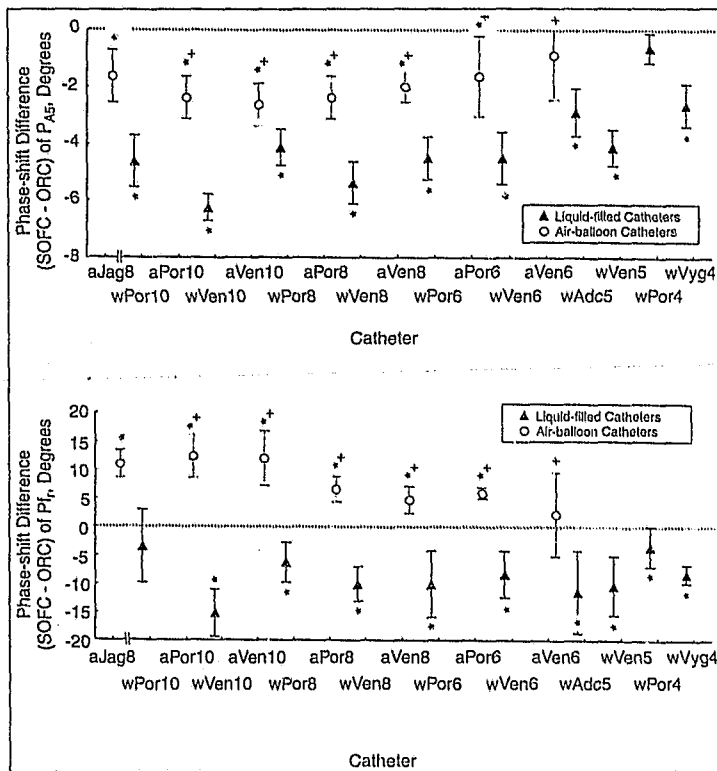
variable-frequency sine-wave generator with a uniform pressure amplitude and waveform response at varying frequencies is difficult [9, 13, 28] and requires the use of a variable-temperature pressure chamber and a temperature-compensated reference transducer. Although certain researchers have experimentally validated the second-order system theoretical models for the resonant behavior of a few intra-arterial blood pressure measurement systems [21, 22] and validated a more complex electrical transmission-line model [9], other researchers have quantitatively shown such theoretical models not to be adequate for their intra-arterial catheters [29-31]. Additionally, the similarity of responses obtained with square-wave response techniques compared to

those obtained from the sine-wave generator technique is shown to be both adequate [32, 33] and inadequate [12, 31] for intra-arterial catheter-manometer systems. Extrapolating the assumption of a second-order system (shown to be valid in certain fluid-filled catheter-manometers) to fluid-filled catheters of different FG sizes, lengths, and material compositions, operated under different conditions and coupled to modern pressure transducers and domes, may be erroneous.

Our results suggest a significant deviation of the fluid-filled PVC catheter-manometers' SOFCs from the ORCs. Mathematical models, from which commonly used equations based on systems assumed to be second order are derived, state that the catheter-manometer acts as a

transmission probe (based on electrical transmission line theory) in the manner of a distributed system [9, 15-17]. These theories, and the equations based on them, incorporate several important catheter-manometer properties influencing the theoretical frequency responses: compliance (catheter-manometer walls and filling-fluid), inertance (axial and radial fluid mass, and radial catheter-manometer wall inertance), viscous resistance (catheter-manometer filling fluid), and hysteresis (catheter-manometer wall hysteresis and filling fluid inelasticity). One obvious difference between fluid-filled feeding catheters used to measure intra-esophageal pressure and catheters used to measure intra-arterial pressure is the soft PVC catheter compound of the former versus the relatively rigid nylon or braided polyurethane of the latter. Whereas wall compliance and hysteresis are validly ignored in the mathematical models applied to certain intra-arterial catheters (by assuming a tube of constant dynamic compliance, with negligible hysteresis losses directly proportional to frequency [9]), PVC NGCs are palpably compliant and may exhibit significant dynamic energy losses through hysteresis. Moreover, in certain catheter-manometer systems compliance has been shown to be frequency dependent [21, 29], as influenced by catheter wall composition. PVC catheter compliance and hysteresis may not only be greater in magnitude, but also be more frequency and amplitude dependent than those of relatively rigid intra-arterial lines assumed to be linear systems [9, 17, 21]. We have not assessed the contribution of such factors here.

Theory predicts that a gas-filled catheter-manometer system may be treated as being linear if the catheter radius is large enough and the frequency low enough, despite the large compressibility of the gas [17]. In highly compressible fluids, such as a gas, the catheter-manometer system's compliance is principally affected by the gas compressibility in A-BCs, whereas catheter elasticity and transducer-diaphragm compliance is primarily responsible for the elastance of W-FCs. In our experiment, even though deviation from second-order systems was less in A-BCs than W-FCs, we did not find an adequate second-order system fit prevailing within the range of clinically used A-BC FG sizes and lengths. The



3. Phase-shift difference (mean \pm SD) between second-order fitted curve and original recorded curve (SOFC-ORC) for phase-frequency response trace variables. X-scale break separates commercial Jaeger adult from laboratory-made air-balloon catheter. SOFC-ORC of P_{As} : SOFC-ORC phase-shift difference at $A = 1.05$ (or f_{As}); SOFC-ORC of P_{fr} : SOFC-ORC phase-shift difference at damped resonance frequency. Catheter: catheter brand and French Gauge size; aPor or wPor: air-balloon or water-filled Portex catheter. * Significant SOFC-ORC phase-shift difference. + $P < 0.05$ for SOFC-ORC phase-shift difference between A-BC and W-FC of same FG size and brand.

SOFC:ORC ratios of our W-FCs deviated significantly more than the A-BCs, even though the W-FCs filling fluid was of lower compressibility. This may be related to the presence of gas microbubbles in the W-FCs, which remained despite our efforts to reduce them. Trapped gas bubbles, which lower the catheter-manometer system elastance, remain an adverse feature of W-FCs in the clinical situation. Their formation is encouraged by the negative intra-esophageal pressures encountered physiologically. We simulated these physiologically negative pressures *in vitro* in this experiment using the laboratory-built sine-wave generator.

Our findings must be interpreted within the context of clinical relevance. The energy contents of most physiological pressure waveforms lie well within f_f , but not necessarily within f_{A5} of a catheter-manometer system. SOFC:ORC deviations and SOFC:ORC phase-shift differences of f_f , A_f , and Pf_f are not as clinically relevant as the deviations of f_{A5} . In our experiment, the magnitude of SOFC:ORC amplitude-frequency response deviation is shown to be greater for f_{A5} than for f_f . This finding is unfavorable because deviations observed for f_f in our experiment are clinically acceptable, while those observed at f_{A5} are clinically relevant (an overestimation of the uniformity of a catheter's amplitude-frequency response is unacceptable) as well as statistically significant. Additionally, the observed magnitude of deviation is greater for W-FCs than for A-BCs. This result is also unfavorable for clinicians because the *in vivo* fast-flush test (square-wave response technique), which is reliant on second-order system theory to predict f_{A5} [12], can currently be performed on W-FCs only and not on A-BCs *in vivo*. Our results suggest that assuming a second-order system is less valid for W-FCs than for A-BCs.

The observed SOFC:ORC phase-shift differences are statistically significant, but relatively small in magnitude. Intra-esophageal pressure is measured to estimate dynamic lung compliance, therefore a simultaneous dynamic lung-volume measurement is always recorded. The SOFC:ORC phase-shift differences may thus be clinically relevant.

We noted significantly increased mag-

nitudes of SOFC:ORC ratios with increasing catheter FG size. Catheter elastance, which decreases with larger catheter FG sizes (wall thickness:outer diameter ratio [13] reduces with increasing FG size in our catheters), may have influenced this. In validating the theoretical assumptions of their mathematical models, most researchers have used only one sample of each catheter for the experimentally obtained (sine-wave generator) frequency response and compared this against the theoretical predicted response. We noted large variances in SOFC:ORC ratios within both the A-BCs and the W-FCs samples ($n = 8$ each in our experiment); large manufacturing tolerances for any particular catheter FG size may be an influencing factor here. Note, however, that differing catheter brands did not significantly alter the SOFC:ORC deviations for any particular FG-size catheter, and the commercially available A-BC's SOFC:ORC deviation was not significantly different from the corresponding laboratory-made A-BCs.

In conclusion, A-BC and W-FC frequency responses do not adequately fit second-order systems. This finding casts doubt on the validity of defining and applying second-order system mathematical models to predict such catheter-manometers' frequency responses. SOFC:ORC deviations are significantly larger in W-FCs than in A-BCs, in large FG-sized catheters, and at f_{A5} than at f_f . The frequency-response system order of differing fluid-filled catheter-manometers should be verified experimentally prior to predicting their frequency responses using the typical equations applied to square-wave response techniques. We recommend that the sine-wave generator, rather than the square-wave response technique, be used to measure *in vitro* frequency responses of compliant fluid-filled catheters.

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Craig G. Hartford was born in Cape Town, South Africa. He received his MB BCH degree at the University of the Witwatersrand in Johannesburg in 1987, and gained further clinical training in academic hospital units until 1990. In 1993, he received his MSc Med by dissertation in cardiovascular physiology. He currently lectures in the department of Physiology and Chemical Engineering at the University of the Witwatersrand in Johannesburg. In 1996, he won the IEEE EMBS Student Whitaker paper competition. He currently is a biomedical engineering PhD student interested in pulmonary compliance and dynamic pressure measurements.



Johan M. van Schalkwyk acquired his medical degree in 1983 at the University of the Witwatersrand in Johannesburg, South Africa, and received Fellowship of the College of Physicians of

South Africa in 1990. He was registered in the sub-specialty of critical care in 1995 and is currently a senior consultant in the Post-operative Intensive Care Unit under the department of Anaesthesia at Johannesburg Hospital. His interests are computer programming (particularly assembly language programming), orthogonal language design, and character recognition.



Geoff G. Rogers was born in South Africa and completed his BSc majoring in physiology at the University of the Witwatersrand, Johannesburg. He obtained his MSc at the University of Pretoria and his PhD at the University of the Witwatersrand in cardiovascular physiology. He is currently an associate professor in physiology at the University of the Witwatersrand, with particular interest in cardiovascular physiology of exercise.



Martin J. Turner was born in South Africa. He received his BSc Elec Eng at the University of the Witwatersrand in Johannesburg and there went on to complete his MSc Eng and PhD in infant respi-

ratory gas-flow measurements in 1991, while lecturing in the department of Electrical Engineering. He was attached to the research unit of the department of Anaesthetics at Oxford University in 1995. He is currently an associate professor in Electrical Engineering at the University of the Witwatersrand, Johannesburg, with particular interest in biomedical engineering cardiorespiratory concepts applied to infants.

Address for Correspondence: C.G. Hartford, Department of Physiology, University of the Witwatersrand Medical School, 7 York Road, Parktown, Johannesburg, 2193, South Africa.

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Primate Pleuroesophageal Tissue Barrier Frequency Response and Esophageal Pressure Waveform Bandwidth in Health and Acute Lung Injury

Craig G. Hartford, M.D., M.Sc., Med.,* Johan M. van Schalkwyk, M.D., F.C.P.(SA),† Geoffrey G. Rogers, Ph.D.,* Martin J. Turner, Ph.D., Eng.‡

Background: Dynamic intraesophageal pressure (Pes) is used to estimate intrapleural pressure (Ppl) to calculate lung compliance and resistance. This study investigated the nonhuman primate Ppl-Pes tissue barrier frequency response and the dynamic response requirements of Pes manometers.

Methods: In healthy monkeys and monkeys with acute lung injury undergoing ventilation, simultaneous Ppl and Pes were measured directly to determine the Ppl-Pes tissue barrier amplitude frequency response, using the swept-sine wave technique. The bandwidths of physiologic Pes waveforms acquired during conventional mechanical ventilation were calculated using digital low-pass signal filtering.

Results: The Ppl-Pes tissue barrier is amplitude-uniform within the bandwidth of conventional Pes waveforms in healthy and acute lung injury lungs, and does not significantly attenuate Ppl-Pes signal transmission between 1 and 40 Hz. At Pes frequencies higher than conventional clinical regions of interest the Ppl-Pes barrier resonates significantly, is pressure amplitude dependent at low-pressure offsets, and is significantly altered by acute lung injury.

Allowing for 5% or less Pes waveform error, the maximum Pes bandwidths during conventional ventilation were 1.9 Hz and 3.4 Hz for physiologic and extreme-case waveforms in healthy lungs and 4.6 Hz and 8.5 Hz during acute lung injury.

Conclusions: In monkeys, the Ppl-Pes tissue barrier has a frequency response suitable for Ppl estimation during low-frequency mechanical ventilation, and Pes manometers should have a minimum uniform frequency response up to 8.5 Hz. However, the Ppl-Pes tissue barrier adversely affects the accurate estimation of dynamic Ppl at high frequencies, with varied airway pressure amplitudes and offsets, such as the Ppl encountered during high-frequency oscillatory ventilation. (Key words: Lung elastance; manometry; respiratory mechanics.)

DYNAMIC intraesophageal pressure (Pes) is measured to estimate intrapleural pressure (Ppl) for the calculation of dynamic transpulmonary pressure and lung compliance.¹ The accurate representation of dynamic Ppl using Pes measurements depends on the amplitude and phase frequency response of the intrapleural to intraesophageal tissue barrier (Ppl-Pes tissue barrier). This response is important for the accurate construction of dynamic lung compliance loops and resistance calculations and for the potential measurement of Pes during high-frequency oscillatory ventilation.^{2,3} One study directly compared Pes and Ppl in healthy adult dogs⁴; however, direct Ppl and Pes comparisons to determine the frequency response of the primate Ppl-Pes barrier have not been published.

Intraesophageal pressure manometers should have a uniform frequency response and linear phase shift over the dynamic Pes bandwidth. Frequency response characteristics of clinically used Pes manometers have been investigated⁵⁻⁷ but suggested minimum frequency response requirements for Pes manometers are based on dynamic airway pressure (Paw) waveform bandwidths.⁸ No data quantifying Pes bandwidth in primates have been published. Assumptions that Pes bandwidth is the same as Paw bandwidth may be invalid because Paw frequency components transmitted to Pes may be amplified or attenuated.

* Lecturer, Associate Professor, Department of Physiology, University of the Witwatersrand Medical School and Johannesburg Hospital, Johannesburg, South Africa.

† Consultant, Department of Anesthesiology, University of the Witwatersrand Medical School and Johannesburg Hospital, Johannesburg, South Africa.

‡ Senior Researcher, Department of Anesthesia, University of Sydney, New South Wales, Australia.

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Address reprint requests to Professor Rogers: Department of Physiology, University of the Witwatersrand Medical School, 7 York Road, Parktown, Johannesburg, 2193, South Africa. Address electronic mail to: craighartford@hotmail.com

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We hypothesize that the Ppl-Pes tissue barrier has a uniform amplitude frequency response within the clinically relevant Pes waveform bandwidth and is uniform, amplitude independent, and lung-condition independent at low and high frequencies. We aim to determine the frequency response of the primate Ppl-Pes tissue barrier using simultaneous Ppl and Pes measurements in healthy mechanically ventilated monkeys, and those with acute lung injury (ALI). Furthermore, we aim to quantify the dynamic response requirements of Pes manometers by determining Pes bandwidth before and after ALI.

Method

Instrumentation

Twelve female Vervet monkeys (*Cercopithecus aethiops*, 3.9 ± 0.60 kg) were anesthetized (20 mg/kg ketamine induction and $10 \text{ mg} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$ ketamine, $> 30 \text{ } \mu\text{g} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$ sufentanil [Janssen-Cilag, Johannesburg, South Africa], and $5 \text{ } \mu\text{g} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$ adrenaline maintenance continuous infusions), paralyzed ($10 \text{ } \mu\text{g} \cdot \text{h}^{-1} \cdot \text{kg}^{-1}$ vecuronium [Omnimed, Johannesburg, South Africa]), intubated orally (cuffed 4.5 mm, Mallinkrodt, Athlone, Ireland), and mechanically ventilated in the supine position with warm humidified 100% O_2 (fraction of inspired oxygen $[\text{F}_{\text{I}\text{O}_2}] = 1.0$) using a high-flow-rate pressure-cycle pressure-limit ventilator (model 105; Preemicare, San Antonio, Texas). University Animal Ethics Clearance (96/113/2B) was obtained. The right femoral vein was cannulated for injection of oleic acid to produce ALI.

Intrapleural Pressure and Intraesophageal Pressure Catheter Design and Pressure Measurements

Intraesophageal pressure and Ppl catheters were adapted for dynamic pressure measurements by sealing the tips of size 7 French gauge transducer-tip catheters (Millar Mikro-tip SPC 470; Millar Instruments, Inc., Houston, Texas) into water-filled latex balloons 2 cm in length. The distal end of the Ppl transducer catheter was enclosed in a right-angled rigid perforated acrylic cylinder, around which the balloon was tied. The cylinder was fashioned with a distal pointed end, such that the catheter would act as an introducer during transthoracic positioning, and, once inserted, the water-filled balloon rested parallel to the chest wall inside the pleural space. A second catheter attached to the Ppl catheter was linked to an underwater chest drain for pneumothorax deflation. The water volumes of the Ppl and Pes catheter

balloons were set to allow maximum balloon-catheter compliance. The frequency responses of the two catheters were amplitude-linear and -equivalent.

With the aid of a transcutaneous cut-down to pleura and dilating trocars, the Ppl catheter was inserted transthoracically in either a cranial or a caudal direction into the left or right sides of the chest ($n = 3$ of each side per group) at the level of the seventh intercostal space in the mid axillary line. The *in vivo* Pes catheter site was chosen according to the best "paralyzed airway occlusion test," in which the airway is briefly occluded and abdominal pressure is applied to assess how faithfully ΔPes reproduces ΔPpl in an isovolumic chest of anesthetized paralyzed subjects.⁹

Airway opening pressure was measured with a piezoresistive differential pressure transducer (Microswitch 170PC; Honeywell, Morristown, NJ) inserted into the proximal endotracheal tube perpendicular to the gas flow direction.

All pressure transducer signals were preamplified using the same apparatus (Hellige Servomed, Freiburg, Germany) and digitized at 500 Hz (Biopac MP100 and AcqKnowledge version 3.3.2; Biopac Systems Inc., Goleta, CA).

Intrapleural-Intraesophageal Pressure Tissue Barrier Frequency Response Determination

Intrapleural pressure waveforms were generated by applying sinusoidal Paw waveforms using the pneumatic driver unit of a high-frequency oscillatory ventilator (3100A; SensorMedics, Bithoven, The Netherlands, and Manta Medical Systems, Johannesburg, South Africa). To generate sine-wave rather than square-wave Paw outputs, the square-wave frequency generator of the ventilator was bypassed, and the DC-coupled amplifier was controlled by a separate sine-wave generator (Dynamic Signal Analyser 3562A; Hewlett Packard, Palo Alto, CA).

Amplitude frequency responses of the Ppl-Pes tissue barrier were calculated by comparing the Ppl and Pes waveform signals generated between 1 Hz (taken as the DC response to which the responses were normalized) and 40 Hz. Swept-sine waves¹⁰ were applied at 0.98 Hz intervals with a 20-s integration time and a 90% integration threshold for each frequency interval (Dynamic Signal Analyser 3562A). The dynamic signal analyzer performs a high-resolution Fourier transform at each measured frequency and extracts amplitude and phase information from the acquired Ppl and Pes waveform signals only at the frequency of interest, thereby ignoring any harmonics created by distortion. In each subject,

10 swept-sine wave sequences (performed by disconnecting the standard ventilator and connecting the high-frequency oscillatory ventilator at 5-min intervals) were averaged at each of two mean Paw offsets: 1 cm H₂O and 10 cm H₂O above atmospheric pressure. These mean Paw pressure offsets were generated during the swept-sine measurements by injecting excess oxygen into the airway and allowing the excess to bleed off under water at the appropriate depth. Frequency response traces during which esophageal peristalsis occurred were recorded.

Frequency response measurements were recorded at two mean Paw offsets (1 or 10 cm H₂O) before and 2.5 h after intervention (oleic acid [ALI group [ALIG], n = 6] or saline [control group [CTRL], n = 6] injection). These measurements were recorded at a low applied Ppl amplitude (low applied Ppl; Δ Ppl waveform mean amplitudes were set to be ± 1.0 cm H₂O at 1 Hz, reducing to ± 0.5 cm H₂O at 40 Hz). At 7.5 h after intervention, the frequency response measurements were recorded at a mean Paw offset of 20 cm H₂O at low applied Ppl amplitude, and again at Paw offset of 10 cm H₂O, but at a larger applied Ppl amplitude (high Ppl amplitude; Δ Ppl waveform mean amplitudes were set to be ± 4.7 cm H₂O at 1 Hz, reducing to ± 1.0 cm H₂O at 40 Hz).

Intraesophageal Pressure Dynamic Waveform Bandwidth

Intraesophageal pressure and Paw measurements were made in six subjects before (baseline, PesB, and PawB) and 5.5 h after (PesA and PawA) oleic acid injection in the ALI group (n = 6). Respiratory rate (RR) and maximum Paw (Paw pk) were adjusted to achieve an arterial carbon dioxide pressure (Pa_{CO₂}) of 30–40 mmHg throughout the experiment (calibrated Stat Profile 3; Nova Biomedical, Waltham, MA). Physiologic PesB and PawB or physiologic PesA and PawA were acquired at a Pa_{CO₂} of 30–40 mmHg. In addition, Pes and Paw traces were acquired during extreme conditions by raising peak Paw 50% above the physiologically required peak Paw and simultaneously doubling the respiratory rate (elevated PesB and PawB, or elevated PesA and PawA).

Trains of 10 PesB and PesA waveform sequences, each containing 10 mechanical breaths, were selected and low-pass filtered using a Blackman (AcqKnowledge version 3.3.2; Biopac Systems Inc.) finite impulse response linear phase filter with minimal phase shift, for which the response was tailored to be near -1 dB at chosen low-pass cut-off frequencies. Twelve low-pass cut-off frequencies were selected that reduced the areas under the

curve (%AUC) of the Pes continuous-power spectrum by predetermined proportions. Power spectra were determined by ensemble-averaging of the power spectra of 10 PesB and PesA breaths.⁸ The mean value was subtracted from each ensemble and the data was padded with zeros before fast Fourier transform (AcqKnowledge version 3.3.2; Biopac Systems). One hundred percent of Pes waveform power was assumed to be contained between 0 and 40 Hz.

The average Pes amplitude between Pes at onset of expiration to Pes at onset of inspiration for each of 10 mechanical breaths was determined manually for the original trains of unfiltered Pes waveforms and compared with those of the incrementally low-pass-filtered Pes waveforms. The maximum waveform amplitude error (% amplitude difference from original Pes waveform) averaged for 10 breaths was determined among the six subjects. The Pes bandwidth, up to which a Pes manometer should have a uniform amplitude frequency response to yield a 3% or less or 5% or less error when measuring the end-expiratory to end-inspiratory amplitude of physiologic or extreme-case Pes waveforms, was determined (Pes EI-EE bandwidth).

Statistical Analysis

Amplitude frequency responses in which the mean Pes-Ppl ratio deviated by more than 10% from 1.0, plus the 95% confidence interval value excluded 1.0 (both conditions met), were considered to significantly deviate from that of uniformity.¹¹ Significant within-group (within the ALIG or within the CTRL) progressive changes were detected using Friedman analysis of variance (repeated measures), followed by identification with the Wilcoxon signed rank test.¹² The Mann-Whitney test was used to determine significant differences between the ALI and CTRL groups (Statistica; Statsoft, Tulsa, OK). Frequency response graphically displayed values are the mean \pm SEM; all ventilation variables are the mean \pm SD; and differences with *P* values < 0.05 are regarded as statistically significant.

Results

Intrapleural-Intraesophageal Tissue Barrier Frequency Response

Mean Pes-Ppl area under the curve ratios were more than 0.90 in all groups for the anesthetized monkey Pes manometer occlusion tests (table 1). Figure 1 depicts the swept-sine amplitude frequency response at baseline in

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Table 1. Anesthetized Monkey Occlusion Test Ratios

Paw Offset	Baseline AUC (n = 12)		Postintervention AUC			
	Pes/Ppl	Paw/Ppl	CTRL (n = 6)		ALIG (n = 6)	
			Pos/Ppl	Paw/Ppl	Pes/Ppl	Paw/Ppl
1 cm H ₂ O	0.94 ± 0.067	0.95 ± 0.108	0.90 ± 0.126	0.94 ± 0.061	0.95 ± 0.092	0.90 ± 0.082
10 cm H ₂ O	0.90 ± 0.080	0.96 ± 0.065	0.90 ± 0.148	0.97 ± 0.163	0.96 ± 0.059	0.92 ± 0.077

AUC = area under the curve, ratio of two pressure waveform AUC values; Paw offset = airway pressure offset during occlusion test; Pes/Ppl = AUC ratio of esophageal to pleural pressure during occlusion test; Paw/Ppl = AUC ratio of airway to pleural pressure during occlusion test; CTRL = control group receiving saline; ALIG = acute lung injury group receiving oleic acid.

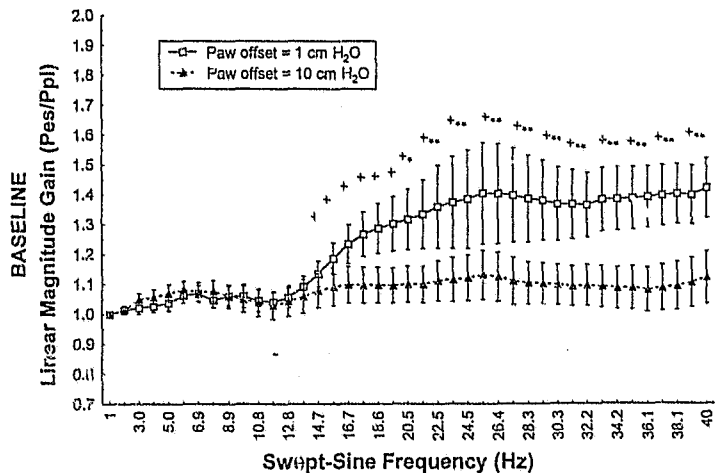
the combined (n = 12) ALIG and CTRL subjects (Paw offset = 1 cm H₂O and 10 cm H₂O). The Ppl-Pes tissue barrier amplitude frequency response was uniform from 1 to 40 Hz when Paw offset was 10 cm H₂O. However, the 95% confidence interval lower limit of the response was greater than unity and the mean response was greater than 1.10 at frequencies more than 14.7 Hz when Paw offset was 1 cm H₂O. From 20.5-40 Hz, the amplitude frequency response when Paw offset was 1 cm H₂O was significantly greater than when Paw offset was 10 cm H₂O (fig. 1).

After control saline injection the CTRL (n = 6) amplitude frequency response was uniform between 1 and 40 Hz at Paw offset of 10 cm H₂O, and the amplitude gain was significantly greater at Paw offset of 1 cm H₂O compared with Paw offset of 10 cm H₂O between 19 and 35 Hz and 38 and 40 Hz (similar to the baseline values in fig. 1). However, unlike the CTRL, the ALIG

(n = 6) amplitude frequency response changed (fig. 2): At Paw offset of 1 cm H₂O, the amplitude response was now uniform from 1 to 40 Hz (before lung injury, it was significantly raised; baseline, fig. 1) and, at Paw offset of 10 cm H₂O, the response was significantly resonant, from 13.7 to 15.7 Hz and from 26.4 to 32.2 Hz (before lung injury, it was uniform from 1 to 40 Hz; baseline, fig. 1). Within the ALIG, the amplitude response was significantly different between Paw offset of 1 cm H₂O versus Paw offset of 10 cm H₂O, from 3.0 to 5.9 Hz and 8.9 to 14.7 Hz and at 30.3 Hz (fig. 2).

At Paw offset of 20 cm H₂O, the CTRL amplitude response was uniform, from 1 to 40 Hz (similar to CTRL baseline at Paw offset of 10 cm H₂O from fig. 1 and to CTRL after saline injection at Paw offset of 10 cm H₂O), whereas the ALIG amplitude response continued to deviate from uniformity between 4.0 and 5.0 Hz and 30.3 and 36.1 Hz (resembling the ALIG amplitude response at

Fig. 1. Baseline intrapleural pressure (Ppl)-intraesophageal pressure (Pes) tissue barrier amplitude frequency responses at low and high mean airway pressure offsets. Hz = swept-sine frequency in cycles/s; Paw = airway opening pressure; Pes-Ppl = amplitude gain of esophageal pressure over intrapleural pressure. *P < 0.05 and **P < 0.01; amplitude gain significantly different for Paw offset of 10 cm H₂O versus 1 cm H₂O; +amplitude response deviates significantly from uniformity (see criteria in Methods).



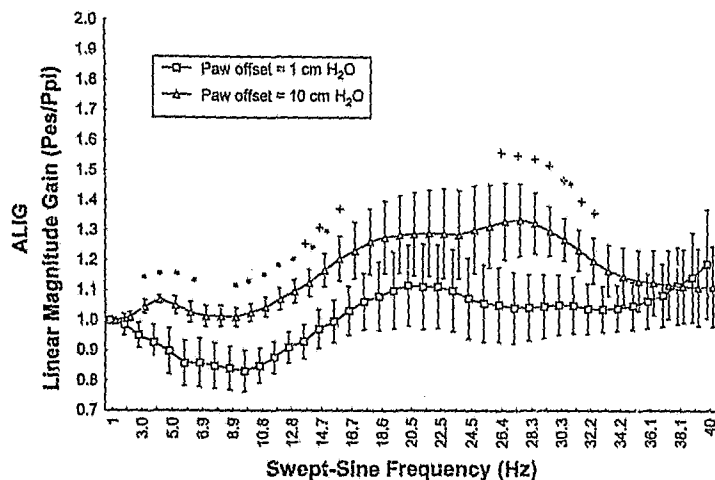


Fig. 2. Intrapleural pressure (Ppl)-intraesophageal pressure (Pes) tissue barrier amplitude frequency responses at low and high mean airway pressure offsets after acute lung injury (ALI; ALI group). Hz = swept-sine frequency in cycles/s; Paw = airway opening pressure; Pes-Ppl = amplitude gain of esophageal pressure over intrapleural pressure. * $P < 0.05$; amplitude gain significantly different for Paw offset of 10 cm H₂O versus 1 cm H₂O; +amplitude response deviates significantly from uniformity (see criteria in Methods).

Paw offset of 10 cm H₂O from fig. 2, which deviated from uniformity after ALI).

At Paw offset of 10 cm H₂O, but with high Ppl amplitude, CTRL was uniform between 1 and 40 Hz (similar to the baseline fig. 1 and postsaline CTRL responses at Paw offset of 10 cm H₂O with low Ppl amplitude), whereas the ALIG significantly deviated from uniformity between 23.5 and 31.3 Hz (similar to the ALIG response at Paw offset of 10 cm H₂O with low Ppl amplitude from fig. 2). Minimum to maximum phase differences were small: -11 to +26° among all frequencies and lung conditions tested.

Intraesophageal Pressure Waveform EI-EE Bandwidth

The physiologic Paw and Pes waveforms, as measured before (physiologic PawB and PesB) and after lung injury (physiologic PawA and PesA) used for Pes EI-EE bandwidth determination are characterized in table 2. The effect of low-pass filtering of physiologic PesB waveforms is shown in figure 3. Incrementally, low-pass filtering between the third and fourth (1.2 Hz) and the second and third (0.8 Hz) harmonic frequencies leads to errors in the end-inspiratory to end-expiratory waveform amplitudes.

The mean ($n = 6$ subjects) frequencies at which power in the Pes waves is 78-90% of total power are shown in figure 4. On average, among all the lung conditions, up to 90% and 78% of Pes waveform power is found to be less than 8.0 and 3.4 Hz, respectively.

Figure 5 shows the maximum Pes waveform error produced by low-pass filtering of Pes of healthy lungs (fig. 5A) and lungs with ALI (fig. 5B). With increasing attenuation of Pes energy, the waveform error increases. The maximum waveform error showed a trend toward being larger for elevated PesB waveforms than for physiologic PesB waveforms. The maximum waveform errors were larger for PesA waveforms (after ALI) than for PesB waveforms (at baseline; fig. 5B, physiologic PesA vs. fig. 5A, physiologic PesB).

Among Pes for all subjects, the highest cut-off frequencies (largest waveform EI-EE bandwidth) that yielded a more than 5% waveform error was 1.9, 3.4, 4.6, and 8.5 Hz for the physiologic PesB, elevated PesB, physiologic PesA, and elevated PesA waveforms, respectively. Corre-

Table 2. Physiologic Ventilation Characteristics for Pes EI-EE Bandwidth Determination

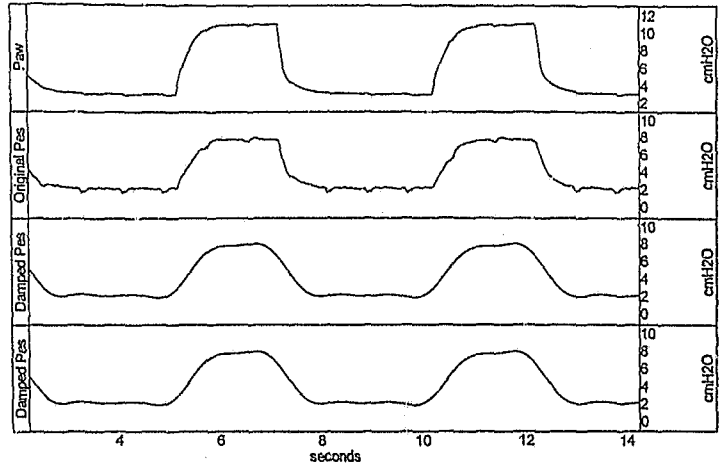
	Before ALI		5.5 hr after ALI	
	PawB	PesB	PawA	PesA
RR	19 ± 4.9		33 ± 10.7	
Paw pk	12 ± 0.9	7 ± 2.4	18 ± 2.9	8.3 ± 2.0
PEEP	3 ± 1.0	1 ± 1.9	5.5 ± 1.3	3 ± 1.2
Paw M	6 ± 0.8	3 ± 2.2	10 ± 1.3	5 ± 1.5

Values are those necessary for Pa_{CO₂} of 30-40 mmHg.

ALI = oleic acid-induced acute lung injury; Paw pk,M = peak and mean proximal airway pressure in cm H₂O; PawB, PawA = physiologic mean proximal airway pressure at baseline and in ALI; PEEP = positive end-expiratory pressure; PesB, PesA = physiologic mean intraesophageal pressure at baseline and in ALI; RR = respiratory rate.

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Fig. 3. Illustration of low-pass filtering effect on intrasophageal pressure (Pes) waveforms. Overdamped Pes acquisitions result in gradual erosion of Pes waveform shape. Paw = original proximal airway pressure waveform; Pes = original and two filtered (low-pass cut-off frequencies, 1.8 and 0.8 Hz, respectively) intrasophageal physiologic pressure waveforms at baseline.



sponding values for a waveform error of more than 3% were 2.1, 4.9, 6.0, and 8.5 Hz.

Discussion

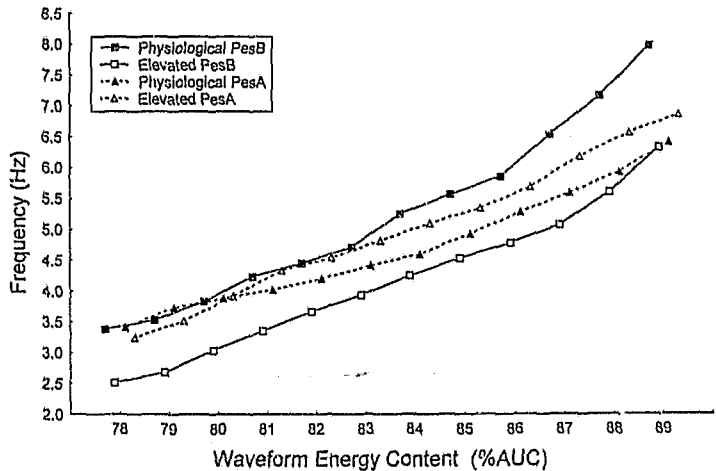
Intrapleural-Intraesophageal Pressure Tissue Barrier Frequency Responses

Concerns pertaining to Pes measurements are raised through findings such as the lung volume dependency and Paw dependency of Pes changes in infants¹³ and adults,¹⁴ and the frequency dependency and Paw dependency of lung compliance values in healthy adult

monkeys.¹⁵ The mechanical properties of the esophageal wall and surrounding structures are a potential cause of signal alteration when estimating dynamic Ppl from Pes.¹⁶

Our Ppl and Pes catheters are comparable to clinically used Pes air-balloon catheters but have a lower volume-displacement coefficient, are amplitude independent, and have a wider dynamic range suitable for assessing the Ppl-Pes tissue barrier at high frequencies. Using direct, simultaneous Ppl and Pes measurements, we have demonstrated that the amplitude frequency response of the Ppl-Pes tissue barrier is uniform within the EI-EE

Fig. 4. Frequency value of power spectrum of intrasophageal pressure (Pes) as a function of Pes waveform energy content, assuming 100% of waveform energy content lies between 0 and 40 Hz. AUC = % energy above 0 Hz remaining under the power spectrum curve relative to that between 0 and 40 Hz (100%); Hz = average frequency recorded for the particular area under the curve value. PesB, PesA = mean intrasophageal pressure waveforms at baseline and after acute lung injury, at physiologic (P_aCO₂ of 30-40 mmHg) or artificially elevated airway pressures.



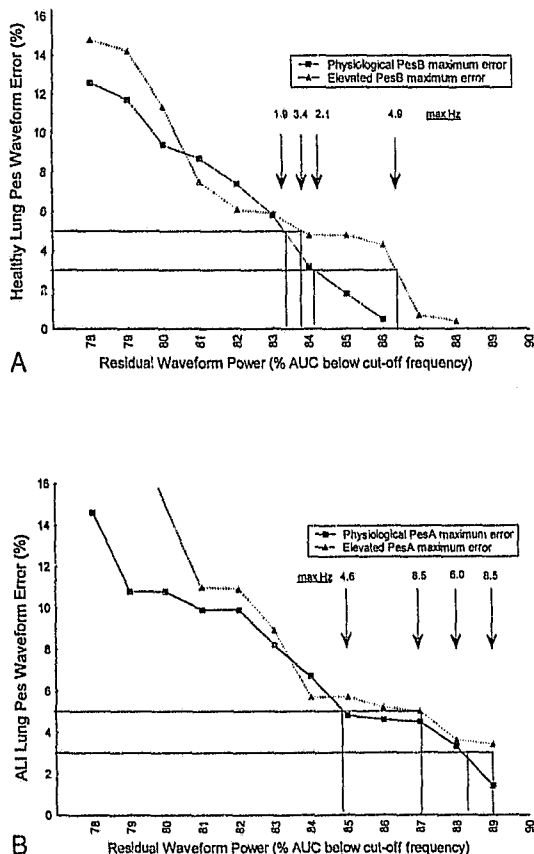


Fig. 5. (A, B) Intraesophageal pressure (Pes) waveform error as a function of reducing Pes waveform energies after low-pass filtering before (A) and after (B) acute lung injury. Waveform error (%) is the maximum value for the end-inspiratory onset to end-expiratory onset amplitude error after low-pass filtering at chosen cut-off frequencies defined by reducing waveform energy contents (reducing % areas under the curve). ALI = acute lung injury; max Hz = highest Pes waveform frequency (largest waveform EI-EE bandwidth) found at maximum waveform errors of 5% or more or 3% or more; PesB, PesA = mean intraesophageal pressure waveforms at baseline (top) and in ALI (bottom), at physiologic (P_{aCO_2} of 30–40 mmHg) or artificially elevated airway pressures.

bandwidth (up to 8.5 Hz) of physiologic Pes waveforms measured in anesthetized mechanically ventilated primates and with healthy lungs and ALI. The barrier does not significantly attenuate Ppl-Pes signal transmission between 1 and 40 Hz. However, at higher frequencies in this range, the Ppl-Pes frequency response resonates

significantly, is amplitude dependent, and is significantly altered in the presence of lung disease.

Studies that used direct Ppl measurements, but with markedly differing methodologies among the studies, have shown that the Ppl-Pes amplitude frequency response in dogs did not deviate by more than 10% from unity between 2 and 20 Hz, and no amplitude dependency was observed by varying the mean Paw offset.⁴ In rabbits there was slight attenuation of Pes measured at discrete frequencies of 30, 40, and 50 Hz.¹⁷

Alterations in the Ppl-Pes tissue barrier frequency response seen after induction of ALI could be caused by changing lung conditions in ALI that affect Ppl-Pes transmission or by reduced amplitudes in the Ppl waveforms during the ALI swept-sine runs, if the system is nonlinear. In the current study, Ppl amplitude power spectra were similar before and after ALI; therefore, the alterations in the Ppl-Pes tissue barrier frequency response seen after induction of ALI probably are related to respiratory system ALI changes. Changes in the Ppl-Pes barrier could result from partial or complete isolation of the Ppl or Pes catheters. This is also unlikely because we inserted the Ppl catheter among subjects into both the left or the right sides of the chest, in caudal or cranial directions, and the Ppl, Pes, and Paw occlusion test results before and after ALI were similar (table 1). The generation of negative pressures in the airways during oscillation, which occurred when mean Paw offset was 1 cm H_2O , may have altered the Ppl-Pes tissue barrier frequency responses. Inaccuracy of Pes measurements has been attributed to chest wall distortion producing uneven pleural pressure distribution.¹⁸ However, this is an unlikely contributing factor because the Ppl-Pes tissue barrier frequency responses at low frequencies did not depend on mean Paw (and thus on negative Paw) in our animals (fig. 1).

When Paw pressure offsets were switched from 1 to 10 cm H_2O , the Ppl-Pes tissue barrier frequency response changed, in both the CTRL and ALIG, although the 1- or 10-cm H_2O Paw offsets at which the Ppl-Pes gain occurred is different in the ALIG vs. the CTRL. Such a change is not seen when the Paw pressure offsets were switched from 10 to 20 cm H_2O . In addition, increasing applied Ppl amplitude at a Paw offset of 10 cm H_2O did not significantly change the Ppl-Pes responses within the ALIG or the CTRL. To avoid the risk of Paw negative pressure trauma, we did not test the effect of a high Ppl amplitude when the Paw offset was 1 cm H_2O . The amplitude dependency lies at lower Paw pressures (1–10 cm H_2O). These findings suggest that, in conditions in

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which peak end-expiratory pressure or mean Paw are higher (such as occur during high-frequency oscillatory ventilation modes), it may be possible to correct the Pes waveform output using an esophageal transfer function to compensate for the Ppl-Pes tissue barrier gain (found during ALI at 10 and 20 cm H₂O Paw offsets) because the Ppl-Pes frequency response exhibited a linear amplitude gain based on the 10- and 20-cm H₂O Paw offsets.

Intraesophageal Pressure Waveform EI-EE Bandwidth

The bandwidth of pressure waveforms is influenced by the type of transform used for frequency content analysis, characteristics of the chosen filters, and the criteria for waveform error.¹⁹ We based Pes waveform error on the Pes amplitude difference between end-inspiration and end-expiration because these are commonly used points of reference for lung compliance calculations in clinical settings.²⁰ Using peak amplitude, or end-inspiratory to end-expiratory amplitude, based on the first points of zero gas flow, as opposed to the method we chose, reduces the calculated Pes waveform error and, thus, plays down the potential distorting effect on dynamic lung compliance loops. Our Pes EI-EE bandwidths represent the maximum likely bandwidths of a range of Pes waveforms encountered in healthy monkeys undergoing ventilation and monkeys with ALI.

The larger maximum EI-EE bandwidths noted in the supraphysiologic (elevated) PesB and PesA waveforms, compared with the physiologic PesB and PesA waveforms, probably are caused by increased energy content found at higher frequencies in some of the elevated Pes waveforms. The larger Pes EI-EE bandwidths noted after ALI (PesA) compared with healthy baseline lungs (PesB) may be caused by increased energy content at higher frequencies in some of the PesA waveforms because of the higher Paw values necessary for ALI (table 2), or because of the ALI condition itself altering the Ppl-Pes transmission of waveform frequency components. The latter is unlikely because the frequency response of the Ppl-Pes tissue barrier was uniform up to the determined EI-EE bandwidths before and after ALI.

Conclusion

Direct simultaneous Ppl and Pes measurement reveals that the Ppl-Pes tissue barrier has a uniform amplitude frequency response within the EI-EE bandwidth of conventional Pes waveforms in healthy lungs and ALI and

does not significantly attenuate Ppl-Pes signal transmission between 1 and 40 Hz. At Pes frequencies higher than conventional clinical regions of interest, the Ppl-Pes barrier resonates significantly, is pressure amplitude dependent at low pressure offsets, and is significantly altered by ALI.

Allowing for 5% or less of Pes waveform error, the maximum Pes EI-EE bandwidths during conventional ventilation are 1.9 Hz and 3.4 Hz for physiologic and extreme-case waveforms in healthy lungs, and 4.6 Hz and 8.5 Hz during ALI. For a 3% or less waveform error, the maximum Pes EI-EE bandwidth is 8.5 Hz.

In Vervet monkeys, the Ppl-Pes tissue barrier has a frequency response suitable for Ppl estimation during low-frequency mechanical ventilation, and Pes manometers should have a uniform frequency response up to 8.5 Hz. However, the Ppl-Pes tissue barrier adversely affects the accurate estimation of dynamic Pp' at high frequencies, with varied airway pressure amplitudes and offsets, such as the Ppl encountered during high-frequency oscillatory ventilation. These findings may facilitate the improvement of the accuracy of primate pulmonary function studies in high-frequency respiratory mechanics.

The authors thank Ernest Somys and the University of the Witwatersrand Central Animal Service, South Africa, for technical assistance.

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THESIS ERRATA

Page vii

Aspects of the research performed in this thesis have also been presented by the candidate as a guest speaker at two international universities in 2000:

- (i) City University of New York, Biomedical Engineering Department, seminar.
- (ii) The University of Kent at Canterbury Electronics Engineering Department, Medical Electronics Division, colloquium.

Page ix

FINANCIAL SUPPORT

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Chapter 3, page 85

BOTTOM: Supplemental Figure S3.B

Air-filled balloon-tip catheter ready for frequency response characterisation

Size 10 French gauge polyvinyl chloride catheter

- ~~i. Size 4 French gauge polyvinyl chloride catheter~~
- ~~ii. Large volume pressure transducer~~
- ~~iii. Small volume pressure transducer~~

Chapter 5, page 161

Supplemental Figure S5.B

Respiratory instrumentation and monitoring during acute lung injury.

- I. Endotracheal tube
- II. In-line inspiratory oxygen temperature and humidity control
- III. Pressure cycle pressure limit ventilator (PEEP, peak Paw, RR)
- IV. Proximal airway pressure (differential pressure transducer, Paw)
- V. Flowmeter (screen pneumotachograph connected to Validyne, pressure transducer, Fa_{airway} flow)
- VI. Animal End Tidal CO₂ monitor (sidestream, rapid response ET_{CO2})
- VII. Plethysmographic tongue monitor (arterial % haemoglobin oxygen saturation SaO₂)

Chapter 5, Page 156; Chapter 6, Pages 217, 220, 223

Airway-opening pressure Proximal airway pressure (Paw)

Chapter 6, Page 203

The right femoral vein was cannulated for injection of oleic acid saline vehicle or oleic acid (OA) to produce ALI.

THESIS ADDENDUM

Chapter 2, Page 67 and Chapter 3, page 111

Notes on the pressure offset and input pressures applied to the in vitro model

In the in vitro model used in this thesis the term "pressure offset" referred to is comparable to the term mean airway pressure due to mechanical ventilation in vivo, and the term "input pressure" is comparable to the ΔP_{aw} applied oscillating about the mean airway pressure in vivo. Dynamic in vivo P_{es} is dependent on the applied P_{aw} (mean and peak to peak), PEEP and $C_{L,dyn}$. Thus P_{es} may be negative in spontaneously breathing subjects reflecting a negative intrathoracic pleural pressure during inspiration or the negative intrathoracic pressure at end-expiration in non-PEEP mechanical ventilation. P_{es} may also be positive during positive pressure ventilation or forced expiration. In order to capture a broad range of P_{es} we applied a positive offset pressure since most infants are ventilated using PEEP, and oscillated the pressure in a sinusoidal fashion about this mean offset pressure to include negative and positive P_{es} pressures.

The values chosen for mean pressure offset and peak to peak oscillating pressures in vitro were initially determined by consulting a paediatric intensive care physician from a large intensive care unit routinely managing respiratory distress syndrome, prior to commencing the experiments of Chapters 2 and 3. Advice was obtained that

a PEEP of 5 cmH₂O and up to 40% transmission of peak Paw to Pes could be expected. These values are confirmed in this thesis (Chapters 5 and 6, see below) and are similar to those reported in the literature where Ppl and Pes magnitude is cited as being up to - 6 cmH₂O in the negative direction^(c), which is similar to the lower limit applied in Chapters 2 and 3, and anything up to + 30 cmH₂O in the positive direction, dependent on the applied Paw and lung compliance ^(a,b,c).

Chapters 5 and 6 of this thesis demonstrate in vivo that the expected magnitude of Pes pressures may vary depending on the applied Paw, the disease state of the lungs and the site of the Pes measurement. From Chapter 6 the mean % delivery of dynamic Paw to Pes, defined by Pes AUC/Paw AUC for 10 respiratory cycle ensembles was $64 \pm 7\%$ and $62 \pm 8.7\%$ for physiological PesB/PawB and elevated PesB/PawB respectively. Following ALI, % delivery values were reduced to 41 ± 6.3 and 43 ± 7.7 for physiological PesA/PesA and elevated PesA/PawA respectively. Thus ALI reduces the % delivery of Paw to Pes, but doubling the RR simultaneously and raising the Paw above that required for physiological PaCO₂ did not significantly affect the % delivery of Paw to Pes, before or after ALI (Chapter 6, Page 226). Physiological (= mechanical ventilation parameters set to yield a normal PaCO₂) peak Pes at baseline and in acute lung injury was 7 ± 2.4 and 8.3 ± 2.0 cmH₂O respectively, and the corresponding mean Pes was 3 ± 2.2 and 5 ± 1.5 cmH₂O.

Thus the -5 to +15 cmH₂O peak to peak oscillating pressure chosen for the in vitro model of chapters 2- 4 comfortably covered the likely upper and lower levels (twice the SD values) of the expected mean and peak Pes values during mechanical

ventilation, and the in vitro sinusoidal waveforms produced using a loudspeaker were suitably minimally distorted at this magnitude.

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- (b) Coates AL, Stocks J: Esophageal pressure manometry in human infants. *Pediatr Pulmonol* 1991; 11:350-360
- (c) Stocks J, Sly PD, Tepper RS, Morgan WJ: *Infant Respiratory Function Testing*. New York, U.S.A., Wiley-Liss, Inc., 1996. Pages 242, 243, 248.

Chapter 4

Notes on the clinical relevance of an invalid second order system assumption

Chapter 4's objective is clearly stated as being aimed at testing whether or not the second order assumption significantly affects the determination of certain frequency response variables, rather than whether or not the invalidity of this assumption will impact on the frequency response regions of clinical interest. Regions of clinical interest are highly variable with requirements differing between, for example, laboratory based investigators and clinicians or the type of waveforms being assessed (HFOV or conventional).

Perhaps the most useful variable measured in Chapter 4 indicative of whether or not the invalidity of the second order assumption could be clinically relevant is the SOFC:ORC at f_{A5} (the lowest frequency at which the mean amplitude frequency response deviates by $\geq 5\%$ from uniformity). This is a variable impacting on the lower end of the frequency response spectrum of the catheters: most physiological pressure waveforms' energy contents lie well within f_r , but not necessarily within f_{A5} of a catheter-manometer system. Chapter 4 shows that by employing the second order assumption essentially all the liquid-filled and air-balloon catheters' resulting f_{A5} values are statistically significantly incorrect (Chapter 4, Page 136). "Significant" here was defined as SOFC:ORC f_{A5} ratios with confidence intervals which excluded the ideal ratio of 1.0 and which additionally had mean ratios ≤ 0.95 or ≥ 1.05 . Note that (i) the significance definition used by the author here is a modest criterion only and (ii) Figure 4.2 (Chapter 4, page 136) presents the SD values (indicated in the legend) rather than the 95% confidence intervals or maxima. Purists might argue that the upper limits of the ratios, rather than the means, should be presented to determine the magnitude of the f_{A5} inaccuracy. Such an approach would have a large effect on increasing the f_{A5} value's reported inaccuracy and inter alia on predicting the clinical relevance of the inaccurate f_{A5} .

In summary, using only a modest statistical significance criterion rather than a stringent one, and presenting the mean f_{A5} inaccuracies rather than the maximal inaccuracies, the f_{A5} of both liquid and air-balloon catheters was shown to be incorrectly estimated when using the second order assumption. The magnitude of this inaccuracy was significantly different for liquid vs balloon catheters, being larger

for liquid filled catheters. The latter catheters are those in which the second order assumption techniques are more likely to be applied in clinical practice. The f_{A5} was also overestimated rather than underestimated; overestimation is potentially of greater clinical concern. However, the exact impact of these findings on clinical Pes measurements is hard to predict since to quantify this the extremes rather than the means of inaccuracy may need to be considered (worst-case observations from both the catheters original f_{A5} values in Chapters 2 and 3, as well as the SOFC:ORC f_{A5} ratios from Chapter 4), and the nature of the Pes waveforms to be measured clinically would need to be defined upfront. This is beyond the scope of Chapter 4's objectives and in any event the f_{A5} inaccuracy problem can be avoided by using an in vitro sine wave generator technique; this remains the concluding recommendation based on Chapter 4's findings.

Chapter 5, Page 161, Figure S5.B.

Notes on the SaO₂ monitoring

This is a supplemental figure included to show the scope of measurements and monitoring required to maintain physiological stability in this experimental model of acute respiratory distress syndrome. SaO₂ is mentioned in the legend to the figure and was monitored as a routine (late) warning device whilst an arterial line was being established or re-established. Suitable in vivo calibration of SaO₂ measurement apparatus remains an unsolved problem to date and this unbenchmarked parameter should probably not be used as a valid scientific endpoint in critical care illness laboratory-based studies. The measurement error in

SaO₂ readings increases with reducing SaO₂, is site-dependent (we found that the monkey tongue was the only position which yielded consistent signals), and the algorithm generating the SaO₂ reading may be species and age dependent. Our SaO₂ tracings (Nellcor pulse oximeter) were digitally captured, however the more accurate PaO₂ was presented as the variable indicative of arterial oxygenation (measured using a fully calibrated Stat Profile 3, Nova biomedical, MA, USA) as per chapter 5, page 167.

Chapter 5, page 174, Table 5.2 and Chapter 6, page 226, Table 6.2

Notes on the different % transmission of Paw to Pes values presented in these tables

The minor differences in % transmission of Paw to Pes between Chapters 5 and 6 were not due to the measurement systems since in both chapters the same animals, Paw transducer and Pes water-filled balloon-tipped transducer tip catheter were used. The minor differences arise from the methodology used to determine % Paw to Pes transmission. In Chapter 5 the Paw and Pes delta end-inspiration to end-expiration value was measured, over 3 respiratory cycle ensembles (Chapter 5, page 167, paragraph 2), at physiological ventilation parameters, whereas in Chapter 6 the Paw and Pes AUC was used, over ten respiratory cycle ensembles (Chapter 6, page 226), at physiological and elevated ventilation parameters. Despite these methodology differences the values between the two chapters are similar in magnitude and direction.

Chapters 5 and 6

Notes on the use of laboratory-modified micro-tip transducers to measure P_{es} and P_{pl} .

Negative reports^(a,b,c,d) currently outweigh positive reports in the literature concerning the ease of use or the validity of using P_{es} micro-tip transducers to estimate P_{pl} for lung compliance determination. However, in none of these validation reports is P_{pl} measured directly and the validity of P_{es} microtip transducers is largely questioned based on the relatively static occlusion test or based on comparisons with conventional fluid-filled catheters.

The author cannot entirely exclude the possibility that in Chapter 5 the C_{Ldyn} measurements could be relatively different to those which may have been obtained had conventional fluid-filled catheters been used to measure P_{es} . However, such an effect would be minimal for the following reasons:

The purpose of this experiment was to compare the C_{Ldyn} of control against acute lung injury subjects. The same P_{es} measurement apparatus was used in control and experimental subjects and the accuracy of the absolute values is thus less important.

The laboratory-modified micro-tip transducer catheters were also validated in vivo in the same fashion as that used to validate conventional fluid-filled catheters in vivo using the occlusion test (Chapter 6, page 215, Table 6.1).

Additionally, any differences between the Pes microtip transducer used and conventional Pes fluid-filled catheters would not have affected the C_{RSdyn} values reported in Chapter 5, pages 174 and 186.

Furthermore, the baseline CTRL and ALIG C_{Ldyn} values obtained are similar to those of human infants⁽⁹⁾ and C_{RSdyn} or C_{Ldyn} values resulting from acute lung injury fall within the ranges described for newborn infants with RDS⁽⁹⁾ and for low birth weight infants with severe RDS⁽⁹⁾.

In Chapter 6 Pes and Ppl was measured directly, using laboratory-modified microtip catheters with similar catheters' structural properties on both sides of the transmission barrier (Ppl-Pes) undergoing evaluation. Therefore concerns raised about the validity of these results based on the inherent structural properties of micro-tip catheters' potential to interfere with the Ppl and Pes measurements are minimised. One obvious problem with micro-tip transducer catheters in comparison with conventional fluid-filled catheters is the reduced intra-esophageal volume over which they measure Pes. This was not a factor in the author's experiments since the micro-tip transducer catheters were adapted in the laboratory to have a water-filled balloon surrounding, unlike conventional micro-tip transducer catheters. The Pes and Ppl manometers used were validated in vitro (Chapter 6, page 213) and equally exhibited an exceptionally wide bandwidth, were linear over a large amplitude, and yet measured dynamic pressure over a large portion of the esophagus and pleura, with which to characterise the Ppl-Pes tissue barrier.

In Chapter 6 the "unconventional" laboratory-modified micro-tip transducer catheters were deliberately used (for reasons outlined in Chapter 6, page 238) to measure dynamic Pes and Ppl at low and high frequencies. These laboratory-modified catheters were validated in vitro, but not in vivo against conventional catheters:

Although it may be possible to validate in vivo the laboratory-modified catheters against conventional fluid-filled Pes catheters for respiratory waveforms of low bandwidth, this would not be possible for waveforms with higher frequency contents since conventional fluid-filled catheters do not exhibit a uniform amplitude frequency response (Chapters 2 and 3).

Note too that conventional fluid-filled Pes catheters' dynamic Ppl estimations have themselves not been validated against direct Ppl measurements anyway.

As per above, the laboratory-modified micro-tip transducer catheters were validated in vivo for Pes measurement in each subject in the same fashion as that used to validate conventional fluid-filled catheters in vivo using the occlusion test (Chapter 6, page 215, Table 6.1).

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Author Hartford C G F

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