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Noncompaction of the ventricular myocardium: Factors associated with the compaction ratio in congenital and acquired paediatric cardiac disease.

Vivienne Hunter

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in medicine, in the field of Paediatric Cardiology.

Johannesburg, 2008

DECLARATION

I, Vivienne Hunter declare that this dissertation is my own work. It is being submitted for the degree Master of Science in medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



This 5th day of May 2009

TO MY FAMILY

For your patience, support and love.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY.

1. Presentation to: Health Sciences research Day, University of Witwatersrand Faculty of health Sciences. August 2006. Winner of Best Junior Researcher award, in category of chronic illness and diseases of lifestyle.

2. Presentation to: South African Heart Association Congress, Cape Town 2006. Winner of 2nd prize, in category of Short Presentations.

3. Clinical meeting of the Paediatric cardiology group at Sunninghill Hospital 2nd June 2007

ABSTRACT

Left ventricular (LV) noncompaction is characterized by the presence of an extensive trabecular myocardial layer within the luminal aspect of the compact myocardium of the ventricular wall. The trabeculae are both excessive in number and more prominent than normal. Noncompaction may occur in isolation usually with clinical features of dilated cardiomyopathy, or it may be associated with congenital or acquired heart diseases. Echocardiography is the reference standard for diagnosis, where a ratio of thickness of trabecular-to-compact myocardium (compaction ratio) of >2 is a major diagnostic criterion. Noncompaction is usually considered to result from persistence of the highly trabeculated myocardium found in early cardiogenesis of the human embryo. If persistence of excess trabeculae is the only determinant of the compaction ratio it would be expected that it would remain a consistent measurement in postnatal life. However, temporal changes in the degree of noncompaction in individual case reports have raised the question as to whether the compaction ratio might be sensitive to haemodynamic or other factors.

In the present dissertation, I assessed echocardiographically whether the compaction ratio is associated with increases in indices of LV volume preload in 100 children or adolescents with ventricular septal defects (VSD), and 36 with chronic rheumatic heart disease (RHD). Compared to 79 normal controls (compaction ratio=1.4±0.07), patients with VSDs (compaction ratio=2.0±0.2, $p<0.0001$) and RHD (compaction ratio = 2.0±0.3, $p< 0.0001$) had a marked increase in the compaction ratio. A compaction ratio>2 was found in 42% of patients with VSDs and 47% with RHD. In VSDs, independent of age and gender, the compaction ratio was positively associated with LV mass index (LVMI) (partial $r=0.44$, $p<0.0001$), VSD size (partial $r=0.4$, $p<0.0001$), LV end diastolic diameter indexed (LVEDD) (partial $r=0.24$, $p= 0.01$), and the presence of additional shunts (partial $r=0.21$, $p=0.02$). In RHD,

independent of age and gender, the compaction ratio was positively associated with LVEDD (partial r=0.62, p=0.0001), and LVMI (partial r=0.48, p=0.005), and negatively with LV ejection fraction (partial r=0.31, p=0.03).

The strong association of indices of LV volume load and the compaction ratio would suggest that haemodynamic influences are contributing to the compaction ratio both in congenital and acquired cardiac disease in childhood. Thus an increased compaction ratio may be the consequence of an increased volume preload, and therefore may not necessarily occur only as a result of persistence of embryonic patterns.

ACKNOWLEDGEMENTS

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PREFACE

Noncompaction of the myocardium has received increasing attention in the medical literature, and has been proposed as a unique cardiomyopathy. Certainly it is a strange abnormality where the myocardium is predominantly trabecular, with very little compact myocardium. Consequently in its severe form it may have drastic clinical implications. However the condition is still poorly understood. The severe form is undoubtedly rare, but milder forms of so-called noncompaction are being diagnosed with increasing frequency, and there is now a danger of over diagnosis.

The potential for over diagnosis is partly derived from the diagnostic criteria which were proposed rather arbitrarily, based on a small patient cohort, and which have been widely accepted and applied. In particular the echocardiographic ratio of trabecular to compact myocardium, which we have termed the compaction ratio is the only objective diagnostic criterion, and is frequently clinically employed. However inconsistencies in the appropriateness of the compaction ratio prompted us to consider whether it might be affected by ventricular preload.

Hence in the following dissertation I have first undertaken a critical review of the literature, and the echocardiographic diagnostic criteria. The pathogenesis of noncompaction is an intriguing question and possibly the key to understanding the difference between true, congenital noncompaction, and a mere increase in prominence of the trabeculae. Therefore, in the introduction I have elaborated on pathogenesis of noncompaction, and speculated on possible mechanisms of noncompaction, trabecular proliferation, and an increased trabecular prominence.

In the present dissertation I have tested the hypothesis that the compaction ratio could be affected by volume preloading. To assess this hypothesis I measured ventricular chamber dimensions and mass and the thickness of the compact and

trabecular layers in both congenital and acquired cardiac disease in children leading to increased volume preloads. I subsequently assessed whether ventricular chamber dimensions and mass are related to the compaction ratio. The methodology for the present study is described in chapter 2 and the results in chapter 3. Finally I have placed my findings in context with comparisons to other published studies in a discussion chapter (chapter 4).

In support of the present dissertation, the studies described within have been presented at the Health Sciences research Day, University of Witwatersrand Faculty of health Sciences. August 2006 winning “Best Junior Researcher award, in the category of chronic illness and diseases of lifestyle”, and was also presented to the South African Heart Association Congress, Cape Town 2006 winning the 2nd prize, in the category of Short Presentations.

LIST OF ABBREVIATIONS

ASD	Atrial septal defect
AR	Aortic regurgitation
BMI	Body mass index
BSA	Body surface area
FSend	Fractional shortening, endocardial
FSmid	Fractional shortening, midwall
IVST	Interventricular septal thickness
LV	Left ventricle
LVEDD	Left ventricular end diastolic diameter
LVEDDI	Left ventricular end diastolic diameter indexed to body surface area $^{0.5}$
LVEF	Left ventricular ejection fraction
LVDV	Left ventricular diastolic volume
LVM	Left ventricular mass
LVMI	Left ventricular mass indexed to body surface area$^{1.5}$
LVNC	Left ventricular noncompaction
LVSD	Left ventricular systolic diameter
LVSV	Left ventricular systolic volume
MR	Mitral regurgitation
MS	Mitral stenosis
PDA	Patent ductus arteriosus

PWT	Posterior wall thickness
RWT	Relative wall thickness
RV	Right ventricle, or right ventricular
VSD	Ventricular septal defect

CHAPTER 1

NONCOMPACTION OF THE VENTRICULAR MYOCARDIUM

A CRITICAL LITERATURE REVIEW AND AIM OF STUDY

1.1 Introduction and definition of noncompaction

Trabeculae are discrete muscle bundles, covered in endothelium, which are found in the apical portions of the left ventricle (LV) in all hearts. Enlarged trabeculae, more than 2mm in diameter may occur in 68% of normal hearts, but are virtually always three or less in number [1]. In hearts with left ventricular noncompaction (LVNC), the lumen contains a prominent network of thin and thick endocardial bands, tendons, filaments and trabeculae that intermingle with each other to form a thick trabeculated layer, extending from the mid-portion of the LV to its apex [2]. Trabeculae are both increased in prominence and excessive in number [3]. The outer, compact layer of myocardium tends to be thinner than normal [4, 5, 6].

Between the network of trabeculae are deep recesses, in continuity with the LV cavity, but not with the epicardial coronary system [3, 7, 8, 9, 10]. In LVNC the most commonly affected segments are the apical and mid-ventricular inferior and lateral walls [11, 12]. The interventricular septum may be infrequently involved [13, 14, 15, 16] and the base of the heart is never involved [6]. Examples of LVNC are shown in Figures 1.1 a-d.

In the present dissertation I have studied the factors associated with the compaction ratio, a measurement used in the diagnosis of LVNC, in a paediatric population with congenital and acquired cardiac disease. Consequently, as an introduction to this dissertation, in subsequent sections of the present chapter I will critically review the evidence to indicate the anatomical abnormality involved as well as the diagnostic criteria, the incidence, the clinical presentation, the clinical consequences or implications and the potential pathogenesis of LVNC, highlighting the controversies within the field.

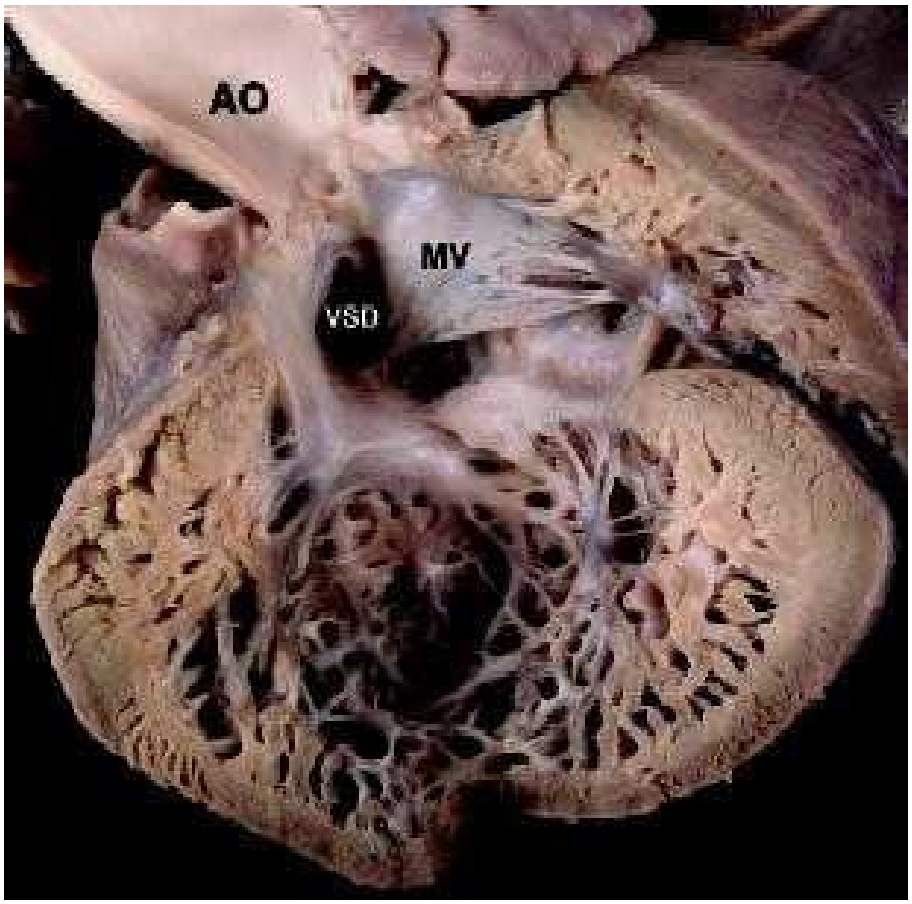


Figure 1.1a. Left ventricular noncompaction in an infant with complex congenital heart disease, isomerism of the left atrial appendages, and a ventricular septal defect. From: Freedom, R.M., Yoo, S., Perrin, D., Taylor G., Petersen, S., Anderson, R.H. The morphological spectrum of ventricular noncompaction. Cardiol Young 2005; 15:345-364. Used with permission.

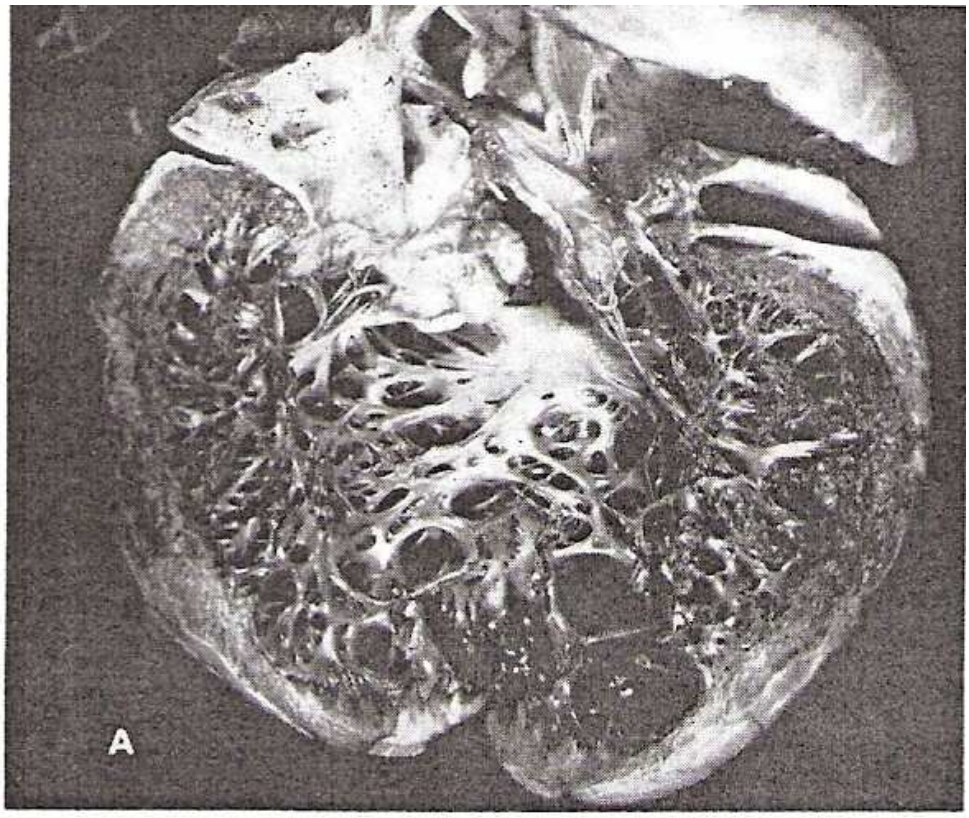


Figure 1.1b Left ventricle in a spongiosum heart with situs inversus totalis. “The trabeculae carnae of the stratum spongiosum underwent differentiation but failed to resorb”. From: Van Praagh, R., Ongley, P.A., Swan, H.J.C. Anatomic Types of Single or Common Ventricle in Man. Morphologic and Geometric Aspects of 60 Necropsied Cases. Am J Cardiol 1964 13; 367-385. Used with permission.



Figure 1.1c. Left ventricle of an infant with noncompaction and a small muscular ventricular septal defect, who died of intractable cardiac failure. Used with permission



Figure 1.1d. Left ventricle in a patient with tricuspid atresia showing multiple trabeculae filling the LV cavity, and probable LVNC. Used with permission

1.2 Normal anatomical architecture of the myocardium

As the diagnostic criteria for LVNC depend on an understanding of the normal myocardial architecture, I will first review the anatomy of the normal architecture of the LV myocardium. The presence of both a trabecular and a compact layer of myocardium is not unique to LVNC. Indeed, the healthy myocardium in the LV normally has a distinct two-layered appearance with an outer compact layer and an inner trabecular layer [1, 17, 18, 19]. As illustrated in Figure 1.2, in the normal LV, the trabeculae consist of many fine, muscular structures, covered in endothelium. Small recesses can be discerned between the trabeculae, and the trabeculae are mainly confined to the apical portion of the chamber, leaving the base and upper third of the septum relatively devoid of trabeculae [19]. In addition, in the normal LV, intracavity structures such as false tendons, which are composed of muscle and connective tissue and which are richly vascularised [20], as well as aberrant bands are common [1, 21, 22, 23].

The fibre orientation of the trabecular and compact myocardium is complex and has been the subject of study for five centuries by prominent scientists such as Vesalius, and Harvey. The myocardial body consists of aggregates of cross-connected myocardial cells in a three dimensional network. Dissection however identifies the long axis of these aggregated cells along preferential pathways, looking something like a ball of wool [24, 25, 26]. Various models (spirals, helices, and geodesics on a nested set of toroidal bodies) of these fibre arrangements have been proposed. Nevertheless the fibre architecture of the entire heart remains contentious, and it is not within the scope of this dissertation to discuss. However, as it pertains to the echocardiographic appearance of the LV, and possibly also to the effect of a volume load on the ventricle, I will discuss the myocardial fibre arrangement corresponding to the position in the LV where LVNC is normally identified.

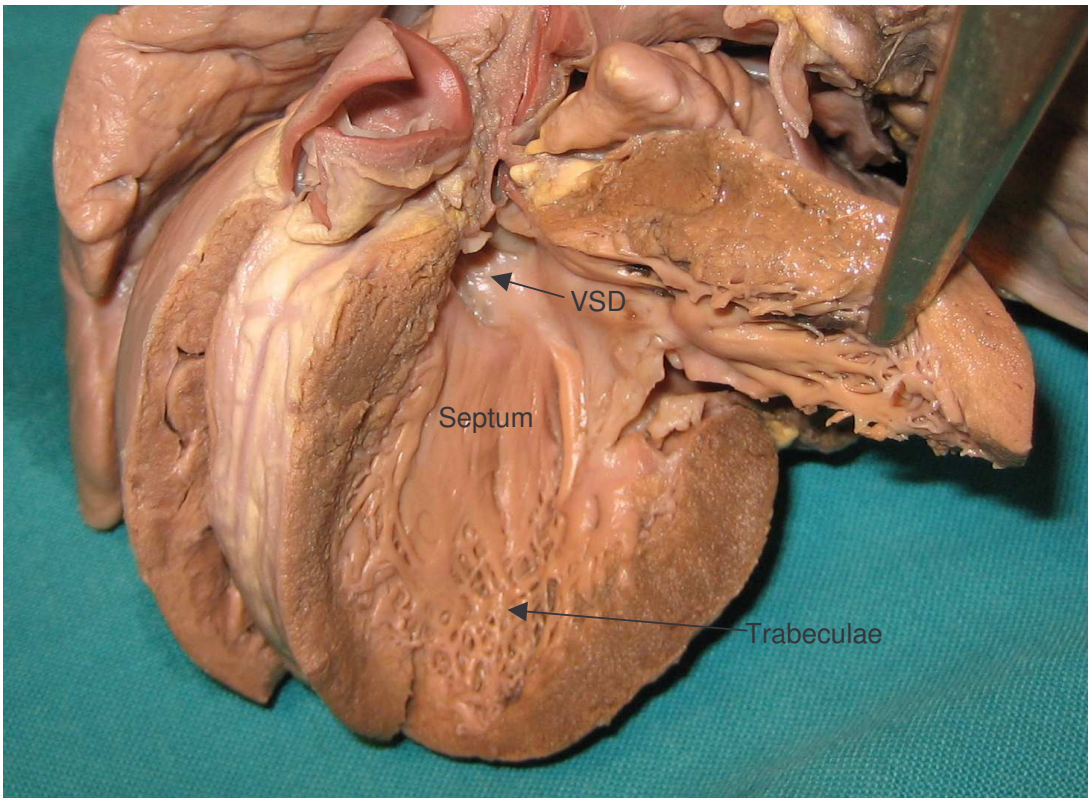


Figure 1.2a. Normal left ventricular trabeculation in a patient who had a perimembranous ventricular septal defect (VSD). The trabeculae are fine muscular structures covered in endothelium, and confined mainly to the apex and free wall. Small recesses can be seen between trabeculae.

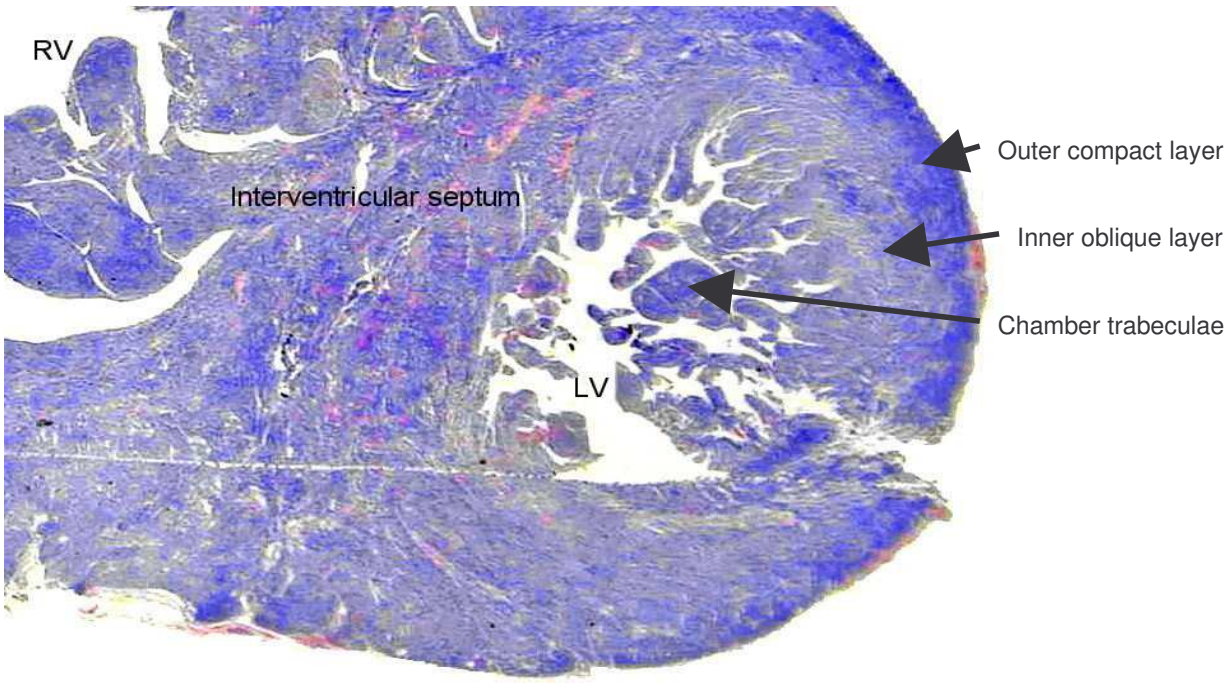


Figure 1.2b Cross section of left ventricle below the level of the papillary muscles, showing the circumferentially orientated outer compact layer, the oblique inner mural trabecular layer, and the longitudinally orientated chamber trabeculae within the LV chamber. Picture courtesy of Dr P. King of the Anatomical Pathology Department of the University of the Witwatersrand. Used with permission.

On gross and microscopic examination of a cross section of the LV between the base of the papillary muscle and the apex, three discernable layers are found [8, 9, 24, 26]). Outermost are fibres that spiral circumferentially [24, 25, 26]. Deep to this layer are the so- called mural trabeculata, a layer of oblique fibres where the tracks crisscross, and where abrupt fibre branchings occur [25]. The bases of the papillary muscles attach directly to this layer and not to the outer compact layer [17]. Spaces between these mural trabeculae exist, but are seldom apparent at autopsy because the heart usually arrests in a contracted state [17]. Within the LV cavity is a network of trabeculae (chamber trabeculae) and tendons that lie predominantly longitudinally [24, 25]. The fibre orientation of the different layers has important implications when discussing the echocardiographic appearance of the myocardium. Furthermore, as will subsequently be discussed, in the present study I assessed hearts in which a volume load resulted in dilatation of the ventricle. It is therefore of note that due to the variations in fibre orientation of the different layers, when stretched, the outer compact layer might tend to elongate in a circumferential direction, whilst the inner trabecular layers may elongate in longitudinal and oblique directions. Furthermore, it has been speculated that dilatation of the LV may reveal recesses between mural trabeculae that were not previously apparent [27].

1.3 The identification of clinical noncompaction: History and the development of current approaches

The first clinical description of LVNC was published by Van Praagh in 1964, and the same case was more fully described by Feldt et al in 1969 [28, 29]. The patient had complex congenital heart disease, congenital heart block and intractable heart failure. The morphological LV had multiple, “bizarre, fine trabeculations” which

Feldt et al (1969) termed “spongy myocardium” (see figure 1b). These authors (Feldt et al 1969) also noted that the spongy myocardium resembled the myocardial pattern found in the human embryo at the time of cavitation of the ventricles. Thus it was thought that these bizarre trabeculae represented a persistence of the embryonic form.

In 1975 Dusek et al published a report describing an anatomical abnormality that appeared to be consistent with LVNC. Unfortunately this led to subsequent confusion because in the described cases the myocardial sinusoids in the LV communicated with both the ventricular cavity and the coronary vascular bed [30]. Persistent intramyocardial sinusoids are a different entity to LVNC, and usually arise in cases of severe congenital LV or right ventricular (RV) outflow tract obstruction, such as pulmonary atresia with an intact septum [31, 32]. In these patients regression of the embryonic sinusoids is impaired during ontogenesis by high luminal pressures, resulting in sinusoids communicating with both the ventricular cavity and the coronary artery system [33, 34]. Because of the inclusion of cases of sinusoids in Dusek’s report, many authors have erroneously linked LVNC to severe left or right ventricular outflow tract obstruction [6, 34, 35, 36, 37, 38, 39, 40]. Subsequent to this, histology of LVNC has indicated that the deep intertrabecular spaces in LVNC never communicate with the epicardial coronary system [3, 9, 27, 36].

In 1990 Chin et al reported 8 cases of isolated LVNC, diagnosed for the first time echocardiographically, and confirmed at necropsy. They proposed an echocardiographic ratio of the distance between the epicardial surface and the peak of trabeculation, to the distance between epicardium and trough of trabeculation, as a way of differentiating a noncompacted myocardium from normally trabeculated myocardium [3]. This ratio was somewhat difficult to use in practice, and never achieved widespread usage. However, following this report [3] the condition became increasingly recognised.

In 2001 Jenni et al proposed that isolated LVNC should be classified as a distinct cardiomyopathy, and described patho-anatomical, and echocardiographic characteristics for its identification [9]. Jenni's criteria have been widely adopted and a plethora of accounts of isolated and non-isolated noncompaction have followed. At this stage the World Health Organisation has still to recognize isolated ventricular noncompaction as a distinct and separate form of cardiomyopathy. In their 1995 report it was considered to belong to the group of unclassified cardiomyopathies [41]. More recently Maron et al (2006) have suggested that noncompaction be grouped with primary cardiomyopathies of the genetic subtype [42].

1.4 Nomenclature of the anatomical anomaly noted in noncompaction

As outlined in the aforementioned discussion, the initial reports termed LVNC "spongy myocardium"l [28, 29, 43]. Later, terms such as myocardial sinusoids, embryonic myocardium, anomalous ventricular myocardial patterns, dysplastic cardiac development, isolated LV abnormal trabeculation, myocardial dysgenesis, ventricular dysplasia, and honey-combed ventricle were used [2, 3, 44, 45, 46]. The terms "noncompaction", or "non-compaction" are now largely accepted, although some authors object to this term because it implies a developmental pathogenesis which has not yet been proven [46]. The term "hypertrabeculation" has been proposed by Stöllberger et al (2004) and is sometimes used interchangeably with "noncompaction" [47]. However these authors (Stöllberger et al 2004) define hypertrabeculation as having more than 3 prominent trabeculations, a definition that has not gained widespread acceptance [48, 49].

1.5 Identification of noncompaction

Whilst noncompaction may affect both ventricles, the normal architecture of the right ventricle (RV) is dominated by a trabecular pattern. This has made the condition less apparent in the RV and diagnosis of RV noncompaction is currently qualitative [36, 50]. Noncompaction is not thought to affect the atria [51]. Thus criteria for the identification of noncompaction of the LV, but not other chambers have been developed. Importantly, there are no age-dependent variations in LVNC [46] and hence age-specific criteria are not required. Although LVNC has been recognised on prenatal echocardiography, where it may be associated with fetal hydrops [52, 53, 54, 55] the focus has been on developing criteria for post-natal identification. Since LVNC is a condition where the trabeculae are both excessive in number and more prominent than usual, it may be recognized using various approaches.

The diagnosis of LVNC may be made at post-mortem on gross inspection combined with histopathological techniques [10, 56]. Left ventricular noncompaction is being diagnosed more frequently as an incidental finding at autopsy, suggesting that in the past its presence has often been overlooked [56]. However, in life, LVNC may be recognized using echocardiography, angiography, magnetic resonance imaging (MRI) or computed tomography [16, 57, 58, 59] (See figures 1.3a,b,c,d., and Figure 1.4).

Quantitative as well as qualitative diagnostic criteria have been proposed for the diagnosis of LVNC using these techniques. However, recognition of LVNC is dependent on an awareness of the condition [60]. Echocardiography is considered the reference standard for the diagnosis of LVNC *in vivo* [38, 61].

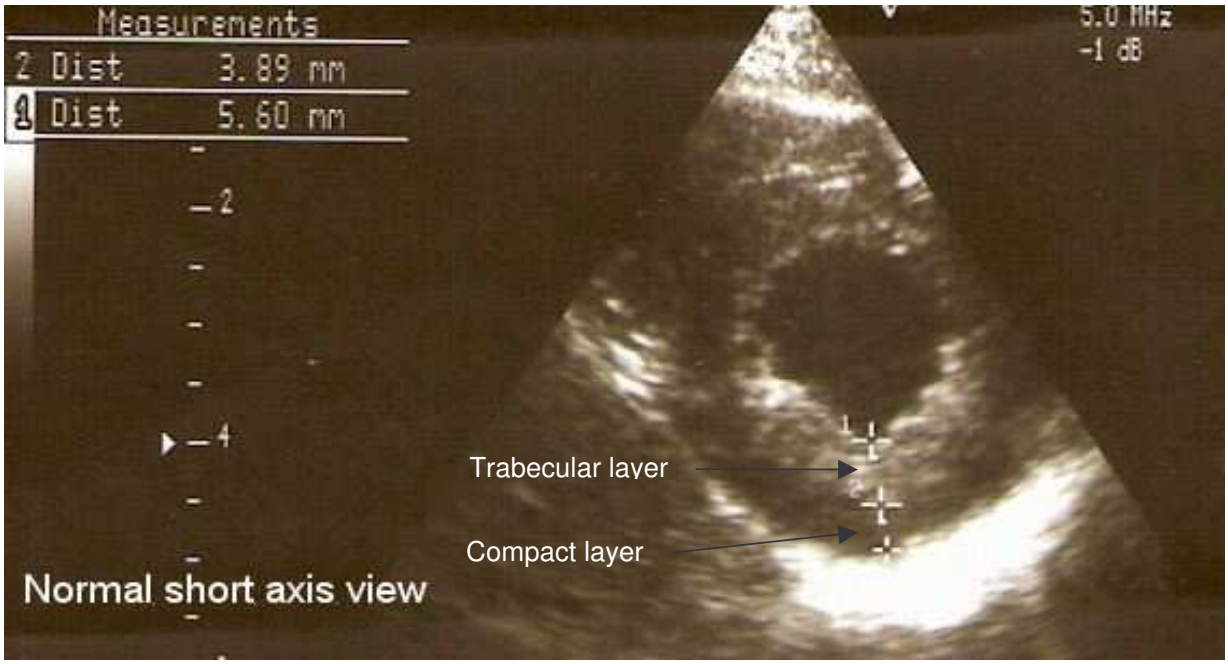


Figure 1.3a Normal LV myocardium on echocardiogram in short axis view. Compaction ratio = 1.4.

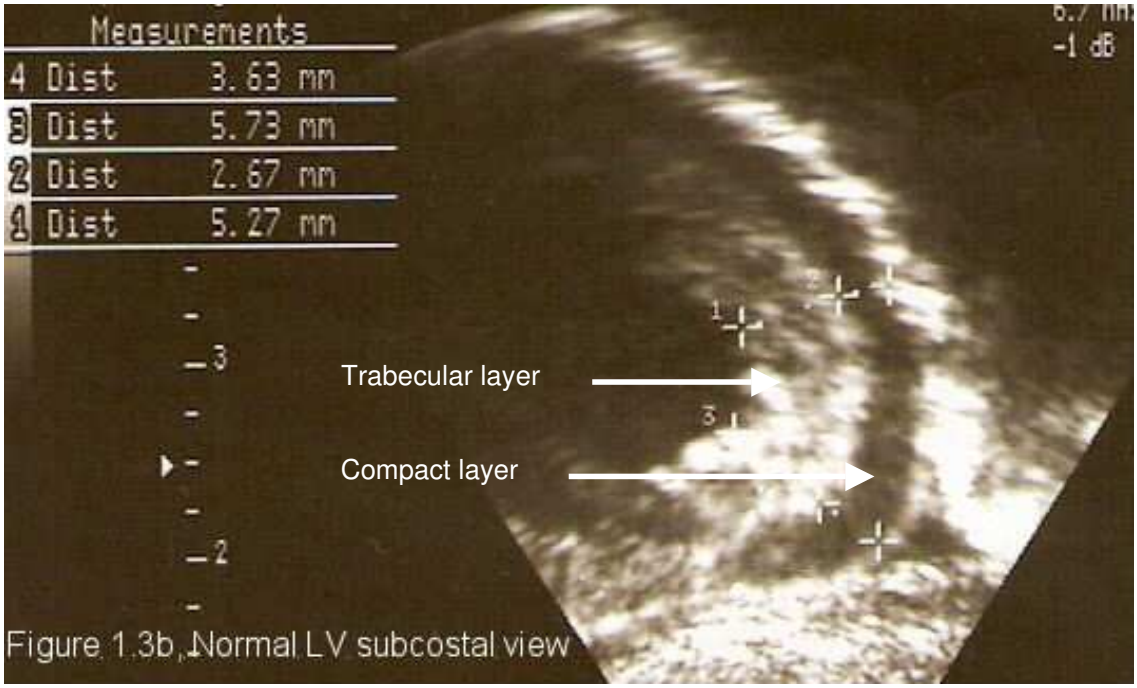


Figure 1.3b Normal left ventricular myocardium on echocardiogram in subcostal view. Compaction ratio, apical = 1.6

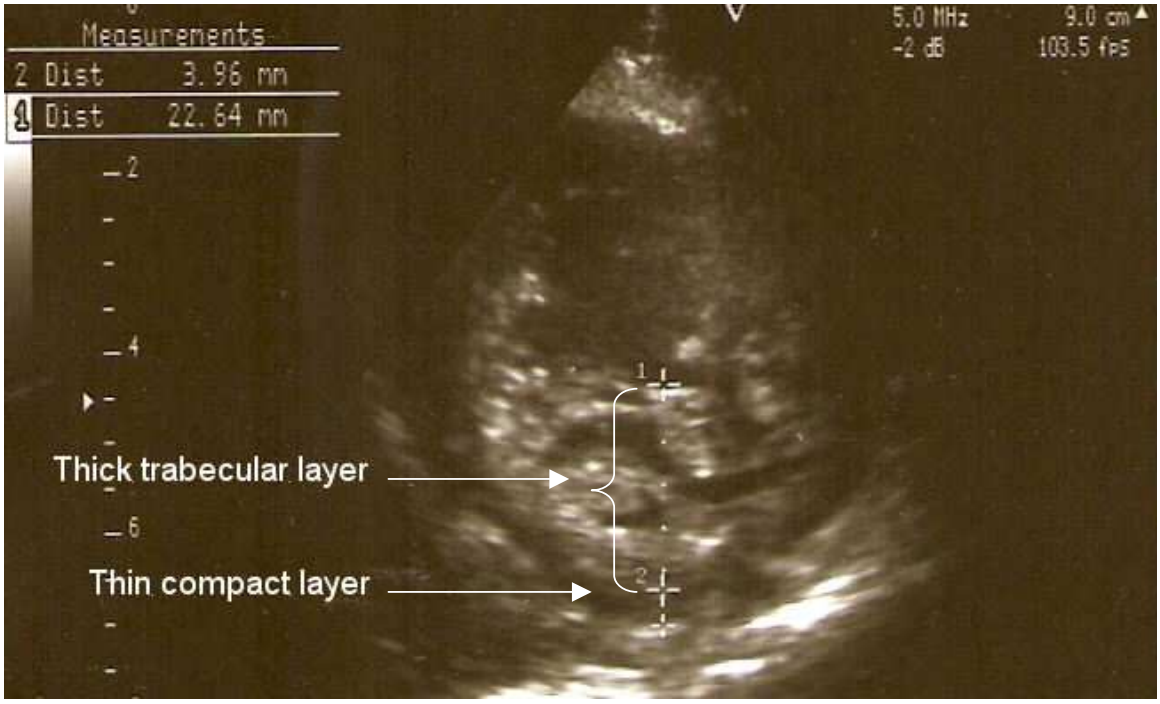


Figure 1.3c Short axis view of the left ventricle illustrating the thickened layer of trabeculae criss-crossing the chamber, in cross section in a patient with angiographically confirmed isolated LVNC. Compaction ratio= 5.7

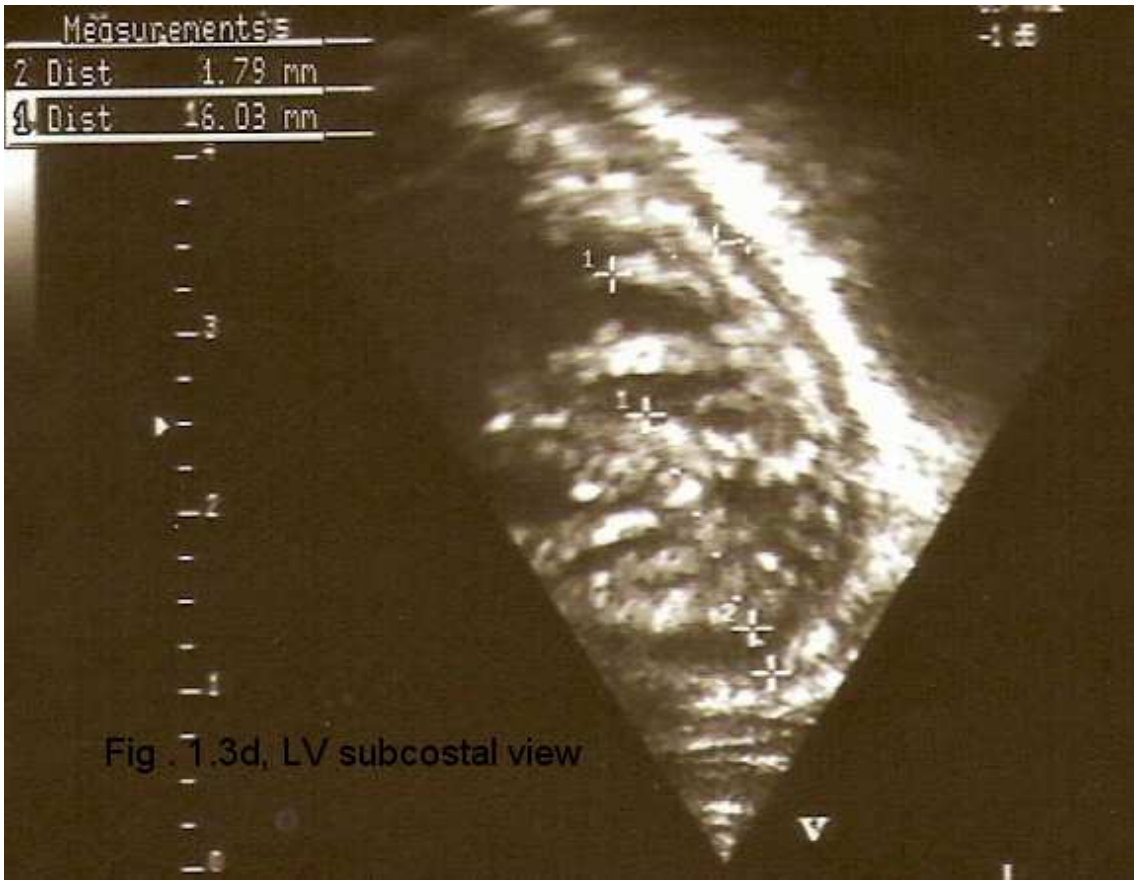


Figure 1.3d Subcostal view of the left ventricle showing thickened prominent trabecular layer, and a thin outer compact layer, in a patient with LVNC. Compaction ratio = 3.4.

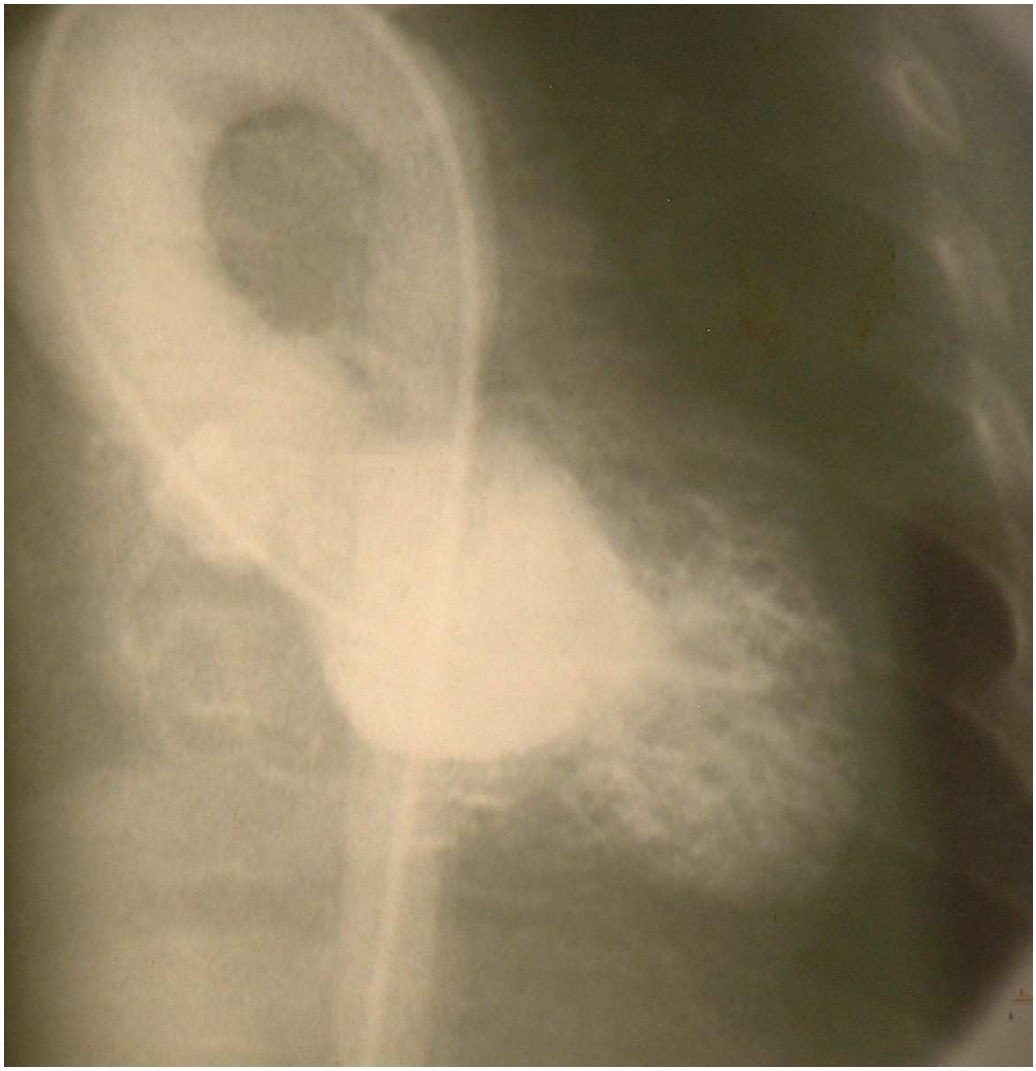


Figure 1.4 A left ventricular angiogram in a patient with LVNC. Note contrast filling of the recesses between trabeculae.

1.5.1 Echocardiographic recognition of LV noncompaction, and diagnostic criteria

To my knowledge no one has explained the 2-layered appearance of the myocardium on echocardiography. From consideration of principles of reflection of ultrasound in tissues, it is likely that the trabecular and compact layers of the myocardium have a distinctly different appearance because the fibres in the layers are differentially orientated (as described in 1.1, above), presenting varying reflective properties to the ultrasound beam. The outer, compact layer appears dark, while the mural and chamber trabeculae appear to combine as a single continuous layer, separate and distinct from the outer compact layer. The mural and chamber trabecular layer have multiple reflective surfaces that make them appear light on echocardiography.

The current echocardiographic diagnostic criteria for LVNC are a) excessive prominent trabeculations and deep intertrabecular recesses in the LV [9]; b) an LV end-systolic ratio of trabecular to compacted layers (compaction ratio) of greater than 2:1, best visualized in the short axis and usually measured at the position where noncompaction is most evident [9] (Figures 1.3 a, b, c and d); c) low scale colour Doppler flow into recesses between trabeculae [9]; and d) a predominant segmental location in the apical and mid-ventricular areas of both inferior and lateral wall [11, 61, 62]. An increased number of myocardial segments having a two-layered structure might be helpful in differentiating LVNC from normal or other pathologies [11, 19]. However, no particular threshold number of myocardial segments has yet been proposed as diagnostic. Further, the diagnosis of *isolated* LVNC requires the exclusion of other heart disease [9].

In adult patients the characteristic appearance of LVNC has sometimes been missed on standard transthoracic echocardiography, but identified on transoesophageal echocardiography [63], contrast echocardiography [64] or MRI [14, 16, 58, 65, 66].

In an attempt to clarify the diagnosis of LVNC, and as a step towards defining noncompaction as a true cardiomyopathy, Jenni et al (2001) proposed the aforementioned echocardiographic criteria, which have been widely accepted, albeit with reservations by some authors [13, 44, 67]. Indeed, the general acceptance of the compaction ratio as a diagnostic criterion is underscored by the fact that it is used to identify non-isolated LVNC, and in addition, the modified ratio has been incorporated into the diagnosis of LVNC in pathological specimens, angiography images and in MRI studies [19, 56, 68]. However, as these diagnostic criteria have been employed in the present dissertation, an appraisal of their utility is important.

1.5.2 The two-layered myocardium and the compaction ratio

In the original publication proposing diagnostic criteria for LVNC, Jenni et al [9] state that ”strictly speaking a two-layered structure is found only in isolated ventricular noncompaction, and not in left ventricular hypertrophy (LVH) or dilated cardiomyopathy (DCM) or any other condition”. Not surprisingly, some investigators have therefore interpreted the presence of a two-layered myocardium *alone* to indicate the presence of LVNC [16, 19]. Indeed, Frischknecht et al (2005) suggested that hypertrophic cardiomyopathy could be distinguished from noncompaction by the absence of a two-layered myocardium in the former [49]. However, as indicated in the aforementioned discussion, as the two-layered appearance is the result of different orientations of the myocyte fibre bundles, it exists in different proportions in

all hearts [69]. Consequently, a threshold of the compaction ratio is essential for the diagnosis.

1.5.3 Colour Doppler flow into recesses

Early descriptions of isolated LVNC, frequently indicated that patients who would now be considered to have LVNC, had previously been thought to have dilated or hypertrophic cardiomyopathy [34, 35, 37, 39, 60, 70, 71]. Jenni et al (2001)[9], in defining the aforementioned diagnostic criteria for LVNC, noted that colour flow into the recesses between trabeculae helped to differentiate LVNC from other pathologies. In hypertrophic cardiomyopathy a thickened two-layered myocardium is present, but the deep intertrabecular recesses characteristic of LVNC are typically less apparent and there is very limited colour Doppler flow within the myocardium [9, 34, 38]. However, colour Doppler flow into recesses does not distinguish normal from noncompacted myocardium. Normal myocardium includes trabeculation at the apex [1, 19] and both normal apical myocardium and noncompacted myocardium will demonstrate colour Doppler flow into the recesses between trabeculae. The difference between normal and noncompacted myocardium is therefore principally determined by the *ratio* of trabeculated to compacted myocardium. The lack of specificity of colour Doppler flow into recesses as a diagnostic criterion is underscored by the finding of Frischknecht et al (2005) that in adult patients, 48% with DCM, 9% with hypertensive heart disease (HHD), 10% with aortic regurgitation (AR), 9% with mitral regurgitation (MR) and 5% with aortic stenosis (AS) had perfused recesses [49].

1.5.4 Excessively prominent trabeculations

The presence of *excessive, prominent* trabeculation and deep recesses between the trabeculae is an important diagnostic criterion for LVNC. In other words there should be noticeably more trabeculae than normal, and they should occupy more of the LV chamber than normal. However this is a subjective criterion. Furthermore, up to 3 prominent trabeculations can be found in 68% of normal hearts at autopsy [1]. Thus, this criterion may have led to over-diagnosis of LVNC in some instances [34]. In reports where LVNC is described as 'mild noncompaction" [14] or "partial penetrance" [72], it is impossible to see how these cases can comply with the diagnostic criterion of "excessive prominent trabeculation".[67]

1.6 Incidence of left ventricular noncompaction

Although initial reports of LVNC suggested that it was very rare [3, 7, 37], with increasing awareness an increased frequency of reports has occurred, suggesting that in the past it has been overlooked [39, 65, 73]. Thus the reported frequency of identification of isolated noncompaction has changed over time (Table 1.1).

The true incidence of LVNC in the general population is unknown because usually only symptomatic individuals are referred for echocardiography. However, asymptomatic cases of LVNC have been discovered on screening [11, 16, 37, 62, 72, 74, 75, 76]. Many authors have pointed out that with increasing awareness of the condition, and better imaging technologies, the frequency of identification of noncompaction is likely to increase [68]. However, ambiguities in the diagnostic

criteria make it uncertain whether the condition might now be over-diagnosed [67]. A recent study suggests that black individuals may have a higher incidence of prominent trabeculations [67].

1.7 Clinical presentation

Although the anatomical substrate of LVNC should be evident at birth, clinical presentation can occur at any age [8, 12]. As indicated in Table 1.2, the clinical presentation of LVNC is varied. Some have indicated that the symptoms may depend on the extent of the noncompacted segments [61], but others have shown weak correlations between the extent of LVNC and ventricular dysfunction or symptoms [14].

Initial reports indicated that the prognosis in LVNC was very poor, often leading to death or transplantation [3, 5, 7, 8, 34, 36, 37, 63, 70, 77, 78, 79]. However, as LVNC is now increasingly recognized, there are numerous reports to suggest that noncompaction may have a spectrum of clinical presentations, including cases with a much more benign course, and that it may even occur in entirely asymptomatic individuals [11, 14, 36, 37, 59, 62, 75, 77, 80]. Asymptomatic cases have a significantly better outcome [80].

The diversity of presenting symptoms and the heterogeneous nature of clinical outcomes raises the question of whether LVNC might be an incidental finding in some cases.

Table 1.1 Reported incidence of left ventricular noncompaction.

Date	Author	Reference	Number of LVNC	Out of	Incidence	LVNC type/Patient cohort
1997	Ritter	[36]	17	37 555 echos	0.05%	Isolated
2001	Neudorf	[7]	7	9000 echos	0.08%	Isolated, in children
2002	Ozkutlu	[35]	12	20 341 echos	0.06%	Included non-isolated LVNC
2003	Nugent	[81]	29	314 cardiomyopathies	9.2%	Isolated, Children
2003	Pignatelli	[76]	36	344 cardiomyopathies	9.5%	Children, including non-isolated LVNC
2003	Hughes	[68]	31	1535 patients	2.0%	Children with CHD
2004	Ali	[13]	15	7250 echos	0.2%	Children, with CHD
2005	Sandhu	[82]	6	348 cardiomyopathies	1.7%	Community hosp cohort
2005	Stöllberger	[83]	77	28524 echos	0.25%	Adults, isolated
2006	Aras	[62]	57	42000 echos	0.14%	Adults, Isolated
2006	Lilje	[84]	66	5220 patients	1.26%	38% isolated 62% non-isolated
2008	Kohli	[67]	47	199 with LV systolic impairment	23.6%	Adults, isolated

Table 1.2. References pertaining to reasons for referral/ presenting symptoms reported in the literature.

Symptom/ reason for presentation	Adult, isolated LVNC	Children, isolated LVNC	LVNC+Congenital heart disease
Heart failure dyspnea, tachypnea, orthopnea,	[8, 34, 36, 57, 62, 64, 66, 74, 75, 80, 85, 86, 87]	[3, 5, 7, 15, 35, 37, 60, 70, 76, 88, 89]	[13, 29, 53, 54, 90, 91, 92]
Palpitations	[8, 36, 38, 62, 74, 80, 93]	[37, 70]	[91] (adult)
Syncope, dizziness	[8, 35, 36, 40, 58, 62, 71, 80, 93]	[16, 35, 37, 70, 76]	
Chest pain	[62, 80]		
Murmurs,		[7, 37, 70, 76]	[13, 76]
CVA/ TIA/ embolic event	[6, 62, 75, 85, 94]		
Failure to thrive		[76] i	
ECG /CXR abnormalities		[7, 37, 76]	[76]
Family screening	[8, 59, 62, 74, 75, 80]	[3, 37]	[13]
Other screening (e.g. school or Down syndrome)		[37, 43, 72, 95]	[13]
*Other	[8, 36, 74, 94]	[3, 15, 76]	[35, 76]

* Other includes nausea, fatigue, dysmorphism, congenital heart disease, pneumothorax, cyanosis seizures, cardiac arrest, myocarditis, pericarditis, mitral regurgitation and acute abdominal pain.

1.7.1 Histopathological findings

In attempting to understand the pathogenesis of the adverse clinical outcomes in LVNC, it is important to recognize that histological changes often characterise hearts with LVNC. However no specific histological finding is diagnostic of LVNC [61]. Within the trabecular zone changes associated with myocardial damage, such as interstitial fibrosis, fat cells, ischaemic regions and areas of subendocardial replacement fibrosis, necrosis, or scarring [7, 8, 9, 10, 36, 56, 61, 84, 87, 96] have been reported. In addition, loosely organized myocyte fascicles, abnormally thin and angulated myocyte fibres, increased perivascular and interstitial spaces, elongated mitochondria, and a reduced number of myofibrils have been observed [15, 84].

Endocardial fibroelastosis is commonly found [3, 8, 12, 15, 56, 88, 97, 98, 99] and poorly defined papillary muscles have been noted [6, 45, 56, 99, 100]. Trabecular hypertrophy or coarse trabeculations have been described [15, 54].

1.7.2 Left ventricular systolic dysfunction

Heart failure and systolic dysfunction is the most common clinical presentation in patients with isolated and non-isolated LVNC. Estimates of patients with heart failure vary from 53- 83%, [12, 36, 62, 76], albeit that LVNC has been described in patients with normal LV size and function [44, 65, 70, 72, 75, 101, 102, 103]. A survey of 238 Italian patients with LVNC indicated that all had a low ejection fraction [51]. Furthermore LV systolic dysfunction may progressively deteriorate [8, 35, 36, 37, 62, 71, 86, 87, 104], or may be undulating, i.e. having periods of recovery followed by deterioration [76]. Patients who are initially asymptomatic may later

develop LV dysfunction, [37] and the onset of symptoms is commonly delayed until adulthood [34, 76].

The reason for LV dysfunction in LVNC is uncertain. One suggestion is that the myocardium in LVNC is morphologically similar to the normal RV trabecular pattern. The RV is known to be less able than the LV to maintain systemic circulation in the case of univentricular hearts, where it is required to generate systemic pressures [3]. It is also possible that pump dysfunction in LVNC is a consequence of a reduced effective muscle mass. Indeed, a reduced ventricular pump function in cases of LVNC with heart failure could occur secondarily to a reduced thickness of the compact layer in relation to the trabeculated myocardium, in regions affected by LVNC. [18]. As will be discussed below (1.6.1) this would be consistent with observations from invertebrate hearts where a highly trabeculated myocardium is an adaptation for circulating large blood volumes, but does not generate high pressures. In animals with very active lifestyles, or those with large bodies, requiring high pressure pump function, the compact myocardium is well developed.

A number of histological changes have also been described in LVNC and these may promote a reduced contractile function (see above). With respect to tissue ischaemia, coronary angiography in LVNC usually demonstrates normal coronary vessels [4, 34, 87, 105], although in some cases coexisting major coronary artery disease is present [47, 57, 82]. Left ventricular dysfunction may nevertheless be the result of relative ischaemia due to mismatch of myocardial oxygen supply and demand [5, 34], or micro-coronary dysfunction as evidenced by restricted myocardial perfusion and a decreased flow reserve in areas of ventricular noncompaction in children [77].

Alternatively, LVNC might not cause LV dysfunction, but may merely be a marker for an underlying cardiac pathology. Indeed, a normal wall motion is more common in noncompacted than in compacted segments [106], and symptoms correlate with systolic dysfunction, but not compaction ratio or the number of

segments involved [80]. Thus, whether LVNC is the cause of LV systolic dysfunction, or is merely a marker for underlying pathology is still uncertain.

1.7.3 Left ventricular diastolic dysfunction

Diastolic dysfunction as manifest by a restrictive filling pattern on echo Doppler or high end-diastolic pressures at catheterization may occur with LVNC [8, 12, 14, 34, 37, 52, 59, 76, 78, 100, 105, 106, 107, 108]. The tei index (a measure of both systolic and diastolic dysfunction) is abnormal, although not predictive of poor outcome [12]. Pulmonary hypertension as a consequence of restrictive physiology and raised LV diastolic pressures has also been noted at cardiac catheterization or during echocardiography [7, 34, 37, 108]. Diastolic dysfunction in LVNC is thought to result from a combination of abnormal ventricular relaxation and restriction to filling caused by the abundance of intracavity trabeculae [34, 37]. Endocardial fibroelastosis is frequently reported [15, 37, 56, 85, 88, 98, 107, 109] and may also play a role in causing a restrictive physiology in LVNC.

1.7.4 Left ventricular dilatation

Left ventricular dilatation may occur in isolated and non-isolated LVNC [3, 5, 8, 16, 63, 75]. LVNC can however occur in patients with normal LV cavity dimensions [78, 80, 102, 108, 110]. A larger LV cavity in LVNC may indicate a poorer prognosis. Indeed, left ventricular end-diastolic diameter (LVEDD) at the time of initial presentation of LVNC is significantly larger in non-survivors as compared to survivors [8], and a poor outcome in LVNC may be predicted by an increased compaction ratio, and/or LVEDD at initial presentation [12]. The association between LVNC and increased LV cavity dimensions is usually attributed to the presence of LVNC leading

to LV systolic and diastolic dysfunction. However, as will be discussed, LV dilatation may accentuate trabeculations and in turn promote an LVNC-like appearance [21, 23, 111]. Thus, again, whether LVNC is a cause of or a marker for LV dilatation has not been established.

1.7.5 Thromboembolism in LVNC

In LVNC, thrombus formation between trabeculae has been detected both histologically in explanted hearts [3] or echocardiographically [3, 37, 62, 64, 76, 77]. Moreover, thromboembolic events have been reported to occur in patients with LVNC [6, 8, 36, 75, 85, 94]. Presumably the mechanism of the thrombus formation in LVNC is through stasis of blood within the trabecular recesses. However, thrombi almost invariably occur in patients with underlying LV systolic dysfunction or atrial fibrillation, a known risk factor. No thromboembolic events were recorded in untreated patients with an LV ejection fraction greater than 30% [80]. Thus it is not certain whether the presence of deep intramyocardial recesses is an independent risk factor for thrombus formation.

1.7.6 Arrhythmias and other electrocardiographic abnormalities in LVNC

A high prevalence (up to 75% of a cohort of 36 children [76]) of diverse electrocardiographic (ECG) abnormalities has been reported to occur in LVNC. These include ventricular hypertrophy [62, 76, 78, 91, 107], which may have extreme QRS voltages similar to those noted in Pompe's disease. In addition, isolated or diffuse T-wave inversion [37, 70], Wolff-Parkinson-White syndrome [3, 35, 37, 58, 60, 65, 76], first degree heart block [71], bundle branch block [8, 34, 35, 58, 60, 62, 64,

88, 103], complete heart block [3, 35, 37, 40, 62, 87, 99, 100, 112, 113, 114], sick sinus syndrome [103, 115], bradycardia [34, 37, 54, 103], atrial fibrillation [8, 34, 36, 37, 40, 62, 78, 80], atrial and ventricular premature contractions, and tachycardias [8, 35, 38, 71, 76, 80, 85] and ventricular fibrillation [3, 8, 29, 34, 36, 37, 52, 60, 71, 76, 85, 87] have been reported to occur in LVNC. In 3 reported series of patients with LVNC, sudden cardiac death accounted for 6/34 [8] , 3/17 [36], and 5/65 [80] deaths. In contrast however, not all studies have demonstrated a predisposition to arrhythmias in LVNC. Indeed, in a survey of 238 patients with LVNC in Italy, only 9 had supraventricular tachyarrhythmias, all atrial fibrillation [51].

The pathogenesis of arrhythmias in LVNC is unclear. Scarring and fibrosis may predispose to arrhythmias [36]. Normal ventricular conduction at 6 weeks, but bundle branch block at 4 months in one patient suggested that delayed ventricular conduction might be due to the development of severe endocardial fibroelastosis [88]. Wolff-Parkinson–White syndrome in the presence of LVNC may be explained by sharing a similar pathogenesis. Wolff-Parkinson–White syndrome is thought to arise from failed regression of developmental embryonic atrioventricular muscular continuity, and it is therefore not inconceivable that it may occur where there has been a failure of myocardial compaction [60].

1.7.7 Prognostic indicators in LVNC

Factors found to contribute to a poorer outcome (transplantation or death) in LVNC include: adults who have heart failure, sustained ventricular tachycardia or an enlarged left atrium [80], presentation of LVNC during childhood [116], the presence of additional congenital heart disease [117], a reduced LV ejection fraction at the initial presentation and New York Heart Association (NYHA) functional capacity [62], and both a compaction ratio greater than 3 and an LVEDD >5cm [12].

1.8 Pathogenesis of noncompaction

1.8.1 Noncompaction as an evolutionary adaptation

In animals noncompaction may represent an evolutionary adaptation related to environment. Indeed, in cold-blooded animals, the cardiac musculature may be almost entirely trabecular or spongy, resembling noncompaction [2, 30, 44]. The blood supply to the myocardium in these cases is mostly by diffusion through the recesses, as there is no well organized epicardial coronary system. This form of myoarchitecture is advantageous, and indeed necessary for circulatory function in many fish, despite its presence being considered to be disadvantageous in humans [2, 118].

Studies in bony fish indicate that there is a relationship between activity patterns (sedentary or active), myoarchitecture, and the pattern of blood supply to the hearts ventricle. Sedentary fish hearts have a predominantly trabecular myocardium, which is perfused through venous channels, have a high mitochondrial density in the cardiomyocytes, and function as low pressure pumps [119]. An example of this is the icefish, *Chaenocephalus aceratus*, which lives in Antarctic waters. It is adapted to an environment of stable low temperature and high oxygen content. The ice fish was once termed the “bloodless fish” because its blood is nearly devoid of haemoglobin and red blood cells. It compensates for this by having a high blood volume (2-4 times higher than most teleosts) [118], ensuring that an adequate amount of oxygen is carried in the dissolved rather than haemoglobin bound form [118]. Its heart, which as indicated consists of a predominantly trabecular myocardium, has a relatively increased weight for body weight, has high ventricular compliance, and works against

a low systemic impedance [2, 118, 119]. There is a high ratio of surface area to cavity volume, assisting in diffusion [118]. Multiple recesses result in an effectively multi-chamber ventricle, and although it handles a relatively large volume, the wall stress is low [118]. It functions as a specialized volume pump moving large stroke volumes at a low heart rate, but it is not able to generate high pressures [118].

In contrast, active fish such as adult tuna *Thunnus thynnus*, have a well developed dense, compact myocardium and arterial coronary supply. The heart of the adult tuna acts as a high pressure pump and is thus able to meet high metabolic demands [120].

In mammals too, noncompaction of the myocardium may represent an adaptive change. Indeed, in vertebrates, the relative amount of compact myocardium is related to the heart mass, i.e. in larger animals who need to generate a greater stroke volume, the compact layer is better developed [121].

1.8.2 Embryonic morphogenesis of the myocardium

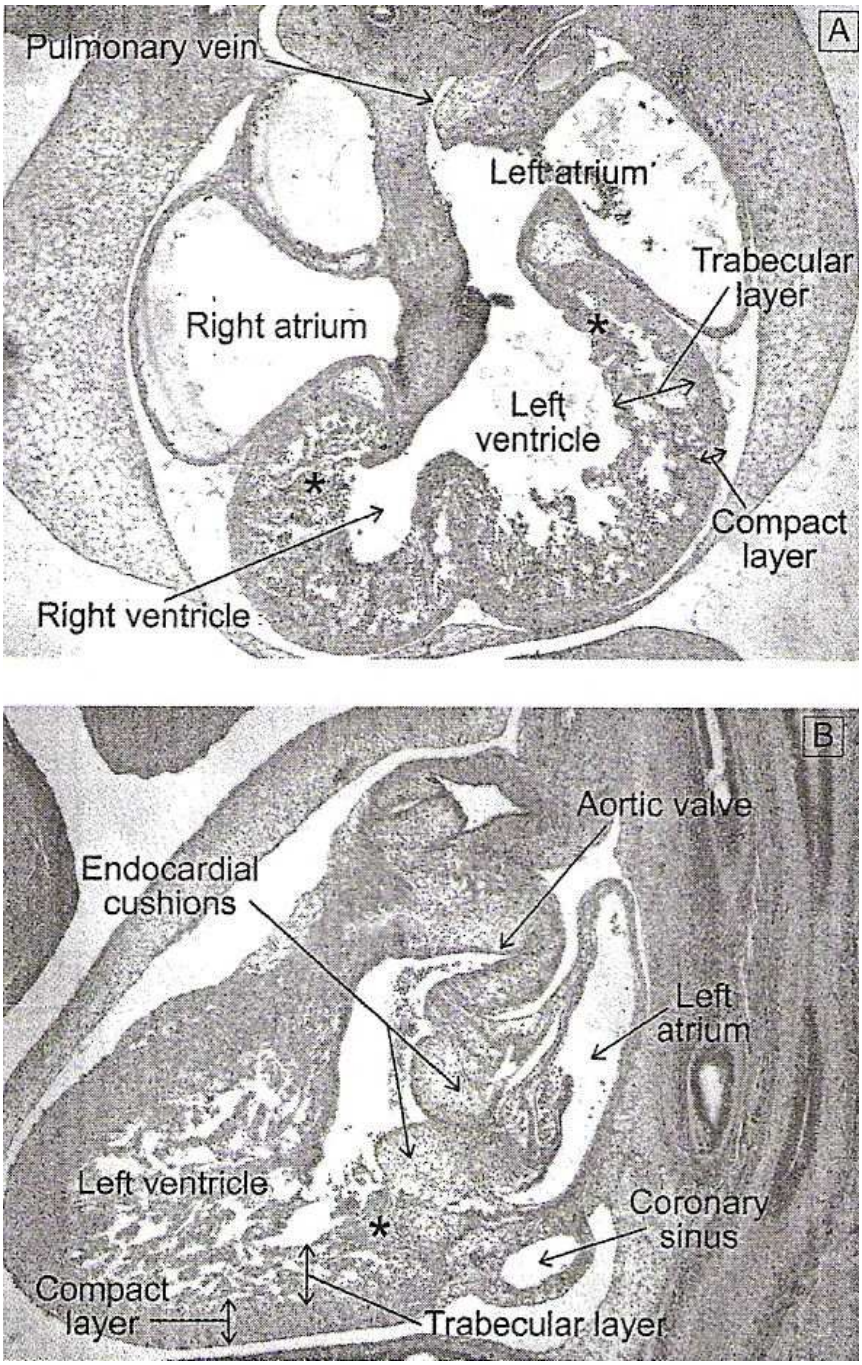
In humans LVNC has generally been thought to occur as a consequence of an abnormal persistence of the highly trabeculated myocardium that occurs during cardiogenesis [2, 3, 29]. Prior to discussing this theory therefore, a description of changes in the myocardium during cardiogenesis is of importance.

Early in cardiac development, at the end of the 4th week of gestation, the heart has a very thin outer compact later and multiple trabeculae within the LV chamber [2] (Figure 1.5). The resulting increase in surface area probably facilitates myocardial blood supply by exchange perfusion. It is likely that during this developmental period the trabeculae generate much of the contractile force of the heart [18, 122]. The trabeculae also have unique viscoelastic properties, and are associated with the terminal branches of the conduction system, thus providing the

morphological substrate for coordinated contraction [122, 123]. Epicardial coronary growth during the second month is associated with the disappearance of “sinusoids” and the transformation of some of the spongy myocardium into a compact musculature [56]. The developing myocardium gradually condenses, and the large spaces within the trabecular network disappear.

Papillary muscles and chordae tendinae develop from compaction (coalescence) of the trabecular layer [124] (Figures 1.5 a, b). The chordae which are initially composed of myocardial cells, are replaced with fibrous tissue [124]. Thus compaction of the myocardium and formation of the papillary muscles are closely linked processes. Papillary muscle abnormalities have been reported in cases of LVNC [6, 45, 56, 99, 100].

Compaction progresses from the epicardium towards the endocardium, and from the base towards the apex [84]. Trabecular compaction is usually more complete in the left side than in the right side of the heart [3, 33].



Figures 1.5 a and b. Sections of human embryo heart at Carnegie stage 16 (a), and 18 (b), showing an extensive trabecular layer, thicker than the compact layer. The trabecular layer becomes compacted to form the papillary muscle (asterisks). From: Freedom, R.M., Yoo, S., Perrin, D., Taylor G., Petersen, S., Anderson, R.H. The morphological spectrum of ventricular noncompaction. Cardiol Young 2005; 15:345-364. Used with permission.

1.8.3 Persistence of embryological patterns

The most widely held view of the pathogenesis of LVNC is that it is a congenital cardiomyopathy, and occurs as a persistence of the embryological pattern of trabeculae found at the time of cavitation of the ventricles [2, 29]. This theory implies that LVNC should be present at birth but that clinical manifestations may be delayed until later in life [9, 37, 60, 70, 75]. Evidence that supports this hypothesis includes the fact that there is a similarity in appearance of the embryonic pattern and the postnatal appearance of the noncompacted heart; that genetic interruptions of that process in the fish, chick, mouse and possibly humans results in persistence of the embryonic pattern, resembling LVNC; that LVNC appears to have a hereditary basis (familial and genetic associations - see below); and that LVNC is often associated with other congenital heart disease [2].

1.8.4 Genetics of LVNC

The prevailing hypothesis for the mechanism of isolated LVNC is that a genetic defect occurs that results in persistence of the embryonic trabeculated myocardium. Indeed, LVNC aggregates in families [3, 6, 8, 13, 14, 15, 36, 38, 52, 72, 74, 75, 76, 85, 97, 125]. The search for a genetic marker for LVNC in humans, has revealed genetic heterogeneity [97, 126, 127, 128]. A growing list of mutations have been associated with LVNC, including mutations of the G4.5 (taffazin) gene located on Xq28 (Barth syndrome) [15, 116, 129], the α-dystrobrevin gene [97], the DTNA gene [126], the Cypher/ZASP gene [130], the lamin A/C gene [131], at 11p15 [132], and 22q11[76] or in other positions [128].

Importantly, the clinical phenotype within families as well as unrelated individuals with the same mutation is highly variable [126]. Indeed, even in familial

cases, LVNC demonstrates a wide phenotypic spectrum that ranges from extreme severity such as prenatal/neonatal lethality to mild forms of noncompaction (not meeting diagnostic criteria) with a complete lack of symptoms [14]. Furthermore, in familial cases, relatives may have features consistent with dilated cardiomyopathy, hypertrophic cardiomyopathy or restrictive cardiomyopathy rather than LVNC [37, 75]. Mutations of the G4.5 gene can result in a variety of cardiac phenotypes, including a dilated cardiomyopathy, endomyocardial fibroelastosis, and a dilated hypertrophic cardiomyopathy [97]. Furthermore these phenotypes have been reported to change over time, possibly in response to therapy [97]. Understanding the genetics of LVNC therefore may depend on clarifying the distinctive diagnostic features and investigating the contribution of all known cardiomyopathy-causing genes with overlapping morphology [128].

In support of a genetic contribution nevertheless, LVNC is also known to be part of various syndromes including Barth, Noonan, Roifman, Melnick-Needles, Nail-Patella, Toriello-Cary, and others [2, 99, 112, 129, 133]. Dysmorphism is occasionally present [3, 37, 74, 76, 80, 85, 103]. However, the majority of these are single case reports and systematic studies are lacking. Therefore, it is uncertain whether these syndromes are always associated with LVNC or whether it is just an incidental finding in some.

1.8.5 Experimental noncompaction supports a genetic mechanism

Left ventricular noncompaction has been experimentally linked to various genetic mutations, thus supporting the likelihood that LVNC is a congenital malformation and has a hereditary basis. Experimentally, LVNC has been shown to result from disruptions in several genetic pathways. Genetic and molecular studies have shown that Bone Morphogenetic Protein 10 (BMP 10) is essential for

maintaining cardiac growth during murine cardiogenesis. If BMP10 is upregulated in hearts deficient in FKBP12, lethal LVNC results [134]. In mice, a deficiency of Jumonji, a nuclear protein necessary for normal heart development, results in ventricular septal defects (VSDs), a double outlet right ventricle, and LVNC [135]. King et al have studied the expression of Peg 1, a gene of unknown function, but which is widely expressed in the mouse embryo [135]. Mice lacking the Peg1 gene are viable, but have intrauterine growth retardation, and develop a subtle alteration in the pattern of myocardial trabeculation similar to that seen in human LVNC [136]. Shou et al (1998) found that mice lacking the FKBP12 gene have VSDs and dilated hearts in which the trabecular pattern mimics LVNC [137].

1.8.6 Noncompaction as an acquired disorder

As indicated in the aforementioned discussion, if LVNC is a congenital malformation, then it should be present in the prenatal and early postnatal period. However, various findings do not fit the congenital cardiomyopathy theory, and questions have been raised as to whether LVNC could be acquired postnatally. Firstly, despite a normal prenatal or early postnatal echocardiograph noted in some infants, these same infants may develop LVNC only later in life [15, 35, 115]. This nevertheless could be attributed to limitations in early imaging [15, 78, 138]. Secondly, a compaction ratio of >2:1 can be found in both congenital and acquired cardiac pathology and this will be described in subsequent sections. Although the presence of LVNC together with other congenital heart disease may not be surprising, the presence of LVNC in acquired pathology raises the question as to whether LVNC is indeed only a congenital abnormality. Thirdly, further suggestive evidence from case series favours a non-congenital mechanism of LVNC. Indeed, the ratio does not appear to be consistent in time [13, 44]. Ali and Godman (2004)

have described a case where ventricular dimensions changed and function improved and that these changes were associated with a reduction of the compaction ratio from 2.2 to 0.9 [13]. Moreover, Stöllberger and Finsterer reported on a case of disappearance of noncompaction [111]. Pignatelli et al (2003) described two cases that they termed the “undulating phenotype” in which the compaction ratio changed over time [76]. Further, Toyono et al reported on a patient who had regression in the degree of LVNC in response to treatment with carvedilol [89]. Pfammatter (1995) described a patient with myocarditis due to Coxiella infection who developed a dilated LV with a spongy appearance and the spongy appearance normalized following treatment and reductions in cavity volume [139]. In addition, several cases of acquired LVNC, or increased compaction ratio following deterioration in LV function have been reported [140, 141, 142, 143]. Furthermore, our group have documented a number of cases where the compaction ratio has changed, following medical or surgical interventions. See Table 1.3, and Figure 1.6a, b.

If LVNC was entirely attributable to a congenital persistence of trabeculae, the compaction ratio should remain constant throughout life. Temporal changes in the compaction ratio related to the LV function or size suggest that perturbations in the volume status of the ventricle, or other influences, may affect the prominence of the trabeculae, mimicking LVNC. Whether these changes are simply due to increased prominence of existing trabeculae, or whether trabecular proliferation might occur in as a compensatory response to unfavourable haemodynamic conditions, will be discussed.

Table 1.3. Examples of our own cases where the compaction ratio has improved over time, following interventions.

Patient	Background	Date 1	LVEDD1 (mm)	EF1 (%)	CR1	Date 2	LVEDD2 (mm)	EF2 (%)	CR2
1*	Cardiac failure, DCMO	30/08/2004	49	12	3.0*	28/06/2007	37	70	1.5*
2	HIV+, DCMO	6/01/2005	55	25	4.4	11/10/2006	45	53	2.0
3	VSD, and AR for surgical closure/repair	22/10/2007	63	8	4.5	02/11/2007 (post operative)	49	48	2.6
4	RHD, MR and mild AR	23/11/2007	54	60	3.1	07/12/2007	46	48	2.7
5	HIV+, DCMO, PTB	16/09/2004	53	46	3.6	11/07/2007	53	58	1.1
6	Large VSD for repair	19/07/2005	37	79	2.5	26/03/2008 (post operative)	30	66	1.4
7	RHD, severe MR, mild AR	20/04/2006	65	68	2.4	27/03/2008 Post MV replacement, residual mild MR/AR	48	63	1.4
8	RHD severe MR, mild AR	07/02/07	77	58	3.3	10/05/07 MV replacement, mild AR	57	40	1.9
9	Large inlet VSD	14/03/2007	45.5	77	2.6	Post VSD closure, with	32.5	84	1.8

						small residual VSD, and moderate LV to RA shunt			
10	Myocarditis	18/07/08	42.9	45	3.2	25/07/08 Post polygam therapy	37.8	66	1.5
11	Multiple VSDs, including large muscular VSD	19/08/2004	30.8, $LVED/BSA^{0.5}$ 48.7	76	3.0	7/08/2008, Post amplatzer closure of large VSD, residual small VSDs	36 $LVED/BSA^{0.5}$ 43.8	59	2.2
12	Congenital mitral regurgitation	13/02/08	39	74	2.1	07/08/2008, Post operative mitral valve replacement	33	66	1.5

CR, compaction ratio; EF, ejection fraction; LVEDD, LV end diastolic diameter; AR: aortic regurgitation, DCMO: dilated cardiomyopathy, PTB, pulmonary tuberculosis, HIV+ human immunodeficiency virus.

* Illustrated case see Figure 1.6

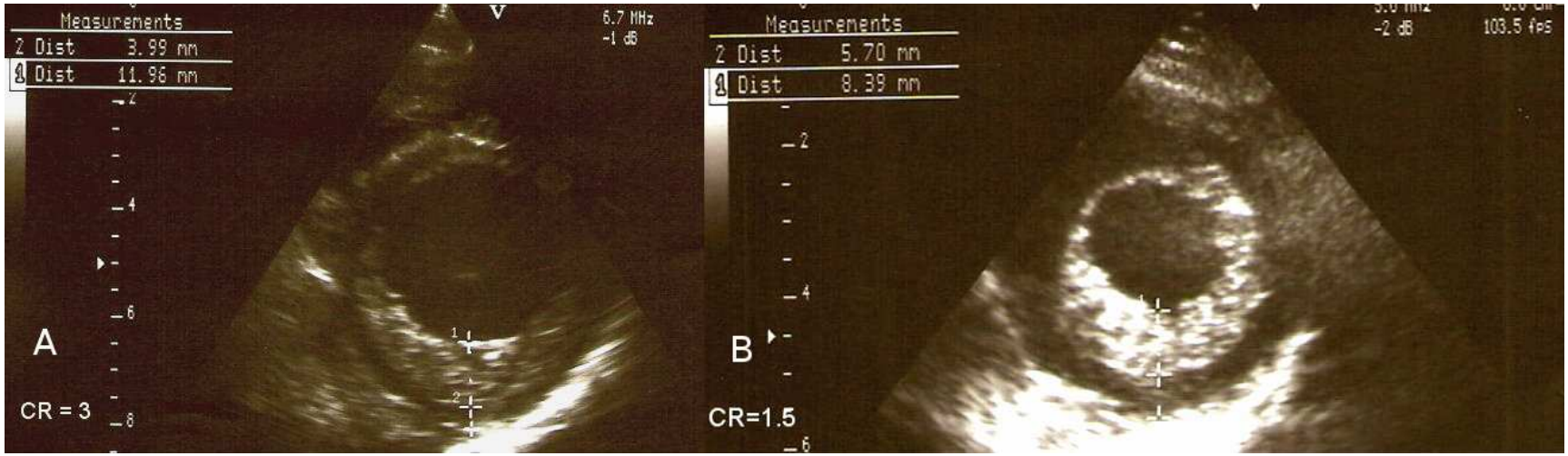


Figure 1.6 Two echocardiograms taken 22 months apart, of the same patient diagnosed with a dilated cardiomyopathy,

Figure 1.6a First echocardiogram, 30/08/2004. Dilated LV, LVEDD 49mm, compaction ratio -3.

Figure 1.6b Repeat echocardiogram, 28/06/2007. Improved LV size and function following medical treatment. LVEDD 37mm, compaction ratio -1.5

These Echocardiograms were taken 4 years apart, on the same patient. In each case the same echocardiographic views were employed. Care was taken in each case to identify the cross section of the ventricle with the most circular shape, between the bases of the papillary muscles and the apex of the heart, and therefore they are comparable views.

1.8.7 Trabecular proliferation as a compensatory response in some cardiac disease

Consistent with the view that in certain species excessive trabeculae may have a beneficial effect (see section 1.5.1 above), Finsterer, Stöllberger and Blazek (2006) have proposed that LVNC may be a compensatory change in some cardiac pathologies [144]. They propose in this regard that an increase in size or quantity of trabeculae could increase the mass and surface area of the LV and hence may improve stroke volume. Further, LVNC may increase the endocardial surface area and hence potentially improve oxygenation via the endocardium [144]. It may assist the impaired myocardium, resisting dilatation by tightening the myocardial structure [144]. It may increase the muscle mass at the apex, the segment of the LV with the highest ejection fraction; and it may enhance viscoelastic properties [123] which might improve ventricular performance in the face of a haemodynamic challenge.

A number of mechanisms may explain trabecular proliferation in a setting of cardiac disease. Generally the adult heart responds to adverse haemodynamics only by cellular hypertrophy and dilatation [145]. However, in neonates and children up to the age of 6 years, gap junctions and fascia adherens junctions, which are distributed over the entire cell surface [146], may facilitate remodelling of the myocardium. Indeed, in chick embryos, experimental changes in loading conditions have been shown to lead to changes in ventricular myoarchitecture. Increased pressure loading leads to an accelerated development of the compact layer (increased number of cell layers) and thicker, coarser trabeculae, with diminished intertrabecular spaces in the LV [145]. In contrast, volume loading of the RV results in an increased *number* of trabeculae, which are thinner than normal [145]. Thus in the chick embryo trabecular proliferation may occur in response to adverse haemodynamic conditions. It is not

known if this effect applies in humans and could continue postnatally and into adult life.

Against the theory that acquired noncompaction is due to trabecular proliferation is the finding that the compaction ratio regresses when LV haemodynamics improve. While an increase in trabeculae in response to adverse haemodynamics has been shown to occur experimentally, a regression would require resorption or loss of trabeculae by some unknown mechanism, and seems less likely.

1.8.8 Acquired noncompaction due to increased prominence of trabeculae

A possible explanation for LVNC in identifiable cardiac pathologies, that does not necessarily negate the other abovementioned notions of the pathogenesis of LVNC has been proposed [111]. Unequivocal, LVNC as seen in figure 1 is a pathological condition and may well be due to persistence of the embryonic pattern. Furthermore, it is not known whether trabecular proliferation may occur as an adaptation to adverse haemodynamic conditions. However, LVNC is defined as a condition in which there are both an increase in the *number* of trabeculae and the *prominence* of the trabeculae in the LV. Echocardiographically it not possible to distinguish whether a thickened trabecular layer is a result of an increase in number of trabeculae or the prominence of trabeculae, or both. It is therefore possible that an increase in the prominence of the trabecular layer may give the appearance of LVNC, but it is a consequence of stretching and thickening of the trabeculae in an overfilled ventricle [111]. An increased prominence of LV bands and trabeculae (including measurement of the compaction ratio), has been previously noted in patients who had LV dilatation, hypertrophy and systolic dysfunction [21, 23, 67, 106].

It is recognized that both dilatation and hypertrophy result from a chronic increase in LV preload. In an overfilled ventricle the interlaced trabeculae act as struts or buttresses, and the spaces between the trabeculae may become enlarged and deeper. Hitherto undetected recesses within the mural trabecular layer might also be revealed. Hence as the ventricle dilates the trabecular layer appears to become thicker. In addition if the individual trabeculae were hypertrophied, they would appear more prominent, and the thickness of the trabecular layer would be increased. The outer compact layer of myocardium composed of circumferentially orientated fibres might become stretched and thinner. Echocardiographically the overall result of these would be an increase in the compaction ratio. This is an *apparent* LVNC, and may be indistinguishable echocardiographically, by current diagnostic criteria from true LVNC (See Figure 1.7 a, b). Importantly, if this were true, the prominence of the trabecular layer could vary under differing haemodynamic conditions. This would distinguish it from LVNC due to excessive numbers of trabeculae, where the compaction ratio would be fixed.



Figure 1.7 Short axis echocardiogram of the left ventricle in patient with rheumatic heart disease and a severely dilated left ventricle showing prominent trabeculae and an increased compaction ratio. Compaction ratio =4.5

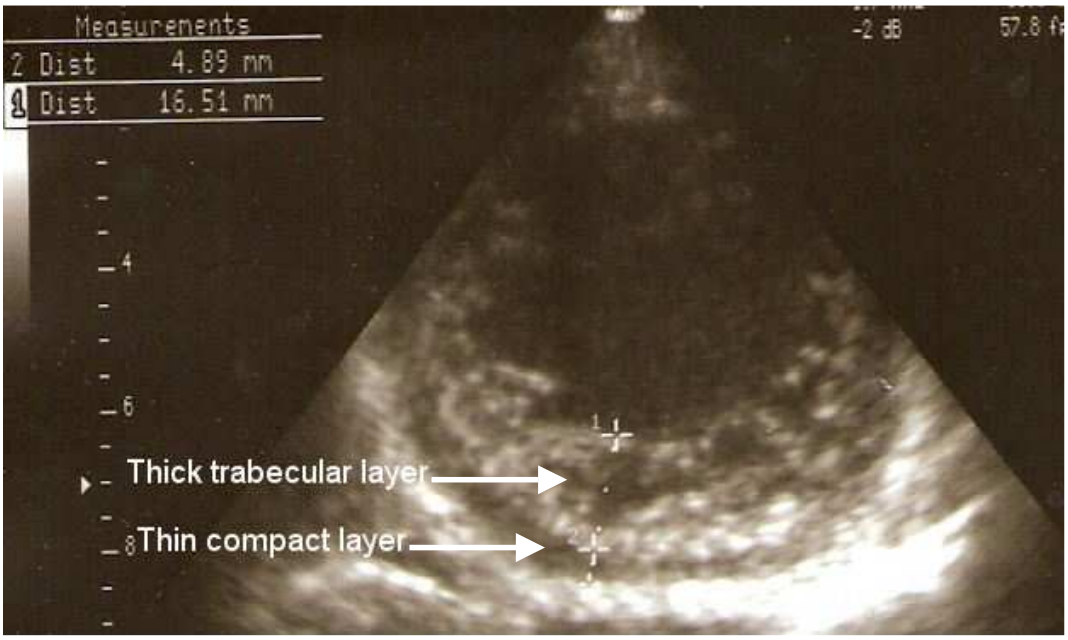


Figure 1.8 Short axis view of a dilated left ventricle in a patient with repaired sub mitral aneurysm, with residual left ventricular dysfunction. Compaction ratio= 3.4.

1.9 Association of LVNC with congenital, acquired and valvular heart disease and the clinical implications thereof

1.9.1 Ventricular septal defects and LVNC

Left ventricular noncompaction is frequently noted in other forms of congenital heart disease. Ventricular septal defects are one of the most common congenital heart abnormalities noted in association with LVNC, appearing in 14/26 (53%) of a survey of reports concerning LVNC and congenital heart disease (Table 1.4). Muscular VSDs may comprise 90% of the total VSD number noted to occur in association with LVNC [84]. Some reports of so-called *isolated* noncompaction, on closer analysis include patients with congenital heart lesions such as small VSDs that were dismissed as haemodynamically inconsequential [12, 14]. This association with VSDs may be coincidental because VSDs are one of the commonest congenital heart lesions accounting for approximately 20% of all congenital heart pathologies. However, there may be a developmental association of VSD and LVNC (See 1.5.5 above describing genetic mutations resulting in both LVNC and VSDs). In this regard it is also of interest to note that in the chick embryo the formation of the interventricular septum has been shown to be the result of coalescence of trabecular sheets[147]. Thus, the formation of the muscular interventricular septum and the compaction of the myocardium may be closely linked processes. Residual small muscular VSDs have been proposed to result from incomplete or abnormal coalescence of embryonic trabecular sheets [147].

Table 1.4. Summary of reports in the literature where LVNC is described with congenital heart diseases.

No.	Author	Reference	Date	Type of congenital heart disease
1	Feldt	[29]	1969	Dextrocardia, transposition great vessels, muscular VSDs, pulmonary stenosis
2	Dusek	[30]	1975	Aortic stenosis, fibroma, anomalous left coronary, pulmonary atresia
3	Allenby	[45]	1988	Muscular VSD, Anomalous RV muscle bands, anomalous papillary muscles
4	Ichida	[37]	1999	VSD(6 cases), PDA, hypoplastic LV, ASD
5	Kamei	[91]	2001	Double orifice mitral valve
6	Dagdeviren	[113]	2002	Atrial septal aneurysm, cleft mitral valve
7	Ozkutlu	[35]	2002	Heterotaxy, complex hearts, anomalous pulmonary venous drainage, multiple VSDs, coarctation of aorta
8	Pignatelli	[76]	2003	VSDs (3 cases), hypoplastic RV+pulmonary stenosis(1), Hypoplastic LV(1)
9	Cavusoglu	[104]	2003	2 cases bicuspid aortic valve
10	Ali	[13, 101, 148]	2002/4	VSDs, including muscular VSDs, mitral valve abnormalities
11	Wald	[12, 149]	2004	ASD2, 2 small muscular VSDs, 2 cases mild Ebstein's anomaly
12	Gorgulu	[150]	2004	Double orifice mitral valve
13	Attenhofer	[151]	2004	3 Cases Ebstein's anomaly
14	Friedberg	[54]	2005	Left Atrial isomerism, complex hearts
15	Freedom	[2]	2005	Left atrial isomerism with VSD
16	Sandu	[82]	2005	VSD, bicuspid aortic valve
17	Dogan	[114]	2005	Congenitally corrected transposition
18	Burke	[56]	2005	4 cases VSD; partial anomalous pulmonary venous return, mitral abnormality, pulmonary and tricuspid valve dysplasia, right coronary stenosis
19	Alehan	[50]	2005	Atrioventricular septal defects, hypoplastic LV, transposition of great arteries, pulmonary atresia
20	Lilje	[84]	2006	VSDs, LV and RV outflow obstruction, Ebstein's anomaly, tetralogy of Fallot, pulmonary atresia

				with intact septum.
21	Sugiyama	[100]	2006	Double orifice mitral valve with mitral regurgitation (2 cases)
22	Johnson	[14]	2006	VSDs
23	Tatu-Chitoiu	[92]	2006	VSD, coarctation of aorta
24	Hughes	[68, 117]	2007	Single ventricle, VSDs, conotruncal abnormalities
25	Unlu	[152]	2007	VSD, bicuspid aortic valve, ruptured sinus of valsalva
26	Bottio	[90]	2007	Pulmonary stenosis, severe mitral incompetence

VSD, ventricular septal defect; PDA, patent ductus arteriosus; ASD, atrial septal defect; RV, right ventricle; LV left ventricle

1.9.2 Clinical implications of LVNC in congenital heart disease

When LVNC is found in association with congenital heart disease, most commonly VSDs and right ventricular hypoplasias, these children have a significantly poorer outcome due to sudden death, or transplantation, or progressive LV dysfunction, than those with equivalent congenital heart lesions who did not have LVNC [68]. An interesting observation, prior to the current widespread awareness of noncompaction, was made in 1989, where Seliem et al showed that “inappropriate LV hypertrophy” (possibly noncompaction) in patients with tricuspid atresia was related to a poorer outcome after the Fontan procedure [153] (See figure 1.1d as an example of tricuspid atresia with probable LVNC). One possible explanation for the poor outcome in children with congenital heart disease and LVNC as compared to those without LVNC is that presence of an intrinsically abnormal myocardium may further impair myocardial performance among patients with underlying haemodynamic problems caused by congenital heart disease [54]. However, Ali et al have documented a patient with LVNC and VSDs, in whom cardiac failure and dilatation of the left sided chambers improved with spontaneous closure of the VSDs [13]. This would seem to indicate that the contribution of LVNC to cardiac dysfunction in VSDs is minor at best. Further work is therefore still required to establish the interpretation of the relationship between LVNC and poor outcomes in patients with congenital heart lesions. One hypothesis is that increased trabecular prominence in congenital heart disease could be associated with increases in cavity dimensions, and hence that the relationship between LVNC and poor outcomes in patients with congenital heart lesions is simply an index of the size of the shunt and the magnitude of the preload on the LV.

1.9.3 Valvular disease and LVNC

There is evidence to indicate that the presence of LVNC is associated with both congenital and acquired disease of the cardiac valves [56]. Organic mitral valve disease, including leaflet and chordal thickening, restricted movement, mal-coaptation, mitral regurgitation (ranging from mild to severe), abnormal chordal attachments, and abnormal papillary muscles have been described to occur in association with LVNC [45, 56, 99, 101]. Double orifice mitral valve is usually a very rare anomaly, yet four cases associated with LVNC have been described [91, 100, 150]. In addition congenital mitral stenosis and cleft mitral valve have been reported with LVNC [113]. Further, there are descriptions of LVNC occurring in cases of acquired mitral valve disease, i.e. rheumatic mitral stenosis and regurgitation [27, 108, 154, 155]. Approximately 5% of patients with mitral regurgitation may have a compaction ratio >2 [49]. In addition many reports describe dilated ventricles with functional mitral regurgitation [34, 59, 71, 80, 86, 90, 105]. It is probable that the relationship in these circumstances is the consequence of the well described association between mitral regurgitation and cavity dimensions.

With respect to other cardiac valves, congenital critical aortic stenosis [2], and calcific aortic stenosis in a tri-leaflet aortic valve, including considerable aortic and mitral regurgitation has been reported [105]. Up to 5% of patients with aortic stenosis may have a compaction ratio >2 [49] Further, an association of Ebstein's anomaly of the tricuspid valve and LVNC has also been described [151].

1.9.4 Dilated cardiomyopathy and LVNC

In a cohort of children with cardiomyopathies, up to 10% have been found to have LVNC [76, 81]. Approximately 26% of patients with dilated cardiomyopathy may have a compaction ratio>2 [49]. However differentiation of LVNC from dilated cardiomyopathy remains contentious. Whilst some authors have confidently assigned study patients into subgroups of dilated cardiomyopathy and LVNC on the basis of: thicker basal interventricular and posterior walls, and better LV function in LVNC [105], less prominent trabeculations [38], or a greater LVEDD (in dilated cardiomyopathy) [49], others have suggested that the difference between dilated cardiomyopathy and LVNC is so ill-defined that transitional variants between dilated cardiomyopathy and LVNC may exist [36], or that LVNC should be classified as a subtype of dilated cardiomyopathy [75].

Importantly, when comparing LVNC and dilated cardiomyopathy with comparable degrees of spherical remodelling and dysfunction, tissue Doppler parameters indicated no difference between the two groups [156]. Moreover, ECG criteria (bundle branch block, atrio-ventricular block, or electrocardiographic signs of LV hypertrophy) were not helpful in discriminating between LVNC, hypertrophy due to hypertensive or valvular disease, and dilated cardiomyopathies [49].

Ambiguity in diagnostic criteria, and failure to appreciate that an increased prominence of trabeculae could result from dilatation of the ventricle, may account for these discrepancies.

1.9.5 Other cardiac or non-cardiac conditions and LVNC

Left ventricular noncompaction has been reported to occur with other acquired heart diseases including LV aneurysm [87], severe coronary artery disease

with stenosis of at least 50% of one main branch coronary artery [57, 62], and myocarditis resulting from dengue fever [157]. The search for associations of LVNC and neuromuscular or metabolic disorders, has revealed an association of LVNC and dystrophinopathy, dystrobrevinopathy, laminopathy, zaspopathy, myotonic dystrophy, infantile glycogenosis type II (Pompe's disease), myoadenylatedeaminase deficiency, Friedreich ataxia and Charcot-Marie-Tooth, mitochondrial disorders and Barth syndrome [3, 76, 85, 97, 129, 158], and it is recommended that all patients suspected of having LVNC also undergo a neuromuscular screening. [144].

As mentioned above, LVNC cases have frequently been misdiagnosed on initial examination, and confused with myocarditis [37, 62], restrictive cardiomyopathy [62], hypertrophic cardiomyopathy [11, 34, 35, 60, 71, 75, 78], hypertensive cardiomyopathy with prominent trabeculations [159], candida sepsis [159], intramyocardial hematoma [78], cardiac metastasis [78], apical cardiomyopathy [37, 38, 66, 74, 103], apical mass/thrombus [34, 49, 62, 74], or endomyocardial fibrosis [37, 49, 62, 74].

The wide variety of cardiac and other diseases noted to occur together with LVNC suggests that LVNC may be an architectural change that occurs in response to factors associated with cardiac disease in general, or may be an incidental finding [67].

1.10 Hypothesis and aim of study

As highlighted in the above discussion, a noncompaction-like increase in prominence of trabeculae (with resultant increased compaction ratio) may occur as a result of haemodynamic perturbations. The compaction ratio is the only non-subjective diagnostic criterion for LVNC, and is widely used to diagnose congenital

LVNC. If however this compaction ratio is sensitive to changes in haemodynamic status it should be interpreted with caution when used to diagnose a so–called congenital cardiomyopathy. However, the relationship between LV dimensions and compaction ratio has not been formally studied. The aim of the present study was therefore to determine whether there is a relationship between the compaction ratio and LV cavity size and mass, in patients with congenital and acquired heart disease associated with known chronic increases in volume loads. To achieve this aim I assessed the relationship between a number of indices of volume preload on the heart and the compaction ratio in children and adolescents with VSDs and mitral valve regurgitation attributed to rheumatic heart disease (RHD).

CHAPTER 2

METHODS

2.1 Justification for the study population selected

To test the hypothesis that volume preload is associated with the compaction ratio I elected to study two groups of patients with cardiac pathology, one congenital and one acquired. Both are well recognized as being associated with an increased LV preload. In this regard, left to right shunts in VSDs lead to an increased pulmonary venous return and hence a volume load on the LV [32]. Similarly, in chronic RHD, mitral valvular regurgitation results in an increased volume load on the LV [160, 161]. Both LV internal diameter and LV mass are related to the size of left to right shunts in VSDs [162], and the severity of chronic valvular regurgitation in RHD [160, 161, 163]. Thus, in both VSDs and RHD with mitral regurgitation, measurement of LV internal diameter (LVEDD) and LV mass (LVM) serves as an index of volume preload. Moreover, as indicated in the introductory chapter to this dissertation, LVNC occurs in association with both VSDs, and mitral valve abnormalities either congenital or acquired. Consequently, in the present study I evaluated the independent relationship between LVEDD or LVM and the compaction ratio in a paediatric population with either VSDs or RHD.

2.2 Study participants

One hundred children with VSDs and thirty six with chronic RHD and mitral regurgitation were enrolled in this study. Patients with VSDs and RHD were compared with a group of 79 healthy controls. The 79 control subjects were referred for assessment of cardiac murmurs, chest pain, or screening for heart disease. On clinical examination, history, electrocardiogram, chest X-ray and echocardiography

they were found to have normal hearts. All participants were sequentially recruited from the Paediatric Cardiology Outpatient Department of the Johannesburg Hospital. Participants gave written informed consent. All data was collected between June 2004 and March 2007.

Patients with VSDs were included if they had an adequate echocardiographic assessment of VSD size, LV dimensions and myocardial measurements. 21 were not included in the study due to poor quality echocardiograms. None had prior surgical or spontaneous closure of their VSD. The majority had isolated VSDs while eleven had an additional secundum atrial septal defect (ASD) or a patent ductus arteriosus (PDA). These patients were included in the analysis as frequently additional shunts such as ASDs and PDAs are associated with larger VSDs, and hence by excluding non-isolated VSDs I would have prejudiced the study towards smaller VSDs. Nevertheless, the presence of an additional shunt was adjusted for as a confounding variable in the statistical analysis. Inlet VSDs were included, but complete atrioventricular septal defects, any form of inflow or outflow tract obstruction or complex heart lesions with VSDs were excluded. Patients with syndromes were included, but because some reports have suggested that LVNC is found more frequently in patients with syndromes, the presence of a syndrome was also adjusted for in statistical analyses. Although large, unoperated VSDs were included, none of the patients had suprasystemic pulmonary artery pressures resulting in a predominant right to left shunt (Eisenmenger).

Children and adolescents with RHD were included if they had an adequate echocardiogram which included assessment of the severity of the rheumatic involvement, a measurement of ventricular dimensions and systolic function, and a measurement of the compaction ratio. Three children were not included in the study due to poor quality echocardiograms. Thirteen patients had had surgical repairs or replacement of the mitral and/or aortic valves. Two had had prior balloon mitral

valvuloplasties, and one surgical valvotomy No participants in any group had symptoms or signs of neuromuscular disease.

Post operative rheumatic heart patients were included because although surgery should have relieved the underlying volume load, most RHD patients post operatively do have a residual MR and in some cases AR. Furthermore the inclusion of postoperative patients into the statistical sample added to the heterogeneity of the group and therefore increased the strength of the relationships demonstrated.

Whilst the principal focus of the present study was on patients with a known cause of increased volume preload, i.e. VSD and RHD, the compaction ratio was also measured in other patients with dilated ventricles, as part of their routine echocardiograms. Thus several patients with dilated cardiomyopathy due to human immunodeficiency virus or of unknown aetiology, and an increased compaction ratio were also identified. These participants were not included in the overall analysis, but rather reported on in the present dissertation as a series of case studies summarised in Table 1.3 to underscore the role of the “undulating” LVNC phenotype. In some cases treatment resulted in improved chamber size and function (See Table 1.3).

2.3 Demographics, anthropometric measurements and clinical data

Date of birth, gender, and the previous medical and surgical history were recorded in all participants. Body height and weight were measured at the time of echocardiography with the participants standing and wearing indoor clothes with no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Body surface area (BSA) was calculated using the Mosteller formula as BSA (m^2) = ([Height (cm) x Weight (kg)]/ 3600)^{½}. All patients

had previously been screened for additional pathology from a clinical history and examination.

2.4 Echocardiography

Echocardiograms were performed using a GE Vivid 5 ultrasound device (model number SN3346VM). Appropriate phased array transducers with frequencies ranging from 2.5 to 10Mhz were chosen in each case. Image optimization including frequency, depth, gain and scale settings was used in all cases. In larger patients tissue harmonic imaging was employed to obtain optimum images. All measurements were performed by a single, experienced operator (V Hunter). Still frame images and video footage were recorded. A complete 2-dimensional, M-mode, colour flow and spectral Doppler imaging echocardiogram was performed in each case. Left ventricular dimensions, including LVEDD and systolic internal diameter, posterior wall thickness and septal wall thickness were measured using two-dimensional directed M-mode imaging according to standard criteria [164]. The largest diameter of the LV was considered to be the LVEDD. LVEDD was indexed for body size using $BSA^{0.5,}$ (LVEDDI) according to the recommendations of Gutgesell et al.[165]

To determine LV chamber and myocardial systolic function, LV endocardial (LV FSend) and midwall (LV FSmid) shortening fractions of the LV respectively were calculated using standard formulae [32, 166] viz.

LV FSend (%) = [LVEDD – LVSD/LVEDD] x 100, *

LV FSmid (%) = [(LVEDD+PWT)-(LVSD+PWT)/LVEDD+PWT]x100).*

* where LVSD is LV systolic diameter and PWT is posterior wall thickness at either end diastole or end systole.

In addition, to determine LV chamber systolic function, LV volume was calculated using the Teichholtz formula [167] $V=[7.0/2.4+D](D^3)$, from m-mode measurements of systolic and end diastolic internal diameters, just beyond the tip of the mitral leaflets, and ejection fraction (LVEF) was derived using the formula:

LVEF(%) = [LVDV – LVSV /LVDV] x100.*

* where LVDV is LV diastolic volume, and LVSV is LV systolic volume.

Relative wall thickness was calculated using the formula:

RWT= PWT/½LVEDD

Left ventricular mass (LVM) was calculated from M-mode measurements obtained, according the method of Devereux et al (1986), viz.

$LVM\ (g)=0.8(1.04[(LVEDD+PWT+IVST)^3 – (LVEDD)^3]+1.06)$ *

* where IVST is interventricular septal thickness, and indexed to $BSA^{1.5}$ (LVMI), in accordance with the method of de Simone et al 1992 [168]. Although the use of this standard calculation of LVM from m-mode measurements assumes a certain geometry of the LV myocardium, and has not been validated in patients with LVNC [8], we nevertheless elected to use the calculation, with reservations, because it has previously been employed in patients with VSDs and RHD [162, 163, 169]. Left ventricular end diastolic diameter or LVEDDI, LVM or LVMI and VSD size (see below) were all considered indicators of LV volume load.

Z scores of were calculated for LVEDD/ $BSA^{0.5}$ and LVM/ $BSA^{1.5}$ using the equation:

$Z = (X - \bar{X})/ s$ where X is LVEDD or LVM, $\bar{X}$ is mean LVEDD or LVM of control group, and s is standard deviation of the control group.

2.4.1 Measurement of the compaction ratio

In their original description of measurement of the compaction ratio, Jenni et al indicated that it is measured in the short axis view in systole, at the position of maximal thickness of the trabecular layer [9]. In the present study we elected to measure the compaction ratio in the same position for all patients viz. on the posterior wall in systole, in the LV short axis between the base of the papillary muscles and the apex of the heart (Figures 2.1 a, b, c). This echocardiographic

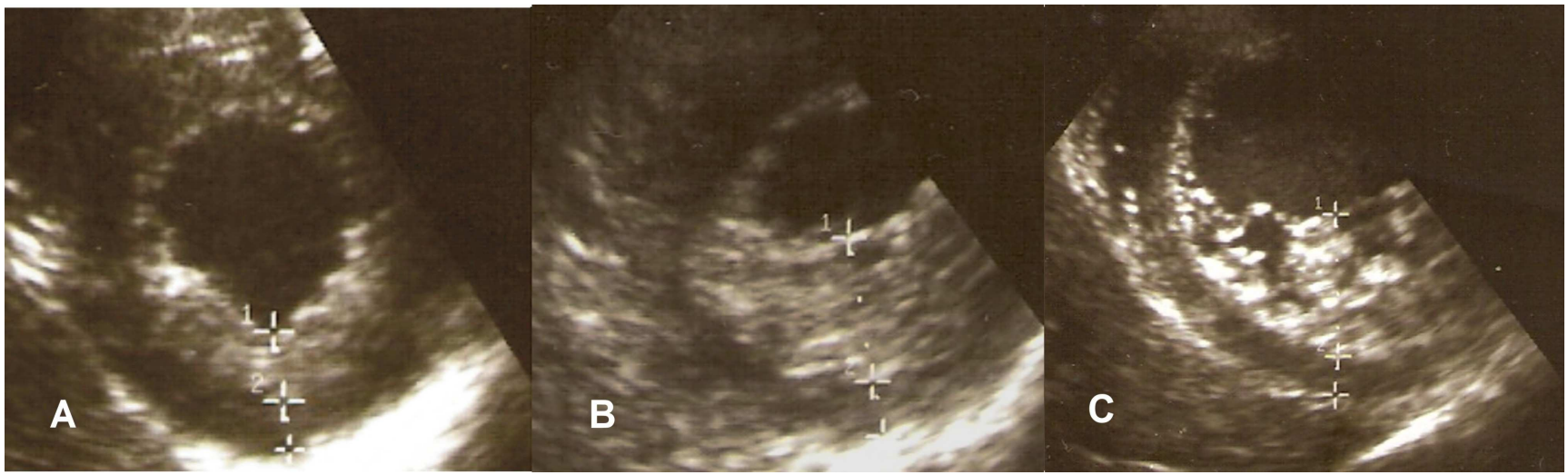


Figure 2.1 Apical short axis view of the left ventricle in (A) normal, control compaction ratio = 1.4, (B) ventricular septal defect, compaction ratio= 2.6 and (C) rheumatic heart disease, compaction ratio= 3.7, demonstrating measurement of the compaction ratio.

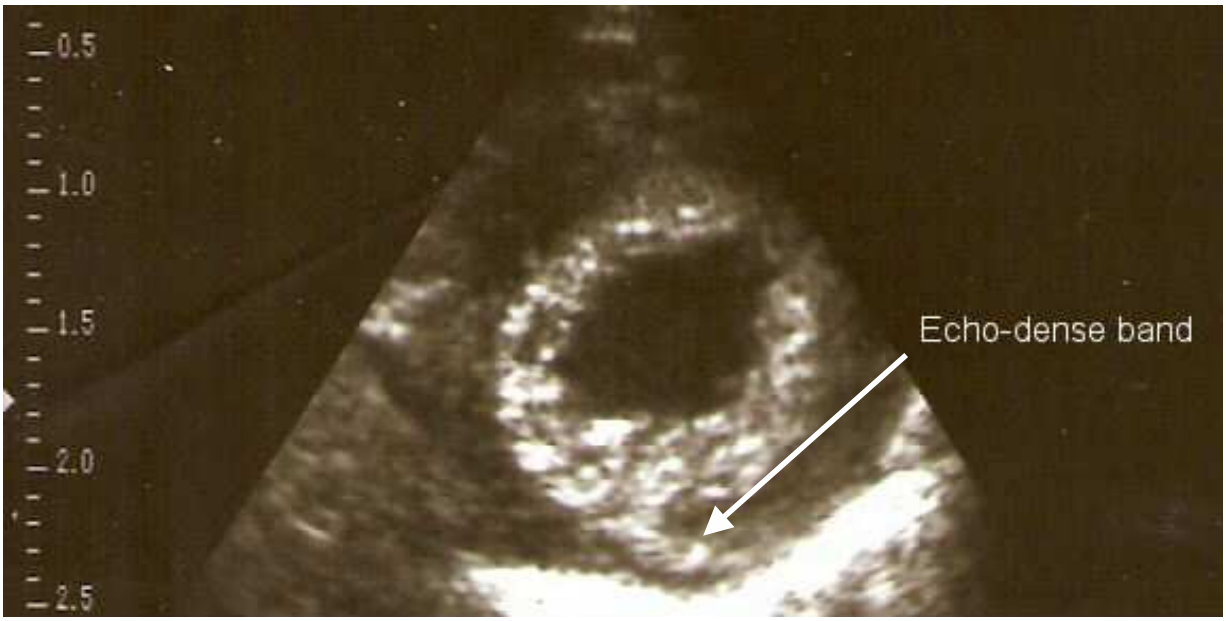


Figure 2.2. Short axis view showing echo-dense band. Repositioning of transducer allows for clearer differentiation of compact layer.

view is generally employed to demonstrate the extent of LVNC, [5, 6, 33, 38, 40, 46, 76, 92, 98, 108, 141, 152] and to measure the compaction ratio [9, 12, 49, 67, 141]. Furthermore the measurement of the compaction ratio at the posterior wall in the short axis has the advantage of best axial resolution for distinguishing the two layers. Moreover it avoids the bases of the papillary muscles as a potential pitfall in measuring the thickness of the trabecular layer. It is usually also the position of the most prominent trabecular layer. The ratio is measured in systole because the borders of the two layers are best defined in systole, while the recesses between the trabeculae are best appreciated in diastole. In accordance with currently accepted criteria a compaction ratio >2.0 was considered to be increased [9]. A short axis view with the most circular LV shape was sought and off axis and oblique views were disregarded. Oblique views were discarded as they may include measures of the length of individual trabeculae, rather than the thickness of the composite trabecular layer. Furthermore, an echo-dense band near the apex sometimes made differentiation of the two layers uncertain, but careful repositioning of the transducer usually resolved this issue (Figure 2.2).

In patients with a markedly trabecular myocardium the compact layer was occasionally difficult to discern, as noted by Kohli et al [67]. However, in our experience a little patience with imaging usually allowed for measurement of both layers.

2.4.2 Segmental analysis

As indicated in the introductory chapter to this dissertation, LVNC is considered to occur where there is both an increase in the number of trabeculae and an increase in the prominence of the trabeculae, i.e. trabeculae occupy a greater than normal volume of the LV chamber. Accordingly, although not strictly a criterion

for identifying LVNC, LVNC may nevertheless also be identified from an increased number of segments of the LV wall that are noted to have prominent trabeculation [8, 16, 19, 62]. A typical distribution of prominent trabeculation has been published [8, 9, 16, 19, 62], but a diagnostic threshold number of segments involved has not been established. In the present study it was nevertheless of interest to compare the distribution of segments with prominent trabeculation in both VSDs and RHD, with those published in cases of isolated LVNC. To achieve this, the appearance of the myocardium in still frame images was analysed, and a 9 segment model of the LV was used i.e. apical, apical septal lateral, posterior and anterior wall segments, and mid LV septal, lateral anterior and posterior wall segments. Each segment was graded as having no trabeculae, mildly prominent trabeculae or marked trabeculation.

In order to asses how often a compaction ratio greater than 2 corresponded to an appearance of excessive prominent trabeculation, a subjective assessment of the degree of trabeculation was determined in each patient, where the degree of trabeculation was assessed as either mild, moderate or marked.

2.5 Classification of congenital and acquired lesions

Ventricular septal defects were categorized by position as a) perimembranous i.e. lying primarily in the perimembranous region, with or without extension into the muscular septum, b) malaligned i.e. with some degree of posterior outlet septal deviation, but without LV or RV ventricular outflow tract obstruction, c) high outlet i.e. occurring at, or above the crista supraventricularis, and closely related to both the aortic and pulmonary valves (also known as subarterial or doubly committed VSDs),

or d) muscular VSDs which were confined to the trabecular portion of the interventricular septum.

For convenience of comparison, VSDs were also subdivided into groups of small, medium or large. The size of a VSD was measured using two-dimensional echocardiography, and compared to the size of the aortic annulus. In VSDs undergoing aneurismal closure or partially closed by prolapse of aortic valve leaflets, the present effective VSD size was used. Small VSDs were considered to be < 1/3 of the size of the aortic annulus, medium sized ≥ 1/3 but < 2/3 of the size of the aortic annulus, and large ≥ 2/3 of the size of the aortic annulus.

Patients with rheumatic heart disease were classified as having mild mitral regurgitation (MR) based on the presence of a small colour jet with a narrow origin, minimal left atrial dilatation, and low pulmonary pressures; moderate or severe MR, when a larger jet filling greater than one third of the left atrium and left atrial dilatation were noted; mixed mitral valve disease (MR and mitral stenosis) when thickening and doming of the mitral leaflets, colour Doppler turbulence of flow across the valve, and reduced mitral valve orifice area were noted. In addition mitral regurgitation was present in all three cases of mitral stenosis. Mixed mitral and aortic regurgitation (AR) was defined as when in addition to mitral regurgitation there was moderate or severe aortic regurgitation. The degree of AR was assessed as moderate or more using a combination of size of colour Doppler jet, height of jet as a ratio of LV outflow tract diameter >1/3, and slope of continuous wave Doppler < 300ms. No patients had isolated aortic regurgitation or aortic stenosis. Post operative patients were classified according to whether they had repair or replacement of either mitral or aortic valves.

The presence of a syndrome was included as an independent variable in the statistical analysis, because in the past it was thought that there may have been an association of syndromes with LVNC.

2.6 Intraobserver variability

Intraobserver variability was assessed in a subset of 38 subjects in whom repeat echocardiographic measurements were performed by the same operator within a two week period of the initial measurements. The Pearson's correlation coefficients for LVEDD, LVMI, trabecular layer thickness, compact layer thickness and compaction ratio were 0.99, 0.76, 0.89, 0.78, 0.84 ($p<0.0001$ in all) respectively. The variances (mean % difference ± SD) were -0.77±5.98%, 5.12±79.17%; 4.42± 17.33%; 00.56±21.58%; and 4.95±24.23% respectively. In addition no significant differences between repeat measurements were evident on paired t-test analysis. ($p=0.90, 0.57, 0.07, 0.82, 0.28$) respectively.

2.7 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.1 (The SAS Institute Inc., Cary, North Carolina, USA). Data from individual subjects were averaged and expressed as mean ± 95% confidence intervals. The χ^2-statistic was used to compare proportions between the three groups (RHD, VSD, control). Comparisons in ventricular size, morphology and function between the three groups were performed using analysis of variance (ANOVA) followed by an appropriate *post hoc* test (Student Newman-Keuls), and including age, sex and body surface area as confounding variables. Relationships between compaction ratios and potential determinants were assessed by multivariate stepwise regression analyses, in which potential determinants and adjustors [age, gender and BSA (where appropriate)] of the compaction ratio, were forced into the regression

equations. As LVM and LVEDD were closely related to each other, the relationships of these with compaction ratios were determined in separate models.

CHAPTER 3

RESULTS

3.1 General demographic and anthropometric characteristics

Table 3.1 shows the demographic, anthropometric and clinical characteristics of the study groups. When comparing demographic and anthropometric data, children and adolescents with RHD were older (mean age 12.9 years, range 5-17years), and hence heavier and taller (greater BSA) than those with VSDs (mean age 4.3 years, range 1day-17years) or the control group (mean 4.1years, range 24 days-15 years). Mean BMI was in the normal to low range for all three groups i.e. normal (16.1±0.5), VSD (15.4±0.7) and RHD (18.0±1.1). The gender distributions in the 3 groups were very similar. The ethnic group was black in 89%.

3.2 Left ventricular internal diameters, mass and geometry

Table 3.2 shows the general echocardiographic characteristics of the study groups. Figure 3.1 shows LVEDDI and LVMI for the three study groups. Consistent with either adverse LV remodelling or an increased LV preload, patients with both VSDs and with chronic RHD had an increased LVEDD and LVEDDI as compared to healthy controls. (Table 3.2). The mean z-score for LVEDDI for VSDs was 0.74, and for RHD was 0.77. However, there was no significant difference in LVEDDI between patients with VSDs and those with RHD (Figure 3.1).

Patients with VSDs and RHD also had an increased LVM and LVMI (Table 3.2 and Figure 3.1), as compared to the control group. ($p<0.0001$ for both). The Z-score for LVMI for VSDs was 1.0, and for RHD was 0.7. However, there was no

Table 3.1. Demographic and anthropometric characteristics of the study subjects

	Controls (n=79)	VSD (n=100)	RHD (n=36)
Age (years)	4.1 (3.1-5.1)	4.3 (3.4-5.2)	12.9(12.0-14.0) ‡*
Gender (% female)	49	49	39
Race (%black)	93	84	95
Height (cm)	90.9(83.0-98.8)	93.6(87.2-100.1)	151.6(146.5-156.8) ‡*
Weight (kg)	15.7(12.9-18.5)	16.0(13.2-18.7)	42.5(37.6-47.4) ‡*
Body surface area (m^2)	0.62 (0.53-0.70)	0.63(0.56-0.7)	1.33(1.23-1.42) ‡*
Body mass index (kg/m^2)	16.1(15.6-16.6)	15.4(14.7-16.9)	18.0(16.8-19.2) †*

Mean (95% confidence intervals). VSD, ventricular septal defects; RHD, rheumatic heart disease.

† $p<0.01$ vs. controls; ‡ $p<0.0001$ vs. controls; * $p<0.0001$ vs. VSD.

Table 3.2. General echocardiographic parameters in subjects

	Controls (n=79)	VSD (n=100)	RHD (n=36)
LV Mass (g)	43.4 (35.0-51.7)	58.7 (48.4-69.0)** †	173.3 (150.9-195.8)‡
LVM/ $BSA^{1.5}$	92.5 (52.4-160.2)	129.3 (49.0-232.6) ‡	117.2 (51.1-224.1) ‡
LVEDD (mm)	29.3 (27.4-31.2)	33.3 (31.3-35.3) †**	50.7 (47.4-54.1) ‡
LVEDD/ $BSA^{0.5}$ ($mm/m^{0.5}$)	39.4 (27.9-50.1)	44.3 (34.5-58.4) ‡	44.6 (31.7-69.0) †
PWT/ $BSA^{0.5}$ ($mm/m^{0.5}$)	6.9 (4.4-10.2)	7.5 (4.5-12.1) †	7.7 (4.5-11.8) †
LV RWT	0.35 (0.34-0.38)	0.35 (0.33-0.37)	0.37 (0.33-0.40)
LV ejection fraction (%)	68.7 (67.3-70.1)	69.4 (67.9-71.0)**	64.5 (61.8-67.2) †
LV FSend (%)	37.2 (36.0-38.3)	38.1 (36.9-39.3)	35.2 (33.1-37.2)
LV FSmid (%)	25.3 (23.9-26.7)	24.0 (22.7-25.2)	22.8 (20.6-24.9) †

Mean (95% confidence intervals). LV, left ventricle; BSA, body surface area; EDD, end diastolic diameter; PWT, posterior wall thickness; RWT, relative wall thickness; FSend, endocardial fractional shortening; FSmid, midwall fractional shortening.

† $p<0.05$ vs. controls; ‡ $p<0.001$vs controls, * $p<0.05$ vs. RHD, ** $p<0.001$ vs. RHD.

significant difference in LVMI between patients with VSDs and those with RHD (Figure 3.1).

Posterior wall thickness indexed to BSA $^{0.5}$ was increased in patients with VSD and RHD compared to controls, however relative wall thickness values did not differ significantly between the groups. A relative wall thickness < 45 is considered normal [170] and all three groups fell below this level.

3.3 Systolic left ventricular function

The mean values for LV FSend, and LV FSmid in patients with VSDs and RHD were unchanged as compared to healthy subjects (Table 3.2). However in RHD the mean EF was normal, but lower than VSDs and the control group. (p=0.005 vs. controls, and p=0.0007 vs. VSDs) In the RHD group the LVEF was a determinant of the compaction ratio (partial r=0.31, p=0.03) (Table 3.9). Furthermore, in the control group a borderline significance level (partial r=0.22, and p=0.05) was found between the compaction ratio and the LV shortening fraction.

In the group with RHD, 4 out of 36 patients had a lower than normal systolic function (LVEF< 57%) (3 post mitral valve surgical repair and one post balloon mitral valvuloplasty).

In the patients with VSDs, despite increased LV internal chamber diameters (Figure 3.1), systolic chamber and myocardial function was preserved. This is a well documented phenomenon attributable to offloading of the ventricular volume into the lower pressure RV chamber in systole [171]. In our patient cohort with VSDs, 5 out of 100 had a lower LVEF (<57%), and no VSDs were post operative. None of the control group had a diminished systolic function.

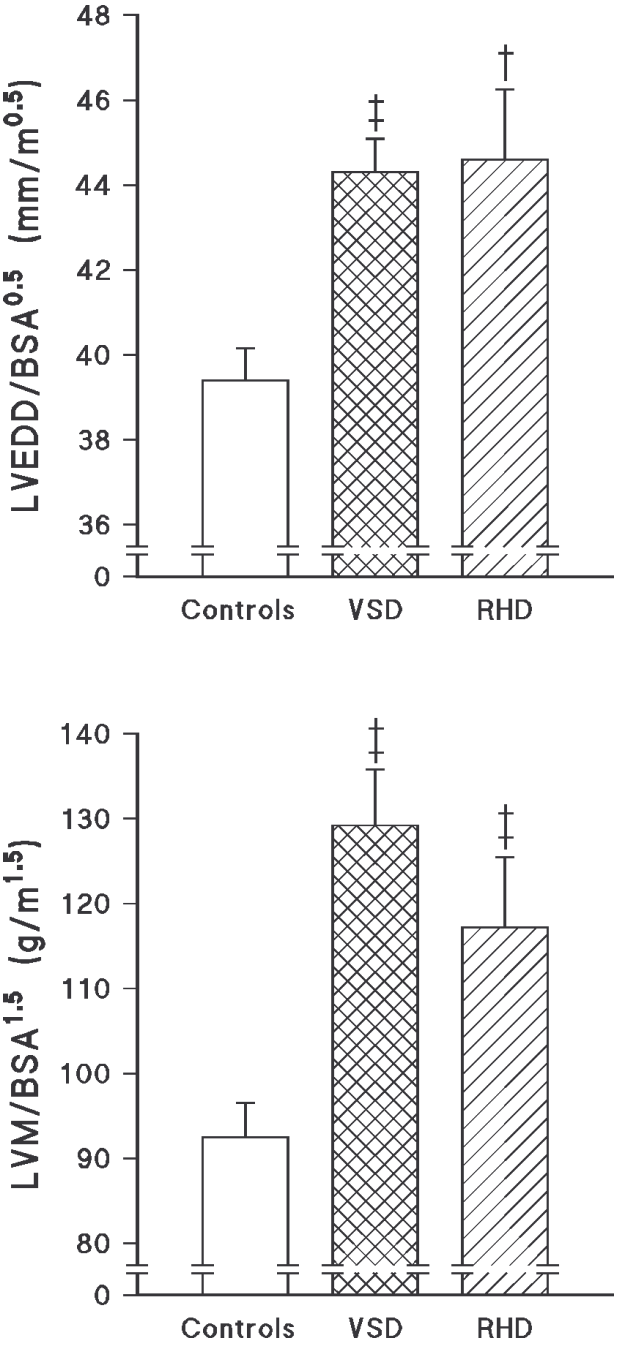


Figure 3.1 Left ventricular end diastolic diameter indexed (LVEDD/BSA$^{0.5}$) and mass indexed (LVM/BSA$^{1.5}$) in normal controls, patients with ventricular septal defects (VSD) and chronic rheumatic heart disease (RHD) with mitral regurgitation.

† p<0.05 vs. controls; ‡ p<0.001vs controls

3.4 Relationship between the size of ventricular septal defects and LV internal dimensions, mass and systolic function

Table 3.3 shows LV chamber dimensions, mass and function parameters in patients with VSDs grouped according to VSD size. Figure 3.2 shows LVEDDI, LVEF, LVMI, LV FSend and LV FSmid values in patients with VSDs grouped according to VSD size. The majority (70%) of patients with VSDs had small VSDs (less than 1/3 the size of the aortic root). Consistent with the notion that in the absence of severe pulmonary hypertension the size of the VSD determines the volume of the left to right shunt, the volume increase of pulmonary venous return, and therefore the volume load on the LV, a strong relationship was noted between VSD size and both LVEDDI ($p<0.0001$) and LVMI ($p<0.0001$) in separate multivariate regression analysis (Figure 3.2). When placed in the same multivariate regression model, LVMI had the stronger relationship ($p<0.0001$, vs. 0.38). No relationship was noted between VSD size and LVFS (either end or mid), however, a negative relationship was noted between LVEF and VSD size. ($p=0.003$), i.e. patients with larger VSDs had poorer ejection fractions. Thus VSD size was closely related to LVEDDI, LVMI and systolic function.

Table 3.3. Left ventricular dimensions, mass, and function in children with ventricular septal defects grouped according to size of the defect.

	Small (n=70)	Medium (n=9)	Large (n=21)
LVEDD absolute (mm)	33.9 (31.8-36.0)	29.7 (23.1-36.3)	33.0 (26.6-39.3)*
LVEDD/BSA$^{0.5}$ (mm/m$^{0.5}$)	42.2 (32.0-53.7)	45.4 (35.2-62.2)	50.9 (38.5-66.5)†
LVM absolute (g)	58.6 (48.5-68.8)	39.2 (20.7-57.6)*	67.4 (30.4-104.4)**
LVM /BSA $^{1.5}$(g/m$^{1.5}$)	104.5(46.0-179.3)	134.3 (52.3-239.4)*	209.6 (116.9-364.0)†‡
LVEF (%)	70.2 (68.5-71.9)	71.0 (66.6-75.4)	66.1 (61.6-70.7)*
LV FSend (%)	38.8 (37.3-40.2)	38.7 (35.1-42.2)	35.6 (32.3-39.0)*
LV Fsmid (%)	24.3 (23.0-25.6)	24.7 (0.9-28.6)	22.6 (18.6-26.6)

Mean (95% confidence intervals) Small: VSD diameter < 1/3 of aortic annular diameter; Medium: VSD diameter >1/3 but <2/3 of aortic annulus; Large: VSD > 2/3 of aortic annular diameter; LVEDD, left ventricular end diastolic diameter; LVM, left ventricular mass, LVEF, LV ejection fraction; FSend, LV endocardial fractional shortening; FSmid, LV midwall fractional shortening.

* $p<0.05$ vs. small VSDs, † $p<0.0001$ vs. small VSDs, ‡ $p<0.0001$ vs. medium VSDs.

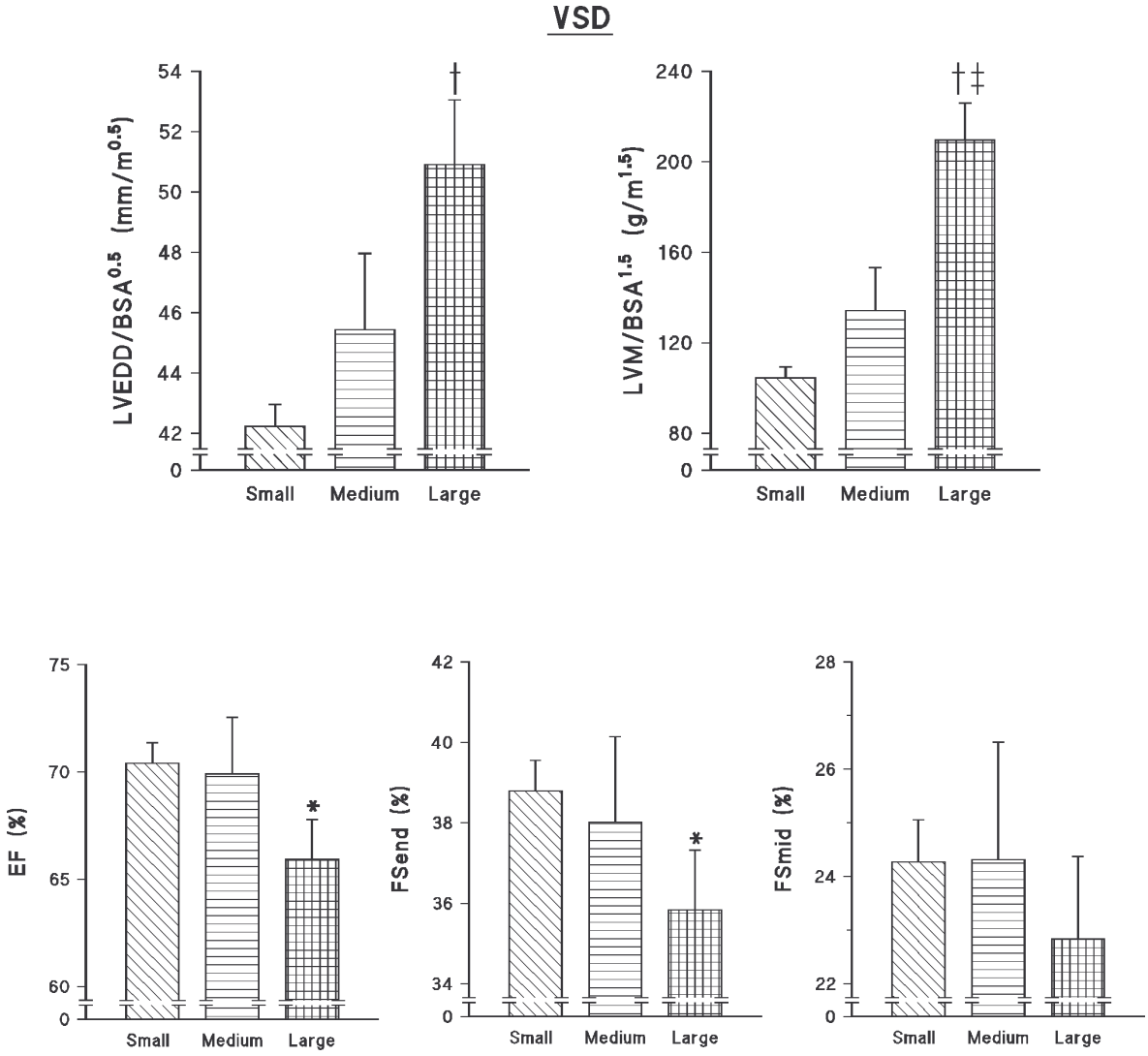


Figure 3.2. Left ventricular end diastolic diameter indexed (LVEDDI), left ventricular mass index (LVMI), ejection fraction (EF), endocardial fractional shortening (FSend) and midwall fractional shortening (FSmid) in patients with ventricular septal defects (VSD) grouped according to VSD size.

* $p<0.05$ vs. small VSDs, † $p<0.0001$ vs. small VSDs, ‡ $p<0.0001$ vs. medium VSDs.

3.5 Relationship between position of the VSD, presence of additional shunts or syndromes, and LV internal dimensions, mass and systolic function

Table 3.4 shows LVEDDI, LVMI and systolic function in patients with VSDs grouped according to the type of VSD, or the presence of an additional shunt or syndrome. The majority of VSDs were perimembranous or muscular. The position or associated characteristics of the VSDs did not significantly influence LVEDDI, LVMI or systolic function. Of 23 patients in the muscular VSD group, 13 patients had small VSDs, 3 had moderate, and 7 had large. However, as can be seen in table 3.4, the muscular VSDs, had a lower mean LVEDD/BSA $^{0.5}$ than any of the other groups, indicating that the association of muscular VSDs and LV trabeculation was probably not due to volume loading, and unrelated to VSD size. There is a weak statistical association of muscular VSDs and compaction ratio, which may have become stronger with a larger sample size. The possible connection between muscular VSDs and noncompaction, unrelated to volume load is addressed in sections 1.9.1, and 4.7.

There was no statistically significant difference in LV chamber size, mass and function in patients having an additional ASD or PDA compared with those who did not.

In the group with VSDs, 14 patients had syndromes of which 10 were Down syndrome. In the control group, 8 children had syndromes, of which 6 were Down syndrome. The presence of a syndrome was not associated with any changes in LVEDDI, LVMI, or LV systolic function. The objective of including syndromic patients as a separate group was to determine whether there was an association of syndromes with increased compaction ratio independent of the size of the VSD,

LVEDD, LVM and function (there was not) and therefore I deemed it unnecessary to further divide the syndromic patients into groups of VSD size. Furthermore subdivision of the syndromic patients by VSD size would have would have resulted in underpowered statistical analysis.

Table 3.4. Left ventricular dimensions, mass, and function in children with ventricular septal defects (VSD) grouped according to position and associated features of the defect

	n=	LVEDD/BSA$^{0.5}$ (mm/m$^{0.5}$)	LVM/BSA$^{1.5}$ (g/m$^{1.5}$)	LVEF (%)	LV FSend (%)
Perimemb	59	45.3 (34.8-62.2)	129.6 (51.2-239.4)	69.7 (67.6-71.8)	38.5 (36.8-40.1)
Muscular	23	42.2 (31.5-53.4)	132.0 (45.8-208.4)	68.6 (64.5-72.6)	37.1 (34.1-40.2)
Malaligned	8	45.8 (38.6-57.1)	128.7 (60.5-209.2)	70.8 (64.0-77.5)	39.4 (33.1-35.6)
High outlet	10	42.5 (35.2-55.5)	121.4 (67.2-364.0)	68.7 (65.9-71.50	37.1 (34.4-39.8)
+Shunts	11	44.3 (29.0-57.8)	157.5 (46.1-306.2)	71.5 (63.8-79.1)	39.5 (33.4-45.7)
Syndromic	14	41.9 (29.0-55.9)	119.3 (24.7-199.3)	73.8 (60.0-86.0)	41.7 (31.0-54.0)

Mean (95% confidence intervals) Perimemb, perimembranous; +Shunts, VSD with additional atrial septal defect and or patent ductus arteriosus, LVEDD, left ventricular end diastolic diameter; LVM , left ventricular mass, LVEF, LV ejection fraction; FSend, LV endocardial fractional shortening.

3.6 Relationship between mitral valve defect and LV internal dimensions, mass and systolic function

Table 3.5 shows LVEDDI, LVEF, LVMI, and LV FSend values in patients with RHD grouped according to the mitral valve pathology. Although patients with severe mitral regurgitation or additional aortic regurgitation had a greater LVEDDI and LVMI, the mitral valve pathology was generally too heterogeneous to show clear relations with either LVEDDI, or LVMI. While LVEF in severe MR was different from mild MR ($p<0.05$), LV FSend did not differ between the groups.

3.7 Impact of congenital and acquired cardiac pathology on the compaction ratio of the left ventricle

Table 3.6 shows the mean thickness of the trabecular and compact layers and the compaction ratios in the study groups. Figure 3.3 illustrates the multivariate adjusted mean thickness of the trabecular and compact layers and the compaction ratios in the study groups. As compared to healthy controls (compaction ratio=1.4±0.08) patients with VSDs (compaction ratio = 2.0±0.2, $p<0.0001$) and RHD (compaction ratio = 2.0±0.3, $p< 0.0001$) had a marked increase in the compaction ratio. After adjustment for age, BSA and gender, there was no difference between compaction ratios of patients with VSDs as compared to those with RHD.

A compaction ratio >2 was found in 42% of patients with VSDs and 47% of patients with RHD. Of the 79 controls, 4 (5%) had a compaction ratio >2 but ≤2.2. Although the adjusted mean thickness of the compact layer was not different between the groups (Figure 3.3), the adjusted mean thickness of the trabecular layer

Table 3.5. Left ventricular dimensions, mass, and systolic function in children with rheumatic heart disease grouped according to the valvular pathology and the surgical procedure

	n	LVEDD/BSA$^{0.5}$ ($mm/m^{0.5}$)	LVM/BSA$^{1.5}$ ($g/m^{1.5}$)	LVEF (%)	FSend (%)
Mild MR	6	40.2 (33.9-47.9)	78.0 (51.1-107.4)	70.0 (63.6-76.4)	39.2 (34.4-44.0)
Mod/severe MR	9	53.4 (38.9-71.7)*†‡	154.5 (51.1-224.1)*†	61.0 (53.5-68.5)*	33.3 (28.4-38.3)
Mixed MR/MS	3	38.0 (34.6-42.0)	107.4 (88.4-134.6)	64.0 (42.8-85.2)	33.3 (10.9-55.7)
MR+AR	5	54.0 (47.6-60.6)*†‡	162.3 (114.5-227.0)*†	66.0 (61.5-70.5)	36.6 (33.0-40.2)
Post surgical	13	39.0 (29.1-50.2)	99.5 (67.3-215.4)	63.9 (58.8-69.0)	34.5 (30.6-38.5)

Means (95% confidence intervals) MR, mitral regurgitation; AR, aortic regurgitation; MS, mitral stenosis; LVEDD, left ventricular end diastolic diameter; LVM, left ventricular mass, LVEF, LV ejection fraction; FSend, LV endocardial fractional shortening.

* $p<0.05$ vs. mild MR, † p, 0.05 vs. post surgical patients, and ‡ $p<0.05$ vs. mixed MR/MS.

Table 3.6. Thickness of the trabecular and compact layers of the left ventricle and the ratios between the thickness values of these layers in study subjects

	Controls (n=79)	VSD (n=100)	RHD (n=36)
Compact layer (mm)adj*	5.15 (4.58-5.66)	4.92 4.69-5.17)	5.37 (4.88-5.86)
Trabecular layer (mm)adj*	7.02 (6.22-7.81)	9.28.50-9.90)‡	11.49.95-12.83)‡
Compaction ratio	1.4 (1.3-1.5)	2.0 (1.8-2.2)‡	2.0 (1.7-2.3)‡

Mean (95% confidence intervals) VSD, ventricular septal defect; RHD, rheumatic heart disease. * Adjusted for age, BSA, gender.

‡ $p<0.0001$ vs. controls

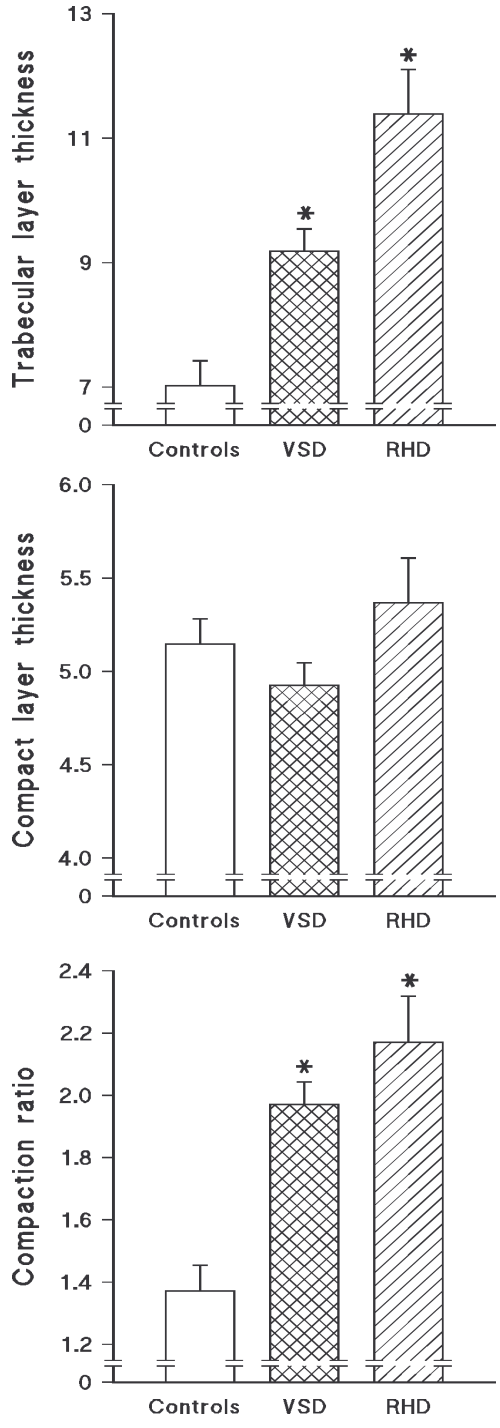


Figure 3.3. Multivariate adjusted trabecular and compact layer thickness values and compaction ratio in patients with ventricular septal defects (VSD) and chronic rheumatic heart disease (RHD) with mitral regurgitation.

* p< 0.0001 vs. controls.

was increased in patients with VSDs and RHD (Figure 3.3). Therefore, an increase in the trabecular layer thickness was the major determinant of the increase in the compaction ratio.

In keeping with the relationship between VSD size and compaction ratio, a greater number of the patients with moderate and large VSDs had compaction ratios over 2 (Table 3.7). Furthermore 9 of the 11 patients (82%) with an additional shunt i.e. a patent ductus arteriosus or atrial septal defect, had a compaction ratio >2 (Table 3.9). Muscular VSDs demonstrated a trend towards higher compaction ratio as compared with VSDs in other positions ($p<0.05$ vs. perimembranous VSDs) (Table 3.9). In 15/23 (65%) of muscular VSDs the compaction ratio was >2.0, whilst 20/59 (33%) of perimembranous, 3/8 (38%) of malaligned and 4/10 (40%) of high outlet VSDs had a compaction ratio >2.0 (Table 3.7). The presence of a syndrome was not significantly associated with the compaction ratio, but 7/14 (50%) patients with syndromes had compaction ratios >2.0 (Table 3.7). In the control group a single syndromic patient (with goldenhar syndrome) had a compaction ratio> 2. None of the control group with Down syndrome had increased compaction ratios.

In patients with RHD when grouped according to valve pathology or surgery, the highest compaction ratios were encountered in the group with moderate or severe mitral regurgitation. (Table 3.8) Of the 36 patients with RHD, 17(47%) had a compaction ratio >2. The greatest proportion of patients with RHD with a compaction ratio >2 were in the groups with severe mitral regurgitation (66%), or with combined mitral regurgitation and mitral stenosis (66%) (Table 3.8).

Table 3.7. Relationship between size and position of the VSD, presence of additional shunts or syndromes, and the compaction ratio

	N	Compaction ratio (CR)	Adjusted CR*	Proportion with CR>2.0
Small	70	1.7 (1.0-3.1)	1.7 ± 0.08	18/70 (25.7%)
Medium	9	2.4 (1.0-3.3) †	2.4±0.24†	7/9 (77.8%)
Large	21	2.7 (1.0-4.2) ‡	2.7 ±0.16‡	17/21 (80.9%)
Perimemb	59	1.9 (1.0-3.4)	1.9 ± 0.10	20/59 (33%)
Muscular	23	2.3 (1.1-3.6) §	2.3 ± 0.17§	15/23 (65%)
Malaligned	8	2.1 (1.2-4.4)	2.1 ± 0.29	3/8 (37.5%)
High outlet	10	1.9 (1.0-4.1)	2.0 ± 0.25	4/10 (40%)
+Shunts	11	2.6 (1.0-3.4)#	2.5±0.24#	9/11 (81.8%)
Syndromic	14	2.1 (1.1-3.3)	2.1 ±0.22	7/14 (50%)

Mean (95% confidence intervals) Small: VSD diameter < 1/3 of aortic annular diameter; Medium: VSD diameter >1/3 but <2/3 of aortic annulus; Large: VSD > 2/3 of aortic annular diameter; Perimemb, perimembranous; +Shunts, VSD with additional atrial septal defect and or patent ductus arteriosus. * adjusted for age, BSA, and gender.

† $p<0.05$ vs. small VSDs, ‡ $p<0.0001$ vs. small VSDs, § $p<0.05$ vs. perimembranous VSDs, # $p<0.05$ vs. without additional shunts.

Table 3.8. Left ventricular compaction ratios and proportion of patients with compaction ratios >2.0 in children with rheumatic heart disease grouped according to the valvular pathology and the surgical procedure

	N	Compaction ratio (CR)	Adjusted CR*	Proportion with CR>2.0
Mild MR	6	1.4 (1.1-2.2)	1.3 ±0.4	1/6 (16.6%)
Mod/severe MR	9	2.7 (1.1-6.2)	2.9 ±0.3†‡	6/9 (66.6%)
Mixed MR/MS	3	2.1 (1.5-2.7)	1.8 ±0.5	2/3 (66.6%)
MR+AR	5	2.3 (1.9-2.8)	1.8 ±0.4	3/5 (60%)
Post Surgery	13	1.7 (1.0-2.8)	2.0 ±0.3	5/13 (38.5%)

Mean (95% confidence intervals) MR, mitral regurgitation; AR, aortic regurgitation; MS, mitral stenosis; MV, mitral valve. * adjusted for age, BSA, and gender.

† $p<0.05$ vs. mild, ‡ $p<0.05$ vs. post surgery.

3.8 Factors associated with the compaction ratio

Table 3.9 shows the factors correlated with compaction ratios in patients with VSDs, RHD or normal controls as derived from univariate analysis. Figures 3.4 and 3.5 show the correlations between either LVEDDI (Figure 3.4) or LVMI (Figure 3.5) and the compaction ratio in patients with VSDs or RHD. On univariate analysis the compaction ratio was associated with LV chamber size and mass in both VSDs and RHD, and was furthermore associated with VSD size and additional shunts in the VSD group. The compaction ratio was not correlated with age, gender or BSA in any group.

Table 3.10 shows the factors independently associated with compaction ratios in multivariate analysis as derived from stepwise regression models with LVEDD and LVM included in separate models. In the control group there was a borderline association of compaction ratio and LV FSend. In the VSD group the compaction ratio was most strongly associated with LVMI and VSD size, while a lesser relationship existed between the compaction ratio and LVEDDI and additional shunts. In RHD the compaction ratio was associated with LVEDDI, LVMI, and LVEF.

Both univariate and multivariate analysis was undertaken in all three groups. Table 3.9 represents the univariate analysis. The relationship of the compaction ratio to LVEF in RHD is not significant on univariate analysis, but becomes weakly significant on multivariate analysis (table 3.10) $p=0.03$. This is likely to imply that there may be other factors which also have an effect causing the LVEF to become significant. The implication is that as stated, the relationship of the compaction ratio with LVEF is minor or tenuous at best. This is further discussed in 4.6 below.

Table 3.9. Factors correlated on univariate analysis with the compaction ratio in control subjects and patients with ventricular septal defects (VSD) and rheumatic heart disease (RHD).

	β-coefficient	**Partial r**	**P value.**
Control group (n = 79)			
LVM/BSA $^{1.5}$	1.39	0.01	0.88
LVEDD/BSA $^{0.5}$	0.01	0.19	0.09
LV EF	-0.01	0.19	0.10
LV FSend	1.39	0.09	0.04
Ventricular septal defects (n =100)			
LVM/BSA $^{1.5}$	0.01	0.42	<0.0001
LVEDD/BSA $^{0.5}$	0.04	0.36	0.0003
VSD size	0.07	0.40	<0.0001
LV EF	1.99	0.11	0.3
LV FSend	1.99	0.01	0.37
Additional shunts	0.66	0.27	0.01
Rheumatic heart disease (n = 36)			
LVM/BSA $^{1.5}$	0.01	0.47	0.005
LVEDD/BSA $^{0.5}$	0.06	0.60	<0.0001
LV EF	2.0	0.22	0.20
LV FS end	2.0	0.17	0.33

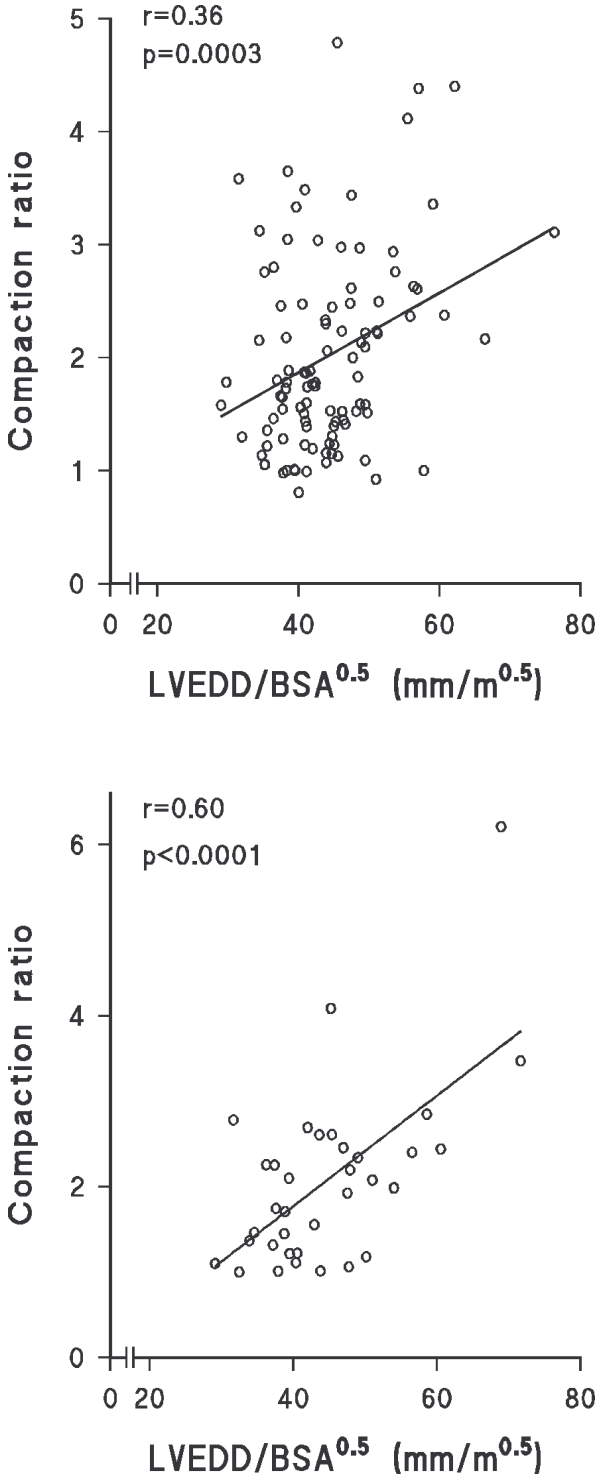


Figure 3.4 Relationship between left ventricular end diastolic diameter indexed to body surface area (LVEDD/BSA$^{0.5}$) and the compaction ratio in patients with ventricular septal defects (VSDs) (top) and rheumatic heart disease (RHD) with mitral regurgitation (below).

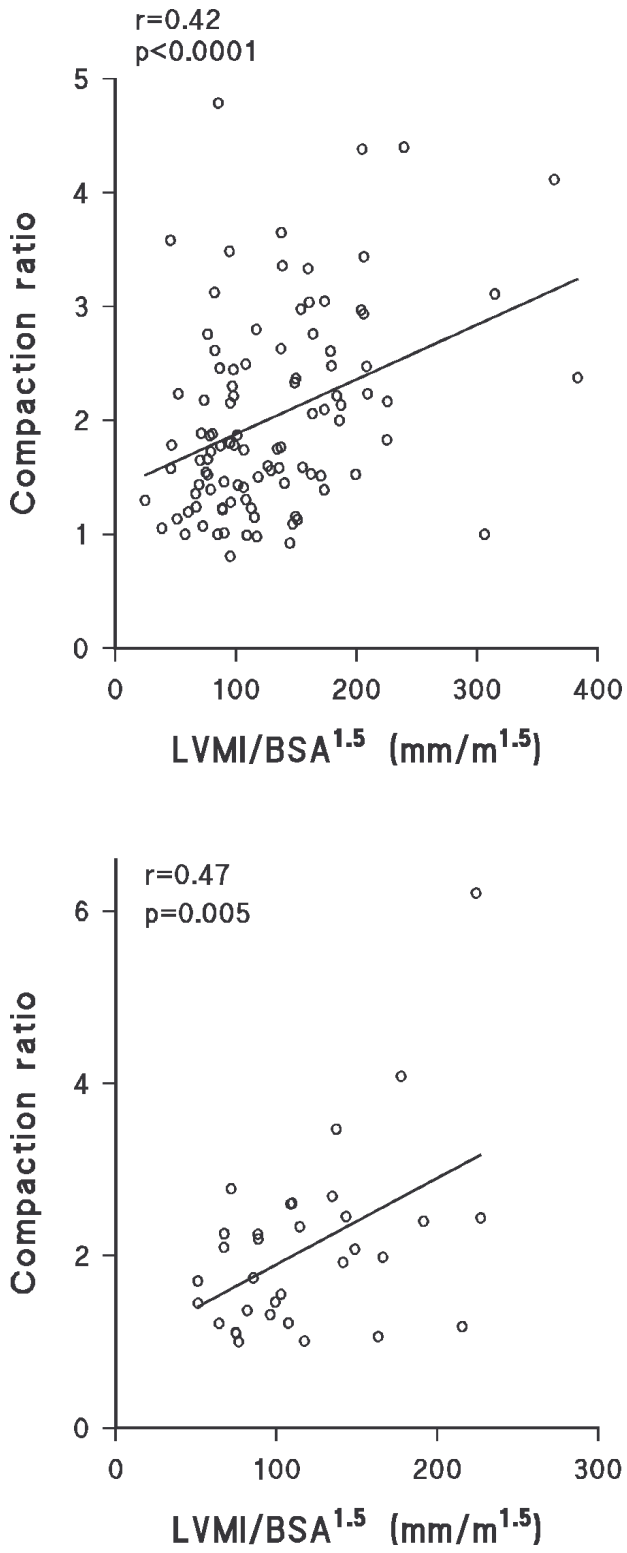


Figure 3.5 Relationship between left ventricular mass indexed (LVMI/BSA $^{1.5}$) and the compaction ratio in patients with ventricular septal defects (VSDs) (top) and rheumatic heart disease (RHD) with mitral regurgitation (below).

Table 3.10. Factors independently associated with compaction ratio in control subjects and patients with ventricular septal defects and rheumatic heart disease on multivariate analysis

	β-coefficient±SEM	**Partial r**	**P value.**
Control group (n= 79)			
LVM/BSA $^{1.5}$*	-0.0006±0.001	0.08	0.46
LVEDD/BSA $^{0.5}$**	0.009±0.006	0.19	0.096
LV EF**	-0.040±0.020	0.17	0.13
LV FSend	0.05	0.22	0.05
Ventricular septal defects (n=100)			
LVM/BSA $^{1.5}$*	0.004±0.002	0.44	<0.0001
LVEDD/BSA $^{0.5}$**	0.040±0.014	0.24	0.01
VSD size*	0.035±0.020	0.40	<0.0001
LV EF*	0.003±0.068	0.02	0.8
LV FSend	-0.002	0.00	0.98
Additional shunts**	0.432±0.249	0.21	0.02
Rheumatic heart disease (n= 36)			
LVM/BSA $^{1.5}$*	0.01±0.004	0.48	0.005
LVEDD/BSA $^{0.5}$**	0.068±0.022	0.62	0.0001
LV EF**	-0.033±0.096	0.31	0.03
LV FSend	-0.001	0.00	0.99

*Model includes age, gender, VSD position and size, midwall fractional shortening, relative wall thickness, ejection fraction, endocardial fractional shortening, additional shunts and syndromes, but not LVEDD. **Model includes age, gender, midwall fractional shortening, relative wall thickness, ejection fraction, endocardial fractional

shortening, and VSD position, size, and additional shunts and syndromes (in the VSD group), but not LVM.

3.9 Segmental analysis of the LV and assessment of the prominence of trabeculation

Figure 3.6 shows the degree of trabeculation in LV segments in patients with VSDs and RHD. Patterns of trabeculation in both VSD and RHD were essentially similar with most prominent trabeculation in both groups being in the apical, apical-posterior and apical-lateral segments. The only mild difference between VSDs and RHD is at the mid chamber level where RHD is slightly more trabeculated anteriorly and VSD laterally. This difference is probably insignificant, as the trabeculation at this level is mild. In order to determine how frequently a compaction ratio over 2 corresponded with a subjectively assessed increase in the degree of trabeculation, the proportion of patients who scored as mild, moderate or severe are tabled vs. the compaction ratio (Table 3.11). In patients with VSDs a compaction ratio <2 was found in 57 patients, of whom 82% had correspondingly mild trabeculation. In these patients with VSDs, 31 had compaction ratios ≥2, but less than 3, and most (87%) of these had moderate or marked trabeculation. Twelve patients had ratios ≥3, and all of these, with the exception of one case appeared to have marked trabeculation. In the patients with RHD, 19 cases had compaction ratios less than 2, and this corresponded with a mild appearance of trabeculation in most (84%) cases. In the patients with RHD, 58% of cases with ratios ≥2 but <3 had moderate or marked trabeculation, and of 3 cases with compaction ratios ≥ 3, all had marked trabeculation. From these observations it is my opinion that a compaction ratio ≥3 is

more reliably associated with subjectively assessed marked trabeculation, than lower values.

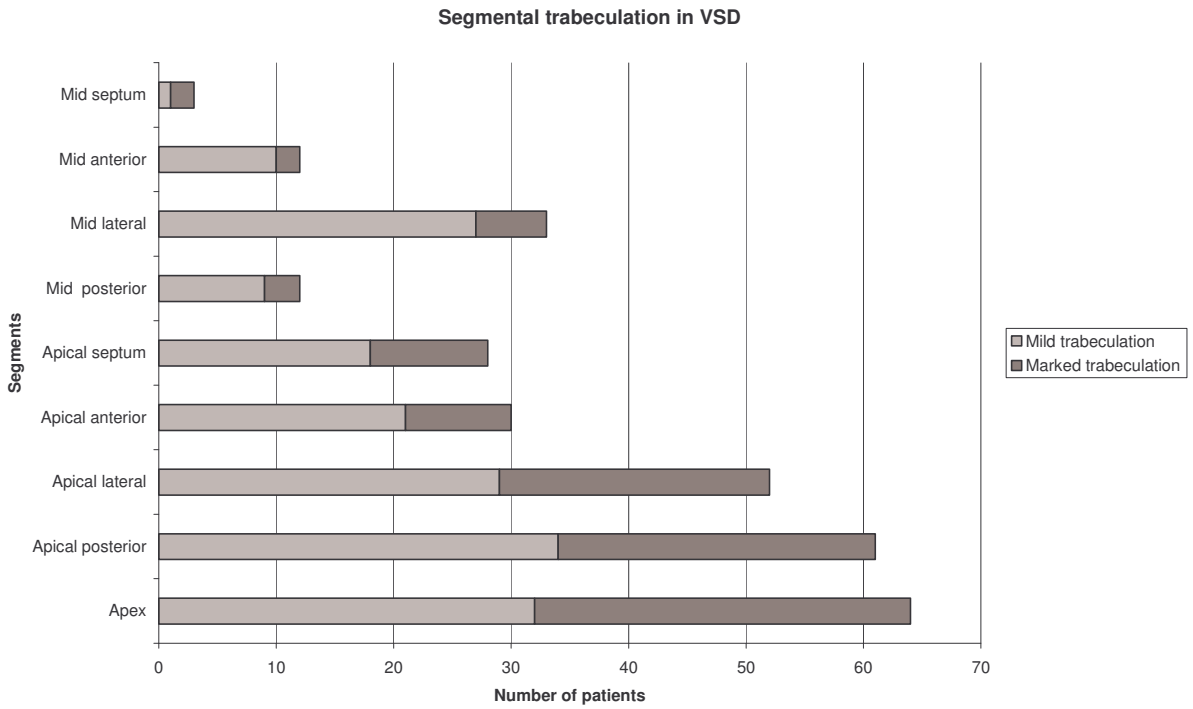


Figure 3.6 Segmental trabeculation in ventricular septal defects

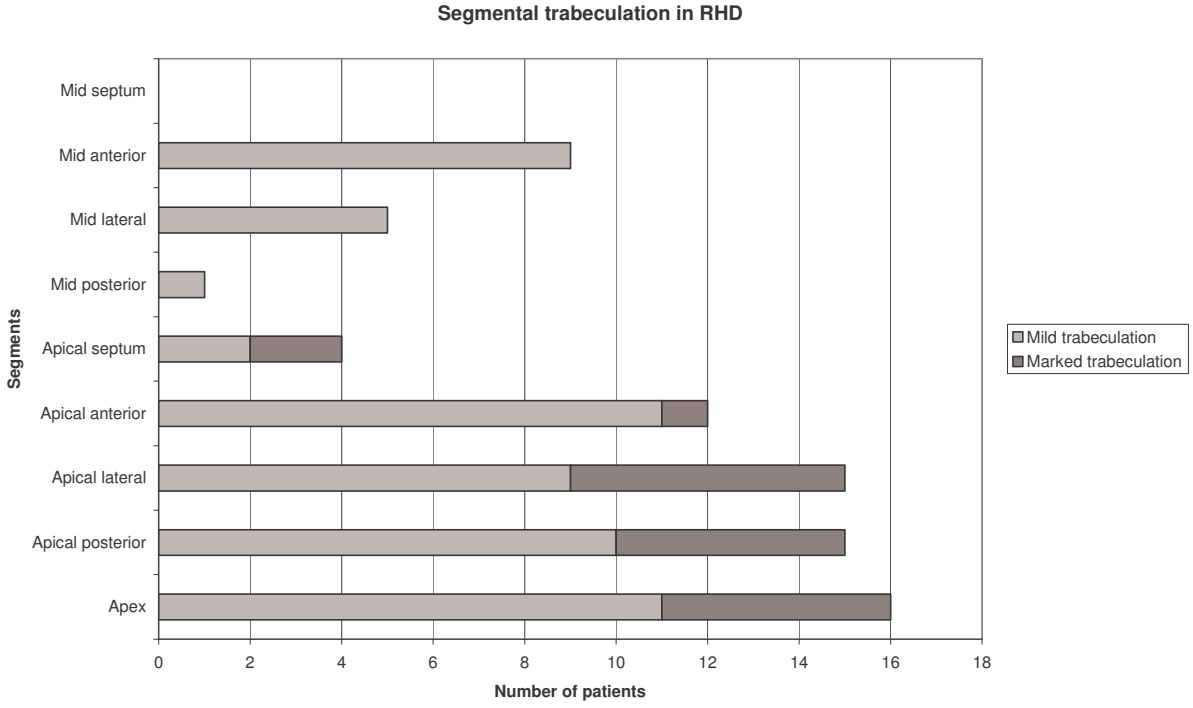


Figure 3.7 Segmental trabeculation in rheumatic heart disease

Table 3.11 Comparison of subjective (mild, moderate and severe) and objective (compaction ratio) assessments of trabeculation in patients with ventricular septal defects (a) and rheumatic heart disease (b)

	<2	≥2and <2.5	≥2.5 and <3	≥3	Total
Mild	47	4	0	1	52
Moderate	8	13	3	0	24
Marked	2	4	7	11	24
Total	57	21	10	12	100

Table 3.11a Comparisons of subjective and objective assessments of trabeculation in ventricular septal defects

	<2	≥2 and<2.5	≥2.5 and<3	≥3	Total
Mild	16	2	1	0	19
Moderate	3	6	2	0	11
Marked	0	1	2	3	6
Total	19	14	5	3	36

Table 3.11b Comparisons of subjective and objective assessments of trabeculation in rheumatic Heart disease

CHAPTER 4

DISCUSSION AND CONCLUSIONS

4.1 Background to this study

As reviewed in chapter 1 of the present dissertation, the prevailing hypothesis for the pathogenesis of LVNC is that it is a congenital defect that exists at birth and remains throughout life, regardless of the haemodynamic status of the ventricle [8, 34, 37, 60, 70, 75]. However, as also outlined in chapter 1, LVNC may in some cases occur together with acquired diseases (see sections 1.6.3, 1.6.4, 1.6.5.). Further, temporal changes in compaction ratios or prominence of trabeculation have been observed [13, 76, 89, 111, 139, 140], and it has been suggested that these changes are related to the volume status of the ventricle [13, 44, 111]. In the present dissertation I hypothesised that while true LVNC may be a congenital condition in which the trabeculae are both more numerous and more prominent than normal, an LVNC–like appearance may occur due to an increased prominence of the trabeculae produced through volume preloads and the resultant cardiac dilatation and hypertrophy. To test this hypothesis I compared the compaction ratio in both congenital (VSDs) and acquired (RHD) cardiac pathology associated with increases in volume preloads with the compaction ratio noted in healthy controls. Further, I assessed the relationship between indices of cardiac preload (LVEDD, VSD size) or hypertrophy (LVMI) and the compaction ratio in patients with VSDs and RHD.

As reviewed in chapter 1, the presence of LVNC is thought to lead to LV systolic dysfunction and dilatation. It might therefore be argued that an association between LV noncompaction and LV dilatation is expected. However, to test the hypothesis that dilatation of the LV might lead to a noncompaction–like appearance, rather than LVNC leads to dilatation and systolic dysfunction, I evaluated patients with cardiac pathology where volume preloads and hence cardiac dilatation are induced through varying pathologies i.e. VSD or valve pathology.

4.2 Main findings of the present study and potential implications thereof

The main findings of the present study are as follows: In paediatric patients with VSDs and RHD with mitral regurgitation, who had striking increases in LVEDDI and LVMI, but a preserved LV systolic function in most cases, marked increases in compaction ratios were noted as compared to healthy controls. A high proportion (43%) of these patients had a compaction ratio that would be considered to reflect a diagnosis of noncompaction. However, a threshold value of >2 did not always correspond with an appearance of excessive, prominent trabeculation. Second, LVEDD, VSD size, LVM and EF were independently associated with the compaction ratio. These data therefore suggest that the compaction ratio in congenital and acquired cardiac pathology in children and adolescents is partly determined by volume preloads on the LV.

4.3 Comparison with previous studies

As reviewed in chapter 1, LVNC has been reported to occur in a number of studies in patients with VSDs and valvular disturbances. However, the present study is the first to evaluate whether a haemodynamic/cardiac remodelling mechanism may, in part, explain these findings. An enhanced prominence of trabeculae in the presence of dilated ventricles has previously been suggested [21, 23, 67, 106]. Furthermore a reduction in the prominence of trabeculae or compaction ratio, following improvement of LV function and decreases in chamber dimensions has been reported to occur [13, 111, 139]. Moreover, noncompaction-like remodelling of the RV has been noted in a case where the RV supported the systemic circulation

[172]. However, the potential role of LV volume load as a cause of apparent noncompaction has been refuted by some authors [49, 173], and reported cases of LVNC in the presence of normal LV dimensions [13, 78, 110] suggest that haemodynamic effects do not account for all cases of LVNC. However, no formal assessment of the relationship between indices of haemodynamic factors and the compaction ratio has been performed.

In a recent study [67], diagnostic criteria for LVNC were assessed in a cohort of adults with systolic dysfunction. In that study [67] 23.6% of the cohort and 8.3% of normal controls met the criteria for LVNC. Moreover, a relationship between LVNC, diagnosed according to standard criteria and a younger age, a larger LVEDD and ethnicity was noted [67]. These authors [67] suggested that the diagnostic criteria for LVNC were excessively sensitive, resulting in an over-diagnosis of LVNC in patients with systolic dysfunction. The findings of the present study concur with this conclusion, and suggest that a reappraisal of LVNC diagnostic criteria is important. However, I noted an even greater incidence of an increased compaction ratio in patients with VSDs and RHD as compared to that reported on in adult patients with systolic dysfunction [67]. There may be many possible explanations for this. As previously indicated [67] either a paediatric age group, or black-African ethnic ancestry, as evaluated in the present study, might be associated with higher compaction ratios. However, I did not find an association between age and the compaction ratio, although this may be attributed to the narrow age range of the participants studied. More importantly, patients reported on in the present study had different causes of dilatation and hypertrophy as compared to those previously studied [67]. Furthermore in the patients with VSD, it is possible that congenital factors may play a role.

The number of noncompacted segments of the LV have previously been shown to be negatively correlated with the LV end diastolic volume index [106]. A negative correlation between the number of LV noncompacted segments and LV

volume is at apparent odds with the finding reported on in the present dissertation of a clear positive association between LVEDD and the compaction ratio. However, LV end diastolic volume index, as determined using the Simpson biplane method, incorporates measures at the apex of the heart, the area where the noncompaction ratio is assessed. An excessively noncompacted LV may therefore reduce the calculated internal volume thus biasing data toward a negative correlation between internal volumes and the noncompaction ratio. It is for this reason that in the present study cavity dimensions were assessed only from the base of the heart, thus avoiding spurious correlations occurring because of measurements being obtained from the same region of the heart.

In the present study, segmental analysis of the LV with the most prominent trabeculations revealed a similar pattern as that described for isolated LVNC [9, 14, 16, 19, 62]. Thus, although not assessed in the present study, it is nevertheless unlikely that apparent as opposed to isolated LVNC can be determined from segmental analysis.

The high incidence of a compaction ratio greater than 2 in the present study would at first glance appear to be at odds with the reported incidence of LVNC (reviewed in chapter 1). However, as demonstrated in Table 3.11, a compaction ratio greater than 2 often corresponded with minor increases in trabeculation as assessed by direct observation. These minor increases are possibly changes that may not reflect LVNC.

4.4 Relationship between LVEDD and the compaction ratio

Although it is well documented that both VSDs and chronic valvular lesions (mitral and aortic regurgitation) place an increased volume load on the LV, resulting

in an increased LVEDD and LVM [162, 174], it may nevertheless be argued that the independent relationship between LVEDD and the compaction ratio noted in patients with VSDs and RHD may reflect adverse structural cardiac remodelling (dilatation) rather than the extent of the volume preload on the LV. However, in the present study there are arguments to suggest that the relationship between LVEDD and the compaction ratio is attributed to a volume preload and not to adverse LV structural remodelling. First, in the present study, whilst the compaction ratio was related to EF in patients with RHD, and SF in the control group, this relationship was absent in patients with VSDs, and was only of borderline significance in the controls. In this regard, maladaptive remodelling occurs in association, for example, with myocardial infarction[175] where pump dysfunction coexists [176]. In contrast, in compensatory (adaptive) remodelling, which occurs for example in mitral regurgitation, although there is an increase in LVEDD, a high stroke volume is maintained and pump function is preserved. Thus a relationship between LVEDD and the compaction ratio, but not between EF and the compaction ratio in patients with VSDs suggests that the positive relationship between LVEDD and the compaction ratio is through mechanisms that are unrelated to changes in pump function. Second, independent relations between LVEDD and the compaction ratio in patients with either VSDs or RHD were noted even after adjustments for EF, a measure of systolic chamber function. Third, an independent relationship between VSD size and the compaction ratio and additional shunts and the compaction ratio was also noted even after adjusting for EF.

4.5 Relationship between LVM and the compaction ratio

In the present study an independent relationship between LVM indexed to BSA $^{1.5}$ (LVMI) and the compaction ratio was noted in patients with both VSDs and RHD. As the relationship between LVEDD and the compaction ratio was abolished with the inclusion of LVM as a confounder in the regression analysis, it is unlikely to reflect a relationship between cardiac growth and increased trabecular prominence, independent of volume preloads. Indeed, despite an increased LVMI in both groups of patients, LV relative wall thickness was unchanged. Thus, LV hypertrophy in this cohort of patients with VSDs and RHD was eccentric in nature, a change that is usually associated with a volume overload [177]. Hence, the relationship between LVMI and the compaction ratio in the present study is again likely to reflect a relationship between volume preloads and the compaction ratio.

4.6 Systolic LV dysfunction and the compaction ratio

Heart failure is a common presentation of patients with isolated LVNC [12, 62, 76]. Symptomatic heart failure is found in approximately two-thirds of patients with LVNC and frequently leads to death or transplantation [18, 102]. As outlined in section 1.8.2 of the present dissertation, heart failure in LVNC could occur as a consequence of either systolic or diastolic cardiac dysfunction or both [36, 37, 76, 78, 109]. The reduced ventricular function in cases of LVNC with heart failure may occur secondary to a reduced thickness of the compact layer in relation to the trabeculated myocardium, in regions affected by LVNC [18]. Other hypotheses have nevertheless been proposed for the development of heart failure in LVNC (see introductory chapter).

Despite a high prevalence of patients with VSDs and RHD with an increased compaction ratio in the present study, few patients had clinical heart failure at the

time of study, and LV EF was normal in the majority of cases. A preserved LV systolic function in the presence of mitral regurgitation or a VSD is considered to be the result of an enlarged LV diastolic volume, and a diminished systolic volume as the ventricle offloads into the lower pressure left atrium in the case of RHD, or right ventricle in VSDs [171, 174, 178]. However favourable preoperative loading conditions might mask underlying myocardial dysfunction, which may in some cases become apparent after surgical intervention [179]. In this regard it is of interest that the mean mid-wall fractional shortening, which may detect latent myocardial dysfunction [180], was in the normal range of 22-26%, in patients with VSD or RHD. However a weak independent negative relationship between EF and the compaction ratio was found on multivariate analysis, and this was not abolished with the inclusion of LVEDDI in the model. Therefore systolic function was, in part, a determinant of the compaction ratio independent of filling volumes in patients with RHD. Since EF is determined by both LV diastolic and systolic volume, it is possible that a relationship between EF and the compaction ratio independent of diastolic diameters is an effect mediated by systolic volume (stroke volume), which in-turn is a function of a hyperdynamic circulation.

An independent relationship between EF and the compaction ratio as observed in the present study supports the proposal of Lofiego et al (2006) who suggested that LVNC represents a marker of associated pathology rather than a primary pathological process [106]. Furthermore, improvement in EF following medical therapy, in patients with LVNC [109] suggests that the underlying congenital malformation associated with LVNC, which is unlikely to be affected by therapeutic agents, is not the main determinant of the LV systolic dysfunction in patients with LVNC [12].

4.6.1 The role of the compact layer in preserving systolic function.

Whilst speculative, I have nevertheless considered the possibility that the preserved LV systolic function in the majority of cases of RHD and VSD in the present study might be a result of a maintained thickness of the compact layer. A thin compact layer in isolated LVNC has previously been reported [4, 5, 6, 18], and is thought to contribute to LV dysfunction. Indeed, in comparative anatomical studies the development of the compact layer is related to the maintenance of higher blood pressures in larger animals, and those with active lifestyles where the heart is required to generate a greater force of contraction [120, 121]. In the group of patients studied in the present dissertation however although there was an increase in the trabecular layer thickness, I was unable to demonstrate thinning of the compact layer. This could have been due to limitations in measurement. Alternatively the volume load may have resulted in concentric hypertrophy with compact layer thickening, whilst simultaneous dilatation resulted in compact layer thinning, the net result being a compact layer that was unchanged. Retention of the compact layer thickness may have subsequently contributed to a preserved LV systolic function.

4.7 The compaction ratio and VSD position

The majority of VSDs in the present study were perimembranous (59%), and the remaining 41% were made up of muscular (23%), malaligned (8%), and high outlet (10%). This is in keeping with published data [181] of 80% of VSDs being perimembranous, 5-20% being muscular and 5-7% being high outlet. In the series of patients reported on in the present study 65% of muscular VSDs had a compaction ratio>2, as compared with 34% of perimembranous, 40% of high outlet and 37% of

malaligned VSDs having a compaction ratio>2. (Table 3.7) The compaction ratio in muscular VSDs was significantly greater than those with perimembranous VSDs ($p<0.05$) This is of interest as muscular VSDs have been described in conjunction with LVNC [29, 45, 84, 101] and an association of LVNC and muscular VSDs was noted by Lilje et al (2006) [84]. This association suggests that congenital factors may be playing an additional role in increasing the compaction ratio in VSDs, especially muscular VSDs, irrespective of the size of the left to right shunt, or LV preload. Indeed, experimental evidence in the chick embryo shows that the muscular septum is formed by the coalescence of trabecular sheets, and small muscular septal defects may result from incomplete compaction [147]. However, whether this can be extrapolated to humans and other mammals is uncertain because in the mouse model the formation of the interventricular septum occurs after trabecular compaction, and is considered to be due to the expansive growth of the apices of both ventricles [69].

4.8 The compaction ratio and the characteristics of the valvular disease.

Of the 36 patients with RHD in the present study, 18 (50%) had a compaction ratio>2. The greatest number of patients with a compaction ratio >2.0 were those with severe mitral regurgitation or those with both mitral and aortic regurgitation. Furthermore these groups also had the largest LVEDDI and LVMI. This is entirely in keeping with the hypothesis that volume loads contribute to the noncompaction-like appearance of the myocardium.

Two out of three patients with combined mitral regurgitation and mitral stenosis also had an increased compaction ratio. A raised compaction ratio in

patients with mixed mitral valve disease involving mitral stenosis may appear at odds with the notion that volume preloads contribute to noncompaction in mitral valve disease, and these patients had lower LVEDDI and LVMI than patients with predominantly regurgitant lesions. However cases of mitral stenosis and LVNC have previously been reported [27, 154, 155, 182]. This apparent contradiction might be explained in several ways. While these three patients were known to have mitral valve thickening and orifice reduction (i.e. mitral stenosis), we cannot be sure whether the haemodynamically predominant lesion was stenosis or regurgitation. Indeed of the three patients, two had undergone balloon valvuloplasties, and one a surgical valvotomy, procedures known to result in valvar regurgitation. It has been reported that an increase in LV mass and LVMI may follow percutaneous mitral valvuloplasty for rheumatic mitral stenosis [163]. Further, it is possible that if the valve pathology began as mitral regurgitation prior to stenosis as typically occurs in the natural history of the progression of rheumatic heart disease in developing countries [183]. Under these circumstances, trabecular hypertrophy or proliferation may exist in patients with mitral stenosis not because of the stenotic valvular lesion, but because of previously high volume preloads resulting from mitral regurgitation. Alternately, an underlying pre-existing increase in trabecular thickness might predispose patients to developing RHD and mitral stenosis. Finally, the small number of patients with mixed mitral disease and increased compaction ratio could be an epiphenomenon due to insufficient patient numbers.

4.9 Noncompaction as an adaptation to adverse haemodynamic conditions

As reviewed in 1.5.7 in the introductory chapter to this dissertation, it is thought that LVNC may be a compensatory change in some cardiac pathologies. Observations from invertebrate hearts which are predominantly trabecular, with very little compact myocardium, and where the heart is adapted as a specialized high volume, low pressure pump, suggest that particularly in cases of increased volume load on the ventricle during cardiac development, an increased trabecular pattern might occur. Finding a raised compaction ratio in the presence of acquired cardiac pathology raises the question of whether true LVNC, including trabecular proliferation, could occur as a compensatory or adaptive mechanism. The independent relationship between indices of LV preload and compaction ratio noted in the present study further highlight this question.

Trabecular proliferation could conceivably be a beneficial adaptive mechanism for the following reasons. An increase in size or quantity of trabeculae would increase the mass and surface area of the LV and hence may improve stroke volume. Moreover, LVNC may increase the endocardial surface area and hence potentially improve oxygenation via the endocardium [144]; it may assist the impaired myocardium by resisting dilatation by tightening the myocardial structure [144]; it may increase the muscle mass at the apex, the segment of the LV with the highest ejection fraction; and it may enhance viscoelastic properties, which might improve ventricular performance in the face of a haemodynamic challenge.

An increased volume load in neonates and children up until the age of 6 years will act on a myocardium that is, because of specialized features of gap junctions and fasciae adherents, particularly susceptible to changes in cellular topology and remodelling of myocardial architecture [146]. In this time period it is therefore plausible that ventricular remodelling, including development of additional trabeculae might occur. Indeed, as indicated in chapter 1, in chick embryos, *volume* loading of the heart results in an increased *number* of trabeculae, which are thinner than normal [145]. Against this hypothesis is the finding in the present study of an absence of a

relationship between age and trabecular layer thickness. If increased numbers of trabeculae developed postnatally in response to a volume load, an age related association might be expected, with neonates having fewer trabeculae and older children more. Clearly further work is required in patients with VSDs and RHD to determine whether early closure of VSDs or repair of the mitral valve, interventions that will presumably reduce the volume preloads, will also prevent the development of an increased compaction ratio. If noncompaction is part of an early change in life, prospective studies will have to be planned to compare changes in the compaction ratio in early as opposed to late closure of VSDs or early as opposed to late repair of mitral valves.

Against the notion that trabecular proliferation might account for an increased compaction ratio is that rheumatic fever occurs most frequently in patients between 10 and 15 years of age [184]. Rarely is rheumatic fever encountered in patients of 5 years or less. Unlike patients with a VSD, the haemodynamic challenge in this older age group would therefore be more likely to produce cellular hypertrophy than trabecular proliferation.

As reviewed in chapter 1 (section 1.5.6), our own observations and documented case studies have highlighted temporal changes in the compaction ratio. In particular where these occurred in older individuals the finding of prominence of the trabecular layer was likely to be due to an enhancement of trabeculae following ventricular dilatation and hypertrophy, rather than trabecular proliferation as an adaptive mechanism. To answer this question, clearly a formal prospective, controlled, intervention study is required to determine whether medically-induced or surgically-induced changes in haemodynamic factors may result in regression of the compaction ratio.

4.10 Potential clinical implications

The scientific literature pertaining to LVNC has been reviewed in previous sections and some inconsistencies highlighted. Many controversies remain concerning the definitions and diagnosis of this pathology. The compaction ratio is the only objective diagnostic criterion, and is in widespread usage to diagnose LVNC. I have shown that the compaction ratio may be affected by the volume load of the LV, and hence is an unreliable diagnostic criterion for diagnosing this congenital malformation (LVNC), in the presence of other cardiac pathologies, congenital or acquired. While this study has been confined to patients where LV dilatation was of a known aetiology, it is likely that the compaction ratio could also exaggerated in cases of dilatation from other causes. In order to avoid unnecessary investigations and treatment in patients and their relatives, the presence of an increased compaction ratio should be interpreted in context, to avoid over-diagnosis of LVNC. Reappraisal of diagnostic criteria is urgently needed.

Furthermore since the compaction ratio is a measure of the haemodynamic load on the LV, and has been shown to be related to mortalities [68] consideration should be given to whether it may be a better marker of LV load than other currently used criteria.

4.11 Limitations of the study.

The major limitation of the present study was that it was a cross-sectional and not a longitudinal study. Thus, whilst the strong relationship shown between LVEDD, LVM and compaction ratio is very likely to be the result of an enhancement in the trabeculae due to dilatation and hypertrophy, the effects of congenital and adaptive responses cannot be dismissed. Further research in the form of a longitudinal study,

following patients before and after interventions would help to clarify these possible confounding effects.

The calculated LVM was derived from m-mode measurements, and has not been validated in patients with LVNC. Nevertheless it has been employed in patients with both VSDs and RHD. The calculation uses thickness of the muscle at the base of the heart and assumes a geometrical shape of the LV which may not be true in the presence of substantial thickening of the LV trabecular layer near the apex.

LV chamber size, wall thicknesses and function were derived using m-mode rather than from three-dimensional measurements. However, inaccuracies in m-mode measurements are more likely to have reduced the sensitivity to detect relationships between compaction ratios and internal dimensions or LVM. Hence, if anything I have biased the study against an ability to detect these relations.

The validity of including post operative patients in the group of RHD could be queried, the argument being that postoperatively the volume load should have been relieved, and therefore they would not be a group representative of chronic volume overload. However, most RHD patients post operatively do have residual MR and in some cases AR. Furthermore the inclusion of postoperative patients into the statistical sample added to the heterogeneity of the group and therefore increased the strength of the relationship demonstrated. Multivariate analysis where these post operative patients were excluded was performed, (results not reported here) and revealed results consistent with those reported in this study where they were included viz. that the primary determinants of the compaction ratio in a multivariate analysis were the LVEDD and LVM. The conclusion is that the relationship between the compaction ratio and the LVEDD and LVM is a strong relationship, and that the inclusion of post operative patients did not affect this outcome. Furthermore the greater heterogeneity of the group with the inclusion of postoperative patients increased the relevance of the statistical findings.

4.12 Conclusions

The present study is the first to formally test the hypothesis that an increased compaction ratio can be attributed to volume loading of the LV. I showed that indices of LV preload viz. LVMI, LVEDDI, VSD size, and additional shunts, were positively and independently associated with the compaction ratio in children and adolescents with VSDs and RHD, while LVEF was negatively correlated. This data suggests that in congenital and acquired cardiac pathology, the compaction ratio is a function of cardiac preload, and thus should be interpreted with caution to avoid over diagnosis of LVNC.

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INVESTIGATORS	Mrs V Hunter
DEPARTMENT	Paediatric Cardiology
DATE CONSIDERED	05.06.24
DECISION OF THE COMMITTEE*	Approved unconditionally

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DATE 05.07.18 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof G Norton

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INVESTIGATORS	Ms VI Hunter
DEPARTMENT	School of Clinical Medicine
DATE CONSIDERED	04.08.27
DECISION OF THE COMMITTEE*	Approved unconditionally

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*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof SE Levin

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Gauteng Department of Health

PERMISSION FOR RESEARCH

NAME OF RESEARCHER V. I HUNTER

TITLE OF RESEARCH PROJECT Noncompaction of the Ventricular Myocardium in children with ventricular septal defects.

METHODOLOGY (briefly or include a protocol) protocol included Echocardiographic study.

CONFIDENTIALITY OF PATIENTS MAINTAINED yes

COST TO THE HOSPITAL None.

APPROVAL OF HEAD OF DEPARTMENT yes

APPROVAL OF CRHS OF WITS UNIVERSITY yes

CLINICAL EXECUTIVE PERMISSIONS

Signature Hunter. Date 14/7/05.

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Dr. D. Wo[illegible]chowska

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Professor Cleaton-Jones
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Request for permission to use photographs of human heart, and echocardiograms for illustration purposes in an M.Sc dissertation.

Dear Prof Cleaton-Jones

I am a student registered for my MSc.(Med) degree at the University of the Witwatersrand. I am currently completing a research dissertation on the subject of noncompaction of the heart in paediatric patients with congenital and acquired heart disease. My supervisors are Prof S.E.Levin and Prof G Norton.

In order to better illustrate to my potential examiner's what "non-compaction" is, I would like to have permission to use photographs, and echocardiographic images of the left ventricle in my dissertation. The photographs of anatomical specimens were taken during monthly teaching sessions, with permission of Prof Levin. The echocardiographic images were taken during the course of routine scans. The names of the patients involved will remain confidential.

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I grant permission for Mrs Hunter to use the pictures taken during teaching sessions, for illustrative purposes in her dissertation.

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