Left ventricular noncompaction – insights into the pathophysiological mechanisms and consequences of left ventricular dysfunction

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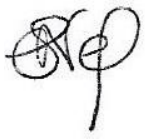
Declaration

I Samantha Heidi Nel declare that this Thesis is my own, unaided work. It is being submitted for the degree of Doctorate of Philosophy at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of Candidate)

06th Day of October 2022 in Parktown, Johannesburg

I certify that the studies contained in this thesis have the approval of the Ethics Committee of the University of the Witwatersrand, Johannesburg. The approval number was M140937.

Dedication

With God all things are possible

My biggest treasure and greatest gift, my family.

Presentations arising from the thesis

Congress Presentations

Samantha Nel, Ferande Peters, Elena Libhaber, Claudia Dos Santos ,Hiral Matioda, Samantha Govender, Nirthi Maharaj, Mohammed R Essop. **An echocardiographic comparison of Isolated Left Ventricular Noncompaction versus Idiopathic Dilated Cardiomyopathy**. Poster presentation at the 15th Annual South African Heart Congress, Sun City, 2014.

Samantha Nel, Ferande Peters, Elena Libhaber, Claudia Dos Santos ,Hiral Matioda, Ruchika Meel, Nirthi Maharaj, Mohammed R Essop. **Unraveling right ventricular dysfunction in isolated left ventricular non-compaction.** Oral presentation at the 16th Annual South African Heart Association Congress, Sun City, 2015.

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Samantha Nel, Bijoy K. Khandheria, Elena Libhaber, Mohammed R. Essop, Claudia Ferreira dos Santos, Hiral Matioda, Sacha Grinter, Nirthi Maharaj, Ferande Peters . **Prevalence and Significance of Isolated Left Ventricular Non-Compaction Phenotype in normal Black Africans Using Echocardiography.**

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Future Submissions for Publication

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Samantha Nel, Ferande Peters, Elena Libhaber, Claudia Ferreira dos Santos, Hiral Matioda, Raquel Duarte, Mohammed R. Essop. **Serum Biomarkers and Ventricular Remodeling: An Analysis of Isolated Left Ventricular Non-compaction versus Idiopathic Dilated Cardiomyopathy in a Black African Population.**

Abstract

Several controversies have emerged in recent years with regard to whether left ventricular noncompaction is a distinct pathological entity or a remodeling epiphenomenon. The presence of more than three trabeculations within the left ventricle, accompanied by a two-layered structure, in which a thin compacta has an overlying prominent trabeculation, with an adjacent intertrabecular space, is the distinct phenotypic hallmark of noncompaction.

Left ventricular noncompaction is a distinct anatomical phenotype, which is detected by imaging in a variety of clinical scenarios. These include congenital heart disease, neuromuscular diseases, valvular disease, pregnancy, sickle cell anemia and other cardiomyopathies, such as hypertrophic cardiomyopathy. Whether noncompaction is a distinct genetic disorder, whether the imaging criteria used are accurate, or whether it is should be considered a normal variant in certain patient populations is key to diagnoses and clinical management. One such population are individuals of African descent in whom it has been postulated by some authors, that hypertrabeculation is a normal variant. The consequence is that some individuals, particularly those with the phenotype of dilated cardiomyopathy may satisfy current imaging criteria for the diagnosis of left ventricular noncompaction. Exactly what the presence of the left ventricular noncompaction phenotype in these clinical scenarios means, has not been systematically studied until recently. The aforementioned controversies and questions are germane to the key issues that were studied in this thesis.

Therefore, this thesis firstly evaluated normal echocardiographic left and right ventricular parameters in a Black South African population. The study revealed that there was a direct correlation between age, RV A' (r=0.468) and inversely correlated with RV E' (r=-0.431) but there was no correlation between BMI and RV linear measurements, however TAPSE and RV A' increase with BMI. Secondly, in a large normal Black South African population 4, 7% trabeculations were found, no subjects fulfilled all four criteria for the diagnosis of ILVNC and similar rotation patterns,

quantitative LV rotation patterns and net twist were shown in both individuals with and without trabeculations

Thirdly, the prevalence and predictors of right ventricular dysfunction in ILVNC with reduced ejection fraction and dilated cardiomyopathy (IDCMO) were evaluated using echocardiography. The main findings indicate that ILVNC had more RV dilatation than IDCMO and that RV systolic functional parameters - RV S' TAPSE and RV FAC were decreased compared to IDCMO. In multivariate regression analysis LVEF was the most relevant predictor of RV dysfunction, followed by LVESD (p=0.013).

Lastly, the question that was explored was whether ILVNC with low ejection fraction differed from IDCMO with regard to myocardial mechanics and biomarkers of LV remodeling. The results showed that patients with ILVNC had more adverse remodeling, evidenced by increased LV dilatation (66.4 ± 10.1 vs 56.1 ± 10.3), LV mass (295.0 (143.0) vs 234.0 (140.0) and lower EF (ejection fraction) (28.5 ± 9.0 vs 33.3 ± 7.7), when compared to IDCMO.Net twist was higher in IDCMO group vs ILVNC [6.5 (3.0) vs 5.4 (4.6)].

Rigid body rotation and regional longitudinal strain was not statistically significant different between both groups. No statistically significant differences are found between the biomarkers of LV remodeling (Procollagen 1, MMP1, TIMP1, and Fas/APO-1). These results should be considered as preliminary, due to the reduced sample size in both groups.

This thesis has provided key normal reference ranges for several echocardiographic parameters that may define normality in this population group using echocardiography. Furthermore, this thesis highlights that normal individuals in this population group do not satisfy current used echocardiographic left ventricular non compaction criteria and will have normal left ventricular rotational parameters.

With regard to a comparison between ILVNC with the dilated phenotype and a reduced EF and IDCMO, it appears that more adverse left ventricular remodeling and its ensuing functional abnormality are more common in ILVNC. The consequence, is that right ventricular dysfunction is more prevalent in ILVNC and that in both instances, the LVEF was the most important predictor of right ventricular dysfunction. This thesis did not find any significant differences with regard to abnormal rotation patterns or regional longitudinal strain between ILVNC and IDCMO

or with regard to the biomarkers studied.

The strength of this research is that it provides guidance to clinicians with regard to identifying normality in individuals from this population group. Overall, the thesis has unraveled some of the controversies, but several issues remain unresolved with regard to the comparison of ILVNC with IDCMO. This may require future larger studies to address different aspects of ILVNC such as genetic analysis, more extensive biomarkers of heart failure, in addition to speckle tracking parameters.

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Manuscripts and Editing

"Prevalence and Significance of Isolated Left Ventricular Non-Compaction Phenotype in normal Black Africans Using Echocardiography"

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List of Abbreviations

ILVNC	Isolated left ventricular noncompaction
IDCMO	Idiopathic dilated cardiomyopathy
BMI	Body mass index
BSA	Body surface area
CHBAH	Chris Hani Baragwanath Academic Hospital
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
EDD	End diastolic dimension
ESD	End systolic dimension
EDV	End diastolic volume
ESV	End systolic volume
EF	Ejection fraction
FS	Fractional shortening
FAC	Fractional area change
HR	Heart rate
IVS	Interventricular septum
PW	Posterior wall
LA	Left atrium
LV	Left ventricle
RA	Right atrium
RV	Right ventricle
SD	Standard deviation
TTE	Transthoracic Echocardiogram
TAPSE	Tricuspid annular peak systolic excursion
DTI	Doppler tissue imaging

2-D	Two-dimensional
PAS	Pulmonary artery systolic pressure
PAP	Pulmonary artery pressure
VTI	Velocity time interval (mean)

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Chapter 4

Chapter 1: Integrated Narrative

1.1 Background

The normal myocardial structure of the left ventricle (LV) has two layers, a thin endocardial trabecular layer with an underlying prominent compacted layer.[1] The endocardial trabecular layer usually develops into less than four prominent trabecular.[1] At autopsy, at least three trabeculae have been observed in approximately 4% of the normal population.[1]

Grant et al reported the first observation of an abnormality of the myocardium, characterised by increased trabeculation, with abnormal embryonal sinusoids.[2] Thereafter, in the 1960's, some patients with congenital heart disease were found to have an abnormal myocardial phenotype, which was identified on either angiography or autopsy, and described as persistent intramyocardial sinusoids or spongy myocardium.[3,4]

Two decades later, Engberding et al, with the use of two dimensional echocardiography reported on a myocardial phenotype similar to persistent myocardial sinusoids, in the absence of any other recognised cardiac disorders.[5] In 1990, Chin et al. described their case series using echocardiography which demonstrated the presence of abnormal trabeculae with an underlying thin compacted layer and coined the term 'noncompaction'.[6] These authors proposed that this was most likely a disorder of endomyocardial morphogenesis. Subsequently the term left ventricular noncompaction (LVNC) has been used, although Stollberger et al. utilised the term left ventricular hypertrabeculation.[7]

ILVNC was considered a rare cardiac abnormality; however, with a combination of increased awareness and advancements in diagnostic imaging, there has been an increased rate of detection of this disease. The prevalence of ILVNC is estimated to be 1:5000 individuals in the general adult population, and 3 to 4% in patients diagnosed with heart failure.[8] In recent years more publications related to ILVNC, with an increasing divergence of opinion relating to several controversies have emerged.

1.2 Disorders associated with ILVNC

ILVNC may occur if there is associated congenital heart disease, myocardial diseases such as hypertrophic cardiomyopathy and myocarditis, or in families where known genetic mutations have been identified, and have revealed other myocardial pathologies.[9,10] LVNC has also been reported in several medical disorders which include several neuromuscular abnormalities, sickle cell anaemia, chronic kidney disease, hypertension and Chagas disease.[11,12,13,14] Physiological states where the ILVNC phenotype has been described also includes pregnancy and athletes.[15,16]

1.3 The characteristic phenotype of ILVNC

The hallmark of the phenotype of ILVNC is characterised by three key features. [2] Firstly, there should be prominent left trabeculations which are not connected to the interventricular septum.[2] Second, is the presence of adjacent accompanying deep inter-trabecular recesses which are perfused by blood within the left ventricular cavity, with no connection to the coronary circulation. [2] Third, is that overlying trabeculations should be a thin compacted layer of myocardium. [2] These three key features create a unique two-layered phenotypic appearance, which is found more commonly in certain areas of the myocardium, with the apex, apical lateral and mid lateral walls being the most common affected ventricular walls.[2]

1.4 Controversies relating to ILVNC

There are several controversies relating to ILVNC, which include the possibility of ILVNC being a genetic disorder, or perhaps merely a remodeling phenomenon. ILVNC is characterised by the American Heart Association (AHA) as a genetic cardiomyopathy, whereas the European Society of Cardiology (ESC) refers to ILVNC as an unclassified cardiomyopathy.[17,18]

A second major controversy is whether this process occurs exclusively as an arrest during embryological development or perhaps post-natal factors such as volume overload may cause the development of the ILVNC phenotype. The documentation of the presence of this phenotype, its reversal in patients with myocarditis and a

normal pregnancy suggest that the embryological theory may not fully explain the development of the ILVNC phenotype.[16,19] The presence of documented ILVNC in athletes and patients with sickle cell anemia have led to postulate that volume overload results in adaptive left ventricular remodeling, which may also result in the ILVNC phenotype.[15]

A third controversy relates to the identification of the ILVNC phenotype with imaging. Several issues arise regarding which imaging technique is the gold standard between echocardiography and Cardiac Magnetic Resonance (CMR). Can the established echocardiographic criteria identifying ILVNC be used as the gold standard, over the CMR criteria?

Echocardiography is often the main investigation used to diagnose ILVNC.[20] This diagnostic imaging tool has in recent years become increasingly widely available, and remains more cost effective than CMR, with improved technology in spatial resolution. [20] The main disadvantage of CMR is its technical feasibility. [20,21,22] Transthoracic echocardiography however has limitations in certain individuals because of poor spatial resolution in certain anatomical area, in particular the left lateral ventricular wall. [20,21,22] Furthermore, it is highly operator dependent, and may lead to under diagnosis of ILVNC, especially if suboptimal images, or off-axis images are obtained. [20,21,22]

The morphological criteria of ILVNC analysed by transthoracic echocardiography were initially proposed by Chin et al.[6] Subsequently, Jenni et al, and Stollberger et al. have proposed criteria for the diagnosis of ILVNC.[23,24]

The Chin criteria evaluates the left ventricle at end diastole, utilising the short-axis and apical views of the LV free wall.[6] The ratio between the distance from the epicardial surface to the trabecular recess, and the distance from the epicardial surface to the trabecular peak of less than 0.5 is the key criterion for the diagnosis of ILVNC.[6]

The Stollberger criteria evaluates the apical long axis views, usually the apical three chamber view which may require some degree of off-axis imaging.[6] The presence of more than three trabeculations on the left ventricular wall, distally or more apically, to the papillary muscles, visible in a single imaging plane, is one of the key criterion.[6]

The presence of perfusion by colour flow Doppler within the inter-trabecular spaces between the aforementioned trabecular is a second key criteria.[6]

The Jenni criteria is the most widely used echocardiographic criteria. This criteria evaluates short-axis imaging of the left ventricle at end systole.[23] A ratio of noncompacted to compacted myocardium greater than two is diagnostic of ILVNC.[23] The Jenni criteria was validated initially at autopsy, and subsequently applied to differentiate ILVNC in hypertensive individuals and in subjects with valvular heart disease.[24,25]

An additional criteria has been proposed by Paterick, et al.[2] The 'Milwaukee' criteria which also suggests that a ratio between the thickness of the noncompacted and compacted myocardium should be greater than two.[2] This measurement is taken at the end of diastole in the short-axis parasternal view.[2] Paterick et al, proposed that this criteria increases the accuracy of the myocardial thickness, however, no prospective studies have been conducted to validate this assertion.[2] These criteria are known to differ in several ways, and thus are not unexpectedly have a low agreement when studied.[2]

A fourth controversy on the identification of the phenotype of ILVNC, which refers to a possible manifestation of a normal variant in certain populations, particularly individuals who have a normal left ventricular ejection fraction (EF). The clinical status of individuals identified with this ILVNC phenotype on imaging, varies from being asymptomatic to displaying life threatening cardiac manifestations such as heart failure, arrhythmias, systemic emboli or sudden cardiac death.[2,26] Thus misdiagnosis of pathology in a normal individual who may be asymptomatic but who may be uncertain of their future clinical course may have serious biological, social, economic and psychological consequences to an individual.

1.5 Is ILVNC a normal morphological variant in Black Africans?

Kholi et al studied the three main echocardiographic criteria in 199 patients and 60 healthy people as a control group.[27] They found that 47 patients met at least one of the criteria.[27] In approximately 30% of this sample, all three criteria were satisfied.[27] Furthermore, 8.3% of normal individuals satisfied criteria for ILVNC.[27] In their

conclusion, Kohli, et al. expressed a concern that over diagnosis of ILVNC may occur, especially in black individuals.[27] These studies findings have been cited numerous times as evidence that ILVNC may be a normal variant in black individuals.[26,28,29]

Further evidence supporting the observation of Kohli, et al. arose from a study of African athletes which showed a high prevalence of myocardial hypertrabeculation, with about 15%of patients satisfying the echocardiographic criteria of ILVNC.[26] However, it is unclear whether this cardiac morphology observed in individuals of African descent is a manifestation of ILVNC or is only secondary to the increase in cardiac preload in these individuals.[27,30]

1.6 Differentiating the normal individual from ILVNC with normal LVEF

The differentiation of a normal heart with increased trabeculation from ILVNC with a normal EF is a key consideration. While merely relying on the traditional echocardiographic criteria may aid in most cases, this remains problematic as some normal cases may satisfy criteria, particularly highlighted by Kohli et al in some black individuals and as previously mentioned by studies of Afrocaribean athletes.[27,30]
To improve the diagnostic discriminatory power, some authors suggested that either a family history or myocardial mechanics be utilized in combination with echocardiographic criteria.[2] Utilizing the presence of a family history is useful, but will not account for sporadic cases of ILVNC. Furthermore, the feasibility of performing family screening amongst individuals where the index case has an equivocal diagnosis may not be feasible and may potentially cause unnecessary added emotional stress in some circumstances.[31]

Thus utilizing myocardial mechanics as a potential additional complementary diagnostic tool is worthy of consideration.[32,33] The left ventricle during systole undergoes four major changes which results in the net contractile action which results in the efficient ejection of blood.[32,33] Myocardial fibres shortens in a longitudinal and circumferential direction, thickens in a radial direction while simultaneously the left ventricle undergoes a rotational deformation, that resembles the wringing of a towel, termed left ventricular twist. [32,33] In the normal individual, left

ventricular twist is the net consequence of the basal left ventricular clockwise rotation and the predominant apical counter clockwise rotation. [32,33]

1.7 The potential link between LVNC and abnormal myocardial mechanics

During embryological development the normal progression of myocardial compaction proceeds from epicardium to the endocardium and from the base towards the apex of the heart.[34,35] Some postulates relating to the genetics and epigenetics of ILVNC may suggest that perhaps an arrest in embryogenesis or a partial arrest in this process potentiated by post-natal factors occurs.[36] The consequences of this is phenotypically the ILVNC phenotype which is most commonly seen to afflict the left ventricular apex, apical-lateral and apical-inferior walls in clinical series.[29,37] The functional consequences of ILVNC is best understood from evidence in patients with low EF and the dilated phenotype. In several studies, the degree of LV dysfunction did not correlate with the extent of LV non compaction.[6,38,39]

One key plausible factor related to the development of left ventricular dysfunction in ILVNC with low EF is the documentation of subendocardial ischemia in ILVNC. Subendocardial perfusion defects have been described in LVNC using both magnetic resonance imaging and nuclear scintigraphic techniques such as positron emission and thallium in the absence of epicardial coronary stenosis.[40,41,42] Jenni et al, demonstrated that diminished coronary flow reserve was present in both noncompacted and compacted segments of myocardium.[40] Junga et al have postulated that reduced subendocardial perfusion and coronary flow reserve in ILVNC may be related to a few potential factors which includes, a mismatch of the coronary circulation with increased ventricular mass, compression of the intramural coronary bed by the hypertrophied myocardium, or both processes.[41]This predisposition to subendocardial dysfunction will predominantly affect the function of subendocardial fibres and may manifest as reduced longitudinal strain and reduced basal clockwise rotation.[40,41,42] The apex is almost exclusively involved and thus apical dysfunction may manifest in potentially greater apical longitudinal strain dysfunction or apical rotation abnormality.[40,41,42]

1.8 Abnormality of global and regional LV function

Longitudinal strain or dysfunction of rotational parameters may thus identify sub-clinical left ventricular contractile dysfunction in individuals with normal EF and the ILVNC phenotype.[32,33,45] Using speckle tracking this may represent a feasible diagnostic technique that requires more detailed study to determine whether additional functional criteria may emerge that may more accurately distinguish normal individuals from pathologic ILVNC with a normal LVEF.[43] Bellavia et al were the first to document in a small cohort using speckle tracking that global longitudinal strain was lower in ILVNC with normal EF versus normal controls.[43] Furthermore they found that left ventricular rotation values are abnormally reduced in patients with ILVNC with normal EF compared with normal controls. [43] These preliminary findings requires more definitive study since discrepant findings using tissue Doppler imaging were found when comparing ILVNC with normal LVEF versus normal controls.[43] Tufekcioglu and coworkers found abnormal systolic pulse wave tissue Doppler imaging values in patients with ILVNC and normal EF versus controls whereas Bellavia et al, did not find any differences in peak velocity of systolic annular motion (S') between patients with ILVNC and EF >50% compared with controls.[43,44] These discrepant findings may represent inconsistencies with the technique of tissue Doppler rather than true abnormality.

Thus, based on the aforementioned issues, we thought it would be prudent to study a large normal, healthy Sub-Saharan black African cohort to determine to whether the conventional clinically utilized echocardiographic criteria would be satisfied by this population. Furthermore, we postulated that normal individuals would have normal myocardial mechanics. A fundamental issue however, would be to firstly determine if a clinically normal individual has a structurally and functionally normal heart. Current limitations of normal echocardiographic reference parameters in the 2015 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) updated recommendations for chamber quantification provides reference ranges of normative echocardiographic values for clinical practice.[31] However, these normative values are based on meta-analysis of data from studies emanating predominantly from the United States. [45]

The established reference ranges may not be accurate in some populations since reports from recent reports from China, Japan, and Iran suggest that “normal” hearts in individuals from those nations have echocardiographic values that are smaller than that reported from American and European studies.[34,35,36,45] An additional factor that contributes to variation of measurements is the lack of standardization of measurement techniques between studies. These differences were addressed in the World Alliance Societies of Echocardiography (WASE) Normal Values Study.[34,35] This study found that echocardiographic dimensions and volumes are similar for people of White and Black race, while smaller for Asians and Mexicans (mixed white/native American race). [34,35]

Prior studies on black individuals such as the Dallas heart study have suggested that black individuals have a greater tendency to have greater LV mass.[46] As mentioned previously; it seems that black individuals may have greater LV trabeculations.[27,30] A key question that emanates from these observations is whether these findings may differ between black individuals from North America, Afro Caribbean individuals and Sub-Saharan individuals. The WASE study included a Nigerian cohort of 107 normal individuals.[34,35] We postulated that a large echocardiographic study of normal black Sub-Saharan individuals would firstly define normal echocardiographic reference ranges, and secondly, would allow us to evaluate left ventricular trabeculation in this population. Accordingly, we undertook a study to firstly evaluate echocardiographic parameters – both left and right heart parameters. Thereafter, we systematically evaluated all studies with regard to defining to what extent a normal black Sub-Saharan population would satisfy conventional clinically utilized echocardiographic criteria for the diagnosis of ILVNC.

1.9 Can myocardial mechanics be used as an additional functional criteria to distinguish DCMO from LVNC with a reduced EF?

Prominent left ventricular trabeculations may be found in both LVNC and DCM, which may make the differentiation of these two entities difficult. While patients with DCM do not satisfy the comprehensive echocardiographic criteria this has not been systematically studied in all populations. The utilization of standard trans thoracic left ventricular echocardiographic parameters has not yielded any robust differentiation

between these two conditions in several prior studies.[47,48] However Nieman et al described a striking difference in regional longitudinal strain in patients with LVNC when using tissue Doppler imaging.[48] They observed that despite a decrement in EF and global longitudinal strain, the basal left ventricular strain was greater than the mid segment strain which in turn was greater than that documented at the apex. This base to apex gradient was strikingly different to DCM where the strain was equally depressed in all regions.[48] They postulated that left ventricular apical function is more adversely affected than the basal regions because an arrest in the normal embryological process of myocardial compaction which leads to greater apical non compaction and consequently more abnormal function compared to the basal regions.[48] This theory may account for the findings of rigid body rotation that was first described by Van Dalen et al in individuals with LVNC.[49] Van Dalen et al found in their 2012 study that no patients with DCM had Rigid body rotation in comparison to 88% of LNVC patients who had RBR.[49]

Ashwal et al in their study utilized speckle tracking and found that patients with LVNC had depressed GLS compared to normal controls.[50] In addition they found that the strain was depressed to a greater degree in the apex compared to the base of the left ventricle.[50] Furthermore, they found RBR in 50% of their population.[50] In contradistinction Huttin et al observed a significant increase in longitudinal function from the base to the apex with more preserved longitudinal strain at the level of the apical NC segments.[51]

In lieu of these diametrically opposed findings, further work is required to clarify the accuracy and relevance of these findings. Furthermore, no direct comparison has been conducted in a Sub-Saharan African population between patients with DCM and LVNC with regard to standard echocardiographic parameters, myocardial mechanics and biomarkers that may relate to the remodeling process. Thus, we decided to study the aforementioned issues in patients with LVNC and DCM.

1.10 Findings of the thesis with clinical relevance

This thesis addresses the following key questions

(1) Are trabeculations in the left ventricle a normal phenomenon or is there a distinct pathological phenotype that can be used to differentiate normality from pathology in normal black Africans?

(2) Are echocardiographic criteria for the diagnosis of LVNC too sensitive, thus resulting in an over-diagnosis?

(3) Are echocardiograpghic criteria for ILVNC satisfied in normal individuals of Sub-Saharan African decent?

(4)Does ILVNC with reduced EF differ from IDCMO with regard to myocardial mechanics and biomarkers of LV remodeling?

(5)What is the prevalence and predictors of right ventricular dysfunction in patients with IDCMO and ILVNC with reduced EF?

1.10.1 The value of this research

Paper 1: Echocardiographic indices of the left and right heart in a normal Black African population.

This is the largest and the first echocardiographic study to define normal echocardiographic parameters using the ASE 2015 chamber quantification guidelines in a Black African population. It highlights what the reference range for a Black Sub-Saharan population may be.

Paper 2: Prevalence and significance of isolated left ventricular non-compaction phenotype in normal Black African using echocardiography.

It is the first study to evaluate the application of all ILVNC criteria in a normal Black African Sub-Saharan population, and represents the largest Sub-Saharan population studied, which is more than four times larger than the control group of Kholi, et al. This is the first study to prospectively evaluate the Paterick/Milwakee criteria.

The two papers listed above confirm that it is not normal for normal black Sub-Saharan individuals to satisfy ILVNC echocardiographic criteria. These findings do not apply to individuals with anemia, athletes or pregnancy woman, since these specific populations were excluded from our study. The application of this research to clinical practice is useful when, and if, an individual has a trabeculated left ventricle, but does not satisfy echocardiographic criteria, has normal tissue Doppler parameters and normal LV twist, the individual should therefore be deemed as normal. The addition of regional and global strain to LV rotation may further prove to be useful, as a discriminating factor that would however require future validation.

Paper 3: Right ventricular function in Isolated left ventricular noncompaction and Idiopathic dilated Cardiomyopathy.

This is one of the first studies to make a comparison between ILVNC with reduced EF versus IDCMO, in a Black Sub-Saharan population, with regard to standard echocardiographic left ventricular parameters, and right ventricular parameters. This study found evidence of more adverse LV remodeling in ILVNC. The most important predictor of RV dysfunction was LV dysfunction. These differences in LV remodeling is at variance with other studies and does require a larger study to be undertaken to further study these differences. The addition of genetic analysis may be useful to understand the differences between these two patient populations.

Paper 4: Serum Biomarkers and ventricular remodeling: an analysis of Isolated left ventricular non-compaction versus Idiopathic Dilated Cardiomyopathy in a black African population.

This is the first study to evaluate a comparison of myocardial mechanics and biomarkers of left ventricular remodeling in ILVNC versus IDCMO. This study found no significant differences between the biomarkers measured (Procollagen 1, TIMP/MMP ratio, Fas/APO -1) in the two groups. Furthermore, there was no significant differences in regional strain or the detection of rigid body rotation. This study was limited by the small sample size, which may have contributed to a sample bias, since the overall population registry of the ILVNC clinic at Chris Hani Baragwanath Academic Hospital was over 120 cases during the study period, and a IDCMO registry of over 800 cases. We consider these findings preliminary and a

larger study size is required together with additional biomarker analyses relating to LV remodeling.

1.11 Study Limitations

Paper 1: First, older individuals (>65 years) were underrepresented due to difficulty recruiting normal healthy older individuals in a peri-urban African environment, and thus the results may only pertain to individuals between the ages of 20 and 60 years. Furthermore, recruitment was on an ad hoc basis and thus resulted in an uneven age and sex distribution.
A second important limitation is that subclinical disease was not excluded since hemoglobin, thyroid hormone, glucose, and lipid levels were not assessed. A third limitation was that demographic data that may be associated with being overweight or obese such as smoking, education level, and degree of physical activity were not systematically recorded. Finally, linear measurements of RV wall thickness, RV inflow, RV outflow, three dimensional generated RV volumes, and RV myocardial performance index were not included in this study.

Paper 2: There are several limitations to our study that may be overcome in future studies. Firstly, older individuals (>65) were underrepresented owing to difficulty recruiting normal healthy older individuals in a peri-urban African environment; therefore, the results may only pertain to individuals between the ages of 20 and 60. Furthermore, recruitment was on an ad hoc basis and thus resulted in an uneven age and sex distribution. A second important limitation is that subclinical disease was not excluded because haemoglobin, thyroid hormone, glucose, and lipid levels were not assessed. A third limitation was that demographic data that may be associated with being overweight or obese, such as smoking, education level, and degree of physical activity, were not systematically recorded. No systematic data were collected about the degree of exercise performed by individuals, but there were no elite/competitive athletes. Lastly, absolute LV rotation and twist values may vary between vendors, and as a result, the quantitative values used in this study may not be applicable to other vendors' technology.

Paper 3: The population comprised of patients referred for further evaluation of heart failure; therefore, it is possible that we have described the prevalence of RV dysfunction in advanced disease. RV dysfunction was defined using an echocardiographic parameter and not CMR, which is the criterion standard. RV loading conditions as well as technical difficulties, thereby affecting the accuracy of the parameters included, may affect RV dysfunction. No invasive data on pulmonary vascular resistance and pulmonary arterial pressure were available. Longitudinal follow-up and biochemistry analysis are needed to imply causality.

Paper 4: This was a small single centre cross- sectional study. A Selection bias in determining biomarkers might have occurred due to the reduced number of patients in the both groups. The sample comprised of patients referred for further evaluation of heart failure; therefore, it is possible that the described prevalence of ventricular dysfunction and ventricular remodeling referred to advanced disease. Although current guidelines recommend testing B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), this biomarker was not measured in this study. Conclusion on the findings of the serum biomarkers have to be read with caution and should be considered as preliminary results.

1.12 Future research: Remaining controversies to be investigated

What is the potential of additional echocardiographic mechanics or mechanical criteria in distinguishing between IDCMO and ILVNC, and could this be useful as a method of distinguishing between the two pathologies.

Would Black professional athletes in Sub-Saharan Africa display similar ILVNC phenotypes as documented in Western counterparts?

1.13 Conclusion

This is the largest and the first echocardiographic study to define normal echocardiographic parameters using the ASE 2015 chamber quantification guidelines in a Black African population.

It is the first study to evaluate the application of all LVNC criteria to a normal Black African Sub-Saharan population, and represents the largest Sub-Saharan population studied, which is more than four times larger than the normal control group of Kohli et al.

Chapter 2 : Paper 1

Echocardiographic indices of the left and right heart in a normal Black African population

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Abstract

Background: It is unknown if ethnic differences occur with regard to right heart echocardiographic parameters. The aim of this study therefore was to establish

normative values of left and right heart parameters in a black African population and to evaluate the effect of age and body mass index (BMI) on specific right ventricle (RV) parameters.

Methods: Two hundred and fifty-three normal subjects were prospectively studied. A standardized echocardiographic examination was conducted with the RV focused view used to derive RV measurements. All left and right heart measurements were made in accordance with the ASE 2015 chamber guideline recommendations. RV free wall strain (RVFWS) was assessed using a RV focused apical 4-chamber view.

Results: The average age was 36.3±12.2 years, with 59% female. The mean LVEF was 62.3 ± 5.7%. RV linear measurements (RV base: 31.0 ± 4.5 mm, mid cavity: 26.3 ± 5.8 mm) were not associated with gender, age or BMI except for the RV length (64.6 ± 8.9 mm) which was greater in males. Tricuspid annular plane systolic excursion (TAPSE) was 21.7 ± 2.8 mm, fractional area change (FAC) 42.1 ± 5.5 %, tricuspid annular peak systolic velocity (RVS') 12.1±1.9 m/s and RVFWS was -31.5±8.6 %. Age and BMI were not associated with right atrial (RA) volumetric measurements, RV linear measurements and all RV functional parameters except TAPSE and RV A', which increased with BMI.

Conclusion

This study establishes normal left and right heart parameters in a Black African population. Ageing was not associated with RA or RV parameters except for RV E' and A'. BMI does not affect RA/RV measurements but may cause variability in TAPSE and RV A'.

Keywords Echocardiography; right ventricle; African, normal

Introduction

Echocardiographic assessment of the right ventricle is technically challenging. However, parameters reflecting right ventricular (RV) function have proven to be prognostically important in several diseases which include coronary disease, valvular disease and heart failure.[1,2,3,4,5] Thus accurate assessment of RV function is crucial but may like most echocardiographic parameters be influenced by ethnicity, age, variations in body habitus and gender.[6] Current guidelines provide reference values

for parameters reflecting RV size and function but are limited in that they do not fully account for differences in body surface area and ethnicity.[7,8,9]

Several studies of RV parameters are based predominantly on data from Caucasians. [8,9,10] A recent study by the ECHO normal collaboration highlighted that ethnic differences may occur with regard to certain echocardiographic parameters.[11] Ethnicity may cause variation in body surface area (BSA) and body mass index (BMI) and thus may directly influence echocardiographic measures.[11,12,13] However, in some instances variability of some echocardiographic measurements may occur among different ethnic groups despite indexing for BMI and BSA. This may reflect differences in genetic factors that may impact cardiac chamber size and remodeling.

There is a paucity of data with regard to certain left heart echocardiographic parameters and no prior studies have been conducted on right heart echocardiographic parameters in normal African populations.[14] Consequently, the applicability of current RV echocardiographic guidelines to this population is unknown. The aim of this study was therefore to firstly establish normative values of RV and RA parameters, and secondly to evaluate the effect of age and BMI on specific RV parameters in a Black African population. A third aim was to document left ventricular echocardiographic parameters in our study population.

Methods

Study population – Normal population

This prospective study was conducted in the echocardiography laboratory at Chris Hani Baragwanath Academic Hospital between 2013 and 2016. A total of 330 subjects were recruited from hospital staff and the surrounding Soweto community following an advertisement. They underwent a clinical evaluation, had a resting ECG and a screening echocardiogram. Only subjects who fulfilled the inclusion and exclusion criteria were enrolled in the study after providing voluntary consent. The inclusion criteria were subjects greater than 18 years, which had to be (1) asymptomatic or (2) normotensive; (3) have a normal 12-lead electrocardiogram; (4) No evidence of cardiovascular disease, diabetes, prior stroke or any chronic medical condition on history and (5) normal physical examination. Subjects were excluded based on: (1) the use of any chronic medication; (2) abnormal 12-lead ECG; (3)

abnormal findings on screening echocardiogram or (4) suboptimal image quality on screening echocardiogram. Once subjects were enrolled, they underwent a subsequent comprehensive echocardiogram, performed in accordance with recent recognized guidelines.[7,8 ,10]

Based on the aforementioned selection criteria, a total of 77 individuals were then excluded from the study. A total of 253 individuals were enrolled between the ages of 18 and 79 years of age. Based on this age range, 4 age categories were chosen. Group1 represented subjects between 18 to 30 years; group 2 subjects were between 30 to 39 years; group 3 subjects were between 40 and 50 years and group 4 represented subjects above the age of 50 years (range 50 - 70 years). Individuals were classified into 3 categories of BMI (<25 kg/m^2, ≥25 to <30 kg/m^2 and ≥30 kg/m^2). This study was approved by the University of the Witwatersrand Ethics Committee (Clearance number M110204).

Echocardiogram

Echocardiograms were obtained according to a standardized protocol on a Phillips iE 33 machine (Amsterdam, The Netherlands) equipped with an S5-1 transducer that transmits a frequency of 1.7 MHz and receives a frequency of 3.4 MHz. All data were transferred to an Xcelera workstation, (Philips) and analysed offline. The RV strain analysis was performed separately offline using Philips Qlab 9.1.

Measurements relating to LV and RV chamber size and function were performed in accordance with the American Society of Echocardiography (ASE) chamber quantification guidelines of 2015 and the 2010 ASE guidelines on right heart assessment.[7,8] Parameters relating to LV diastolic function were measured and interpreted according to the consensus ASE/European Association of Cardiovascular Imaging (EACVI) (2016) for the evaluation of LV diastolic function by echocardiography.[15] The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method. Relative wall thickness was calculated using the formula: (2×PWTd)/LVIDd and LV mass with the formula:

LV mass = 0.8 {1.04 (LVEDD+ IVS+PW)^3 —(LVIDd)^3 }+ 0.6 g

The RV linear parameters were measured at end diastole on a RV focused apical 4-chamber view according to the chamber guidelines of 2015. The right atrial (RA) parameters (area and volume) were measured at end systole on an apical 4-chamber view modified to optimize the right atrium visualization. The right atrial volume was measured using the single plane method of discs by tracing an outline of the right atrial blood-tissue interface ensuring that the right atrial appendage, SVC, and IVC were excluded. The tricuspid tenting area was also excluded. RV systolic function was evaluated by measuring fractional area change (FAC) (calculated as diastolic area – systolic area / diastolic area)**,** tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (RVS')[7,8]

RV free wall longitudinal strain (RVFWS) was assessed by tracing the free wall in diastole, in a RV focused apical 4 chamber view, with a frame rate >50 frames per second, with the region of interest (ROI) reduced sufficiently to exclude the pericardium.[16] When the quality of the tracking was suboptimal, the tracking positions were manually edited at end-diastole and the width of the region of interest was adjusted to include the entire RV myocardium. RVFWS could only be successfully tracked and analyzed in 205 study participants. The base, mid and apical free wall segments were averaged to determine the longitudinal strain of the RV free wall.[16] Four Cardiac Technologists performed the echocardiographic measurements, of which the average of 3 repeated measurements for each Doppler parameter was included in the final report, whereas for 2D echo measurements a single measurement was made. Figures 1 and 2 demonstrate examples of linear measures of RV, and RVFWS.

Statistics

Statistica 13.3 (StatSoft Inc.,Tulsa, OK) package was used to analyze the data. Descriptive data for continuous variables are presented as means ± standard deviation and categorical data as frequencies and percentages. Comparisons of means between sex were performed by independent t-test or Mann- Whitney tests. Continuous variables among age and BMI categories were compared using ANOVA, or Kruskal-Wallis test when the distribution was non-normal. Chi-square test and

Fischer's exact-tests (as appropriate) were performed to compare categorical variables. Pearson correlation coefficients were calculated between RV functional parameters and age. Significance was assumed at a two-sided p-value <0.05.

Univariate and multiple linear regression analysis were used to determine the independent relationships between left and right heart measurements in separate models including age, sex (coded as Male=1 and female=0), BMI and systolic blood pressure. For the parameters (EF, Mid RV, FAC and RVFWS) where the independent variables: age, sex, BMI and SBP attained a p-value ≥0.20 only univariate regression analysis was performed.

Inter-observer variability

Two cardiac technologists performed the same conventional and deformation analyses on 25 study participants, each blinded to the results. Inter-observer variability was calculated as the mean differences (percentages) divided by the mean of the repeated measures. Intra-class correlation coefficients were also obtained.

Results

Clinical and echocardiographic parameters of the overall population:

The clinical and echocardiographic characteristics of the study population are presented in **Table 1**. The mean age was 36.3 ± 12.2 years, 150 (59%) participants were female. Three subjects were above the age of 65 years. The mean LVEF was 62.3 ± 5.7%. All patients had LV diastolic pulsed wave (transmitral E and A waves) and tissue Doppler measurements within the normal accepted guideline range. Males had higher systolic blood pressure, body surface area, LV end-diastolic and LV end-systolic dimensions and volumes, left ventricular mass. Left atrial volume indexed to BSA were higher in females.

The RA area and volume indexed to BSA were higher in males. In terms of RV measurements at the base and mid segment, there were no differences between males and females whereas the RV length was greater in males. With regard to RV functional parameters, no gender differences were detected in the FAC and RV strain whereas all functional data derived from the tricuspid annulus i.e: TAPSE and

all Tissue Doppler Imaging (TDI) parameters (systolic and diastolic) were lower in males compared to females.

Influence of age on right heart parameters

Table 2 shows an age-related increase in systolic and diastolic blood pressure (p=0.0006 and p=0.0001, respectively) between age groups 2 and 3, with the exception of patients above the age of 50 years. There were no statistically significant differences with regard to RA volumetric measurements, RV linear measurements or RV systolic functional parameters (TAPSE, FAC and RV strain). Furthermore, an age-related decline in tricuspid E' and an increment in A' was noted (p<0.0001 respectively).

Clinical and echocardiographic indices according to BMI

Table 3 shows that 30% (n=75) were overweight and 32% (n=81) were obese. A greater percentage of females were overweight and obese whilst males constituted 55% of the normal category. A significant increase in age (p=0.01) and systolic blood pressure (p=0.03) was noted with increasing BMI. There were no statistically significant differences with regard to RA volumetric measurements, RV linear measurements and RV functional parameters except for RA area, TAPSE and RV A' which increased with an increasing BMI.

Correlation of RV functional parameters with age

No correlation was found between RV linear parameters and age. There was no correlation between age and functional parameters such as TAPSE, Tricuspid S', FAC and RVFWS. However, age was positively correlated with RV A' (r=0.4678; p<0.001), and inverse correlated with RV E' (r=-0.4310; p<0.001), but both correlations were weak.

Univariate and Multivariate linear regression analysis for RV and LV parameters

Table 4 depicts the beta coefficients with the p-values obtained by performing multiple linear regression analysis between the left and right heart parameters with age, BMI, sex and blood pressure. EF, RA volume indexed, Mid RV linear measurements, FAC and RV free wall strain were not associated to age, sex, BMI or

blood pressure. All other LV and RV measurements with adjustment for blood pressure were independently associated to age, sex and BMI to varying degrees as illustrated in **Table 4**.

Reproducibility of right ventricle parameters

The inter-observer variability is shown as mean percentage differences and ICC for the following right ventricle parameters respectively: RV base =3.17%, ICC=0.55; RV mid =16.25%, ICC=0.25; RV length =5.6%, ICC=0.75; RA volume =8.76%, ICC=0.78; RA area =0.59%, ICC=0.82 and FAC =0.18%, ICC=0.30.

Discussion

This study establishes normal left and right heart values in a sub-Saharan Black population. Gender differences may affect RA volume, RV length and tricuspid TDI measurements, but has no effect on other measurements recommended in the guidelines for right heart measurements. Age and BMI does not affect right ventricular linear measurements. RV functional parameters were not affected by age whereas BMI was associated with variability in TAPSE.

The aim of utilizing quantitative values in echocardiography is to provide greater objectivity in decision-making. This is based on defining normality for the population under study. Echocardiographic parameters may vary with gender, age, body surface area and race. The echocardiographic normal study suggested that sex and/or ethnic appropriate echocardiographic reference values are indicated for many measurements of LA and LV size, LV mass, and EF.[11] The African cohort in the echocardiographic normal study was derived largely from the normal individuals from the Heart of Soweto study which utilized mainly M-mode measurements for the LV parameters and did not measure LV volumes.[17]

Our study represents the first large systematic study of normal sub-Saharan African individuals where all LV measurements were made in accordance with the 2015 chamber recommendations and the consensus ASE/European Association of Echocardiography (EAE) guidelines for the evaluation of LV diastolic function by echocardiography. This study population has linear and volumetric parameters indicating normal LV cavity size with no evidence of LV volume overload. While

using linear measurements, some individuals may fall into the category of LVH based on the calculation of LV mass not indexed but when indexed to BSA; they do not fulfill the criteria for LVH. Thus, this study population has normal LV geometry and normal systolic and diastolic function, which implies that the current guidelines recommendations can be confidently utilized to detect abnormality in Africans.

The 2015 combined ASE/EACVI chamber guidelines have standardized RV measurements and suggest that utilizing these measurements may be more accurate and reproducible in clinical practice.[8] The guidelines defined the right ventricular focused image as the standard view for making two dimensional echocardiographic measurements.[7,8] The current study is the first performed in black Africans to measure right heart parameters (RA and RV) and utilize guideline based techniques of measurement in a large cohort of normal individuals. We found that the upper limit of the normal reference ranges for all parameters measured in our study population are smaller than the reference values from the ASE 2015 chamber quantification guideline document. The ability of the guideline cut off point to identify abnormality is robust since variability in some measurements in our study population, which relate to gender, age and BMI remain well above or below the designated cut off points for abnormality. The reproducibility of most RV parameters was good except that of the mid RV measurement and FAC. This variability may reflect that the RV mid wall and apex is more trabeculated in some individuals and thus identifying the true borders in these areas is challenging. This leads to errors and variations in border tracing.

Age associated changes in vascular and cardiac function is a risk factor for cardiovascular mortality.[18] While ageing is associated with abnormality of left sided functional parameters, data on age related RV changes have been less extensively documented in particular with the use of the RV focused view to derive measurements.[19,20] This study showed that all parameters relating to 2D measurements of the RA and RV, as well as systolic functional parameters like TAPSE and FAC do not differ with age and fall within the guideline recommended value range. The changes observed with TDI in diastole (declining E' and increasing A') are similar to that seen with LV diastolic function with ageing and may reflect a decrement of early RV diastolic function and greater reliance on late diastolic filling.

The TDI findings of the present study concur with previous studies.[21,22] The difficulty in subjects with advancing age however lies in differentiating physiological from pathophysiological changes.

Obesity trends appear to be increasing in Africa with increments in BMI documented in both men and women and some regions appear to have BMI's higher than the global average.[23] Mickelsfield et al studied a population from Soweto and found a significant sex difference with regard to BMI with a greater percentage of women being overweight and obese.[24] In view of these trends we analyzed our data and found that 61.7% (n=156) of normal volunteers had BMIs above 25 kg/m^2 which occurred more commonly in women. We found that indexed measurements of RA and RV parameters were not affected by BMI and that parameters reflecting RV systolic function do not decline with increasing BMI. Our finding of an increasing TAPSE with increasing BMI cannot be fully explained and is discordant from other surrogates of tricuspid annular function namely tricuspid RV S' and RV free wall strain that we measured which were not independently related to BMI. Our findings do differ from Yuksel, et al, who found that weight loss was associated with an increase in RV S' and RV E' in obese individuals.[25] Wong, et al, showed that in a Caucasian population, an increasing BMI, is associated with RV dysfunction.[26]

The results of the aforementioned studies differ compared to our findings and most likely reflect differences in these study populations, which may have included older individuals and had a greater prevalence of hypertension and sleep apnea. An additional factor is that all measurements in this study are based on the focused RV view and not the traditional apical 4- chamber view, which older studies employed. These factors may therefore account for differences in measurements.

Our study has revealed that several left and right heart echocardiographic parameters may be influenced by age, gender or BMI to varying degrees. However, in many instances the magnitude of this variability may not translate into overt clinical relevance. It is reassuring that several RV measurements that are utilized in clinical practice (linear and functional) remained unchanged in relation to age and BMI and that for those parameters that do vary the magnitude of variability is small. Thus, utilizing the current RV guideline cut off points for normality may represent the most practical way of using these echocardiographic measurements in clinical practice. We also noted that RVFWS did not vary with age, gender or BMI in our

study population. These findings cannot be universally applied and may differ with other studies on RVFWS due to differences that may arise from the use of various vendor software versions for strain analysis.

Study Limitations:

There are several limitations to our study, which may be overcome in future studies. Firstly**,** older individuals (>65) were under represented due to difficulty recruiting normal healthy older individuals in a periurban African environment and thus the results may only pertain to individuals between the ages of 20 to 60 years. Furthermore, recruitment was on an ad hoc basis and thus resulted in an uneven age and gender distribution. A second important limitation is that subclinical disease was not excluded since haemoglobin, thyroid hormone, glucose and lipid levels were not assessed. A third limitation was that demographic data, which may be associated with being overweight or obese such as smoking, education level and degree of physical activity, were not systematically recorded. Finally, linear measurements of RV wall thickness, RV inflow, RV outflow, 3D generated RV volumes, and RIMP (RV myocardial performance index) were not included in this study.

Conclusion

This study establishes normal left and right heart parameters in a Black African population. Ageing was not associated with RA or RV parameters except for RV E' and A'. BMI does not affect RA/RV measurements but may cause variability in TAPSE and RV A'.

Source of Funding

This study was funded by the Cardiology Division at Chris Hani Baragwanath Academic Hospital.

Disclosures

None

Tables

Table 1: Clinical and echocardiographic characteristics according to gender				
Variables	**Overall (n = 253)**	**Females (n= 150)**	**Males (n= 103)**	**p-values**
Clinical parameters				
Age, years	36.3 ± 12.2	37.1 ± 12.5	35.0 ± 11.6	0.23
BSA, m^2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	**0.0002**
Systolic blood pressure, mmHg	121±12	119 ± 12	124 ± 11	**0.0009**
Diastolic blood pressure, mmHg	76 ± 10	75 ± 10	77 ± 10	0.17
Heart rate, bpm	76 ± 12	79 ± 11	72 ± 12	**<0.0001**
BMI, kg/m^2	27.9 ± 6.2	29.6 ± 6.4	25.5 ± 5.0	**<0.0001**
Two-dimensional LV measurements				
LV end diastolic diameter, mm	43.0 ± 4.5	41.9 ± 4.4	44.5 ± 4.3	**<0.0001**
LV end systolic diameter, mm	28.2 ± 3.9	27.2 ± 3.4	29.1 ± 3.7	**0.0001**
Septal wall thickness, mm	8.9 ± 15	8.8 ± 1.5	9.1 ± 1.5	0.06
Posterior wall thickness, mm	8.7 ± 1.3	8.6 ± 1.4	9.0 ± 1.3	**0.008**
Relative wall thickness, ratio	0.40 ± 0.83	0.37 ± 0.09	0.37 ± 0.81	0.83
LV mass, g	124.3±32.5	117.1±30.7	134.8±32.3	**<0.0001**
LV mass/BSA index, g/m^2	68.2±15.9	65.5±15.4	72.1±15.9	**0.002**

End diastolic volume/BSA, indexed, ml	48.9±12.0	47.7±11.8	50.7±12.1	**0.03**
End systolic volume/BSA indexed, ml	18.6 ± 5.1	17.9 ± 4.6	19.7 ± 5.5	**0.005**
Ejection fraction, %	62.3 ± 5.7	62.7 ± 5.7	61.7 ± 5.6	0.13
Left atrial volume/BSA index, ml/m^2	18.1 ± 5.5	18.8 ± 5.4	17.0 ± 5.5	**0.009**
LV diastolic parameters				
E peak, m/s	80.5 ± 16.9	81.9 ± 17.9	78.6 ± 15.3	0.09
A peak, m/s	57.4 ± 14.5	59.6 ± 15.5	54.2 ± 12.3	**0.003**
E/A, ratio	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	0.49
Deceleration time, ms	155.7 ± 80.5	160.6±92.9	148.7 ± 57.6	0.70
Medial E', m/s	10.0 ± 6.6	10.1 ± 8.3	9.9 ± 2.4	0.44
Medial A', m/s	8.0 ± 1.9	8.0 ± 1.9	8.1 ± 1.9	0.73
Lateral E', m/s	14.2 ± 3.4	13.8 ± 3.6	14.7 ± 3.1	**0.04**
Lateral A' ,m/s	7.8 ± 2.2	7.9 ± 2.4	7.7 ± 2.0	0.47
RA parameters				
RA volume, ml	29.7 ± 9.4	27.9 ± 8.8	32.3 ± 9.6	**0.0002**
RA volume/BSA index, ratio	16.3 ± 4.8	15.6 ± 4.5	17.3 ± 5.1	**0.003**

RA area, cm^2	12.3 ± 2.5	11.8 ± 2.5	12.9 ± 2.4	**0.0004**
RA area/BSA index, ratio	6.6 ± 1.6	6.4 ± 1.6	6.9 ± 1.5	**0.02**
RV linear and systolic parameters				
RV base, mm	31.0 ± 4.5	30.6 ± 4.4	31.7 ± 4.5	0.08
Mid RV, mm	26.3 ± 5.8	25.9 ± 6.0	26.9 ± 5.5	0.19
RV length, mm	64.6 ± 8.9	62.2 ± 8.3	68.2 ± 8.5	**<0.0001**
TAPSE, mm	21.7 ± 2.8	22.2 ± 2.8	21.0 ± 2.8	**0.01**
FAC, %	42.1 ± 5.5	42.1 ± 5.9	41.9 ± 4.9	0.75
IVC, mm	15.6 ± 3.2	15.3 ± 3.0	16.2 ± 3.3	**0.01**
RVFWS, %	-31.5±8.6	-31.0±8.8	-32.0±8.2	0.32
RV diastolic parameters				
RV E', m/s	11.6 ± 3.3	11.9 ± 3.1	10.9 ± 3.4	**0.005**
RV A', m/s	10.2 ± 3.1	10.7 ± 3.2	9.4 ± 2.9	**0.0007**
RV S', m/s	12.1 ± 1.9	12.4 ± 1.9	11.7 ± 1.7	**0.0008**

LV (left ventricle); RV (right ventricle); BSA (body surface area); BMI (body mass index); RA (right atrium); RV E' (early diastolic annular velocity); RV A' (late diastolic velocity); RV S' (systolic ejection velocity); TAPSE (tricuspid annular plane systolic excursion); FAC (fractional area change); IVC (inferior vena cava); RV free wall strain (RVFWS)

Table 2: Clinical and echocardiographic parameters according to age categories					
Variables	**Group 1 (n=92) (age<30)**	**Group 2 (n=65) (age ≥30 to <40)**	**Group 3 (n=54) (age≥40 to ≤50)**	**Group 4 (n=42) (age>50)**	**p- value**
Clinical parameters					
Age, years	24.0 ± 3.1	34.4 ± 2.8	43.7 ± 2.9	56.5 ± 5.8	**<0.0001**
Male, no (%)	42 (46)	26 (40)	19 (35)	16 (38)	0.63
BSA, m^2	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.1	0.58
Systolic blood pressure, mmHg	118 ± 11	119 ± 11	126 ± 12	125 ± 13	**0.0006**
Diastolic blood pressure, mmHg	73 ± 10	76 ± 8	81 ± 9	77 ± 9	**0.0001**
Heart rate, bpm	77 ± 13	77 ± 11	77 ± 11	74 ± 13	0.43
BMI, kg/m^2	26.5 ± 6.0	27.6 ± 6.0	29.7 ± 6.3	29.5 ± 6.0	0.94
Two-dimensional LV measurements					
LV end diastolic diameter, mm	43.8 ± 4.2	42.8 ± 4.7	43.1 ± 4.2	41.5 ± 5.1	**0.03**
LV end systolic diameter, mm	28.9 ± 3.6	27.7 ± 3.8	28.9 ± 3.9	26.5 ± 4.4	0.09

Septal wall thickness, mm	8.6 ± 1.5	8.8 ± 1.5	9.1 ± 1.4	9.3 ± 1.5	0.06
Posterior wall thickness, mm	8.4 ± 1.3	8.8 ± 1.4	8.9 ± 1.2	9.4 ± 1.3	**<0.001**
End diastolic volume, ml	88.8 ±23.5	93.7 ± 25.3	89.7 ± 23.0	78.5 ± 19.6	**0.02**
End systolic volume, ml	34.2 ±10.1	34.9 ± 9.6	35.3 ± 10.8	29.3 ± 8.1	**0.02**
Ejection fraction, %	62.8 ± 6.2	62.2 ± 4.9	61.8 ± 5.7	62.1 ± 6.0	0.77
Left atrial volume index, ml/m^2	17.4 ± 5.6	18.0 ± 5.1	19.1 ± 5.8	18.4 ± 5.5	0.27
LV diastolic parameters					
E peak, m/s	86.7 ± 14.4	81.6 ± 16.2	78.7 ± 17.5	67.9 ± 15.3	0.267
A peak, m/s	**53.2 ± 13.6**	**55.8 ± 15.0**	**60.9 ± 12.5**	**64.5 ± 14.5**	**<0.0001**
Medial E', m/s†	11.1 ± 2.0	11.6 ± 1.2	8.6 ± 2.0	7.1 ±1.8	**<0.0001**
Medial A', m/s†	7.3 ± 1.8	7.6 ± 1.7	8.9 ± 1.7	9.1 ± 1.8	**<0.0001**
Lateral E', m/s††	16.0 ± 3.2	14.8 ± 2.9	12.7 ± 3.0	11.1 ± 2.4	**<0.0001**
Lateral A', m/s††	6.9 ± 2.0	7.9 ± 1.8	8.6 ± 2.5	8.8 ± 2.2	**<0.0001**
RA parameters					

RA volume, ml	29.4 ± 9.0	30.2 ± 10.9	28.9 ± 8.8	30.7 ± 8.7	0.67
RA volume/BSA index, ratio	16.4 ±4.4	16.6 ± 5.7	15.3 ± 4.2	16.8 ± 4.9	0.44
RA area, cm^2	12.1 ± 2.4	12.3 ±2.9	12.3 ± 2.4	12.6 ± 2.3	0.64
RA area/BSA index, ratio	6.5 ± 1.6	6.7 ±1.6	6.6 ± 1.2	6.8 ± 1.7	0.82
RV linear and systolic parameters					
RV base, mm	30.8 ± 4.8	31.3 ± 3.9	31.2 ± 4.9	31.2 ±4.0	0.77
Mid RV, mm	26.6 ±6.1	26.4 ± 6.3	26.3 ± 5.6	25.9 ± 4.9	0.99
RV length, mm	64.6 ± 8.6	65.4 ± 10.0	64.2 ± 8.5	64.1 ± 8.4	0.52
TAPSE, mm	21.5±3.0	21.9±2.9	20.9±2.4	22.6±2.4	0.17
FAC, %	42.3±6.0	41.1±4.9	42.4±5.8	42.6±5.8	0.52
IVC, mm	15.9±3.0	15.7±3.0	15.2±3.1	15.8±3.1	0.71
RVFWS %	-32.2±8.3	-30.3±7.5	-31.9±8.5	-31.7±10.7	0.69
RV diastolic parameters					
RV E', m/s	**13.0 ± 3.4**	**11.4 ± 3.0**	**10.6 ± 2.9**	**9.8 ± 2.3**	**<0.0001**
RV A', m/s	**9.1±2.9**	**10.1±2.8**	**11.1±3.4**	**11.2±3.4**	**<0.001**
RV S', m/s	12.4±2.1	12.1±1.8	12.3±1.4	11.4±1.4	0.09

LV (left ventricle); RV (right ventricle); BSA (body surface area); BMI (body mass index); RA (right atrium); RV E' (early diastolic annular velocity); RV A' (late diastolic velocity); RV S' (systolic ejection

velocity); TAPSE (tricuspid annular plane systolic excursion); FAC (fractional area change); IVC (inferior vena cava); RV free wall strain (RVFWS)

Table 3: Clinical and echocardiographic parameters according to BMI Categories				
Variables	Group 1 (n=97) (BMI<25)	Group 2 (n=75) (BMI ≥25 to <30)	Group 3 (n=81) (BMI≥30)	p-value
Clinical parameters				
Age, years	33.6±11.5	36.7±12.9	39.0±11.7	**0.01**
Male, no (%)	53 (55%)	29(39%)	21(26%)	**0.0002**
BSA, m^2	1.7 ± 0.1	1.8 ± 0.1	1.9 ± 0.2	**<0.0001**
Systolic blood pressure, mmHg	120 ± 14	119 ± 12	124 ± 10	**0.03**
Diastolic blood pressure, mmHg	76 ± 9	75 ± 10	77 ± 10	0.43
Heart rate, bpm	75 ± 9	77 ± 11	77 ± 10	0.23
Two-dimensional LV measurements				
End diastolic volume, ml	83.7 ± 22.7	89.2 ± 23.3	93.7 ± 24.2	**0.02**
End systolic volume, ml	32.8 ± 8.9	33.4 ± 9.6	35.3 ± 11.3	0.23

Septal wall thickness, mm	8.4 ± 1.4	9.2 ± 1.4	9.3 ± 1.3	**<0.0001**
Posterior wall thickness, mm	8.5 ± 12.3	8.7 ± 1.3	9.2 ± 1.3	**<0.0001**
Ejection fraction, %	61.2 ± 4.8	63.1 ± 6.4	62.9 ± 5.9	0.05
Left atrial volume index, ml/m²	16.8 ± 5.7	18.3 ± 5.5	18.6 ± 5.8	0.08
LV diastolic parameters				
E peak, m/	80.7 ± 17.1	79.8 ± 17.0	80.9 ± 16.7	0.91
A peak, m/s	**54.4 ± 12.6**	**57.0 ± 16.0**	**61.3 ± 14.2**	**0.006**
Medial E', m/s	11.7 ±10.0	9.4 ± 2.5	8.7 ± 2.2	**0.005**
Medial A', m/s	7.5 ± 1.7	8.4 ± 1.8	8.4 ± 2.0	**0.001**
Lateral E', m/s	15.1 ± 3.3	14.3 ± 3.8	13.0 ± 2.9	**<0.001**
Lateral A', m/s	7.4 ± 2.1	8.0 ± 2.0	8.2 ± 2.5	**0.03**
RA parameters				
RA volume, ml	28.0 ± 8.8	30.6 ± 9.4	30.9 ± 9.9	0.08
RA volume/BSA index, ratio	16.2 ± 4.8	16.8 ± 4.8	15.8 ± 4.8	0.37
RA area, cm²	11.8 ± 2.3	12.4 ± 2.5	12.7 ± 2.7	**0.03**
RA area/BSA index, ratio	6.8 ± 1.5	6.7 ± 1.5	6.3 ± 1.5	0.11

RV linear and functional parameters				
RV base, mm	30.4 ± 4.3	31.5 ± 4.1	31.3 ± 4.9	0.21
Mid RV, mm	26.2 ± 5.7	26.9 ± 5.6	26.1 ± 6.2	0.65
RV length, mm	64.9 ± 8.5	65.2 ± 8.6	63.7 ± 9.5	0.52
TAPSE, mm	20.9 ± 2.4	21.6 ± 2.7	22.7 ± 3.2	**0.005**
FAC, %	41.5 ±5.1	42.6 ± 5.2	42.3 ± 6.2	0.49
RV E', m/s	12.0 ± 3.3	11.4 ± 3.6	11.1 ± 2.8	0.16
RV A', m/s	9.1 ± 2.9	10.5 ± 2.7	11.1 ± 3.4	**<0.0001**
RV S', m/s	11.8 ± 1.7	12.2 ± 1.8	12.4 ± 2.0	0.12
RVFWS , %	-29.4±7.0	-32.9±9.7	-30.9±9.1	0.18

LV (left ventricle); RV (right ventricle); BSA (body surface area); BMI (body mass index); RA (right atrium); RV E' (early diastolic annular velocity); RV A' (late diastolic velocity); RV S' (systolic ejection velocity); TAPSE (tricuspid annular plane systolic excursion); FAC (fractional area change); IVC (inferior vena cava); RV free wall strain (RVFWS)

Table 4. Univariate and Multivariate regression analysis of LV and RV measurements as dependent variables and age, sex, BMI, SBP as independent variables for each model

	Univariate regression	**Multivariate regression**				
	Parameters, β coefficients±	**AGE**	**SEX (Male)**	**BMI**	**SBP**	**Multiple R**

	SE* and significance	**(β coeff±SE*, p-value)**	**(β coeff±SE*, p-value)**	**(β coeff±SE*, p-value)**	**(β coeff±SE*, p-value)**	**p-value**
LVEDD	Age -0.16±0.06† Sex 0.27±0.06††† BMI 0.16±0.06† SBP 0.16±0.06†	-0.23±0.06 p<0.001	0.34±0.06 p<0.0001	0.30±0.06 p<0.0001	0.09±0.06 p=0.13	**R=0.45 p<0.0001**
LVESD	Age -0.22±0.06† Sex 0.24±0.06† BMI -0.05±0.06 SBP 0.09±0.06	-0.25±0.06 p<0.001	0.22±0.07 p=0.004	0.06±0.07 p=0.34	0.10±0.06 p=0.14	**R=0.35 p<0.0001**
LVEDV	Age -0.11±0.06† Sex 0.18±0.06† BMI 0.17±0.06† SBP 0.14±0.06†	-0.17±0.06 p=0.008	0.23±0.07 p<0.001	0.27±0.07 p<0.001	0.10±0.06 p=0.16	**R=0.35 p<0.0001**
LVESV	Age -0.13±0.06†	-0.17±0.06	0.27±0.07 p<0.001	0.22±0.07 p<0.001	0.07±0.06 p=0.29	**R=0.35 p<0.0001**

	Sex 0.23±0.06†† BMI 0.11±0.06 SBP 0.12±0.06	p=0.007				
LA vol index	Age 0.06±0.06 Sex 0.16±0.06† SBP 0.08±0.06	0.018±0.07 p=0.78	-0.18±0.06 p=0.007	**N/A**	0.11±0.07 p=0.10	**R=0.20 p=0.026**
EF	Age - 0.05±0.06 Sex - 0.08±0.06 BMI 0.11±0.06 SBP 0.001±0.06					
LV Diastolic Parameters						
E peak	Age - 0.41±0.06††† Sex - 0.10±0.06 BMI - 0.005±0.06 SBP - 0.02±0.06	-0.45±0.06 p<0.001	-0.15±0.06 p=0.021	0.02±0.06 p=0.73	0.08±0.06 p=0.21	**R=0.44 p<0.0001**
A peak	Age 0.32±0.06†††	0.27±0.06 p<0.001	-0.13±0.07 p=0.045	0.11±0.06 p=0.08	0.08±0.06 p=0.21	**R=0.39 p<0.0001**

	Sex -0.18±0.06†† BMI 0.22±0.06†† SBP 0.14±0.06†					
Medial E'	Age -0.25±0.06††† Sex -0.02±0.06 BMI -0.22±0.06†† SBP -0.07±0.06	-0.22±0.06 p=0.001	-0.12±0.07 p=0.08	-0.22±0.07 p=0.001	0.05±0.07 p=0.44	**R=0.32 p<0.0001**
Medial A'	Age 0.40±0.06††† Sex 0.06±0.06 BMI 0.20±0.06†† SBP 0.21±0.06††	0.37±0.06 p<0.001	0.07±0.06 p=0.28	0.14±0.06 p=0.03	0.08±0.06 p=0.20	**R=0.44 p<0.0001**
Lat E'	Age -0.57±0.05††† Sex 0.13±0.06† BMI -0.23±0.06†† SBP-0.20±0.06†	-0.53±0.05 p<0.001	0.07±0.06 p=0.20	-0.08±0.06 p=0.12	-0.07±0.06 p=0.19	**R=0.58 p<0.0001**

Lat A'	Age 0.33±0.06††† Sex - 0.05±0.06 BMI - 0.15±0.06† SBP 0.07±0.06	0.33±0.06 p<0.001	0.004±0.07 p=0.95	0.10±0.06 p=0.12	-0.02±0.07 p=0.75	**R=0.36 p<0.0001**
RA parameters						
RA Vol	Age 0.02±0.06 Sex 0.23±0.06†† BMI 0.17±0.06† SBP 0.11±0.06	-0.01±0.06 p=0.85	0.32±0.07 p<0.001	0.27±0.07 p<0.001	0.005±0.07 p=0.94	**R=0.35 p<0.0001**
RA Vol index	Age -0.15±0.06 Sex 0.17±0.06† SBP 0.04±0.06	0.009±0.06 p=0.85	0.17±0.07 p=0.009	**N/A**	-0.04±0.07 p=0.93	R=0.17 p=0.05
RA area	Age 0.06±0.06 Sex 0.22±0.06†† BMI 0.20±0.06† SBP 0.11±0.06	0.02±0.06 p=0.72	0.32±0.07 p<0.001	0.30±0.07 p<0.001	-0.01±0.07 p=0.87	**R=0.36 p<0.0001**
RV linear and functional parameters						

RV base	Age 0.03±0.06 Sex 0.12±0.06 BMI 0.11±0.06 SBP 0.07±0.06	0.02±0.07 p=0.79	0.18±0.07 p=0.012	0.17±0.07 p=0.014	-0.0003±0.07 p=0.99	**R=0.22 p=0.036**
Mid RV	Age -0.03±0.06 Sex 0.08±0.06 BMI 0.01±0.06 SBP 0.09±0.06					
RV length	Age -0.04±0.06 Sex 0.33±0.06††† BMI -0.04±0.06 SBP 0.08±0.06	-0.03±0.07 p=0.61	0.35±0.07 p<0.0001	0.08±0.07 p=0.21	0.006±0.07 p=0.93	**R=0.35 p<0.0001**
TAPSE	Age 0.06±0.08 Sex -0.20±0.08† BMI 0.32±0.08††† SBP 0.08±0.06	-0.03±0.08 p=0.71	-0.11±0.09 p=0.19	0.29±0.09 p=0.001	0.006±0.08 p=0.94	**R=0.33 p=0.0015**
FAC	Age 0.03±0.07 Sex -0.01±0.07					

	BMI 0.03±0.06 SBP - 0.04±0.07					
RVE'	Age - 0.37±0.06††† Sex - 0.15±0.06† BMI 0.27±0.06 SBP - 0.12±0.06	- 0.37±0.06 p<0.001	-0.21±0.07 p=0.002	- 0.07±0.06 p=0.29	0.02±0.06 p=0.77	**R=0.40 p<0.0001**
RVA'	Age 0.30±0.06††† Sex - 0.21±0.06†† BMI - 0.08±0.06††† SBP 0.10±0.06	0.23±0.06 p<0.001	-0.14±0.07 p=0.03	0.16±0.07 p=0.014	0.05±0.07 p=0.43	**R=0.38 p<0.0001**
RVS'	Age - 0.14±0.06† Sex - 0.21±0.06†† BMI 0.13±0.06† SBP - 0.06±0.06	- 0.18±0.06 p=0.006	-0.19±0.07 p=0.006	0.11±0.07 p=0.11	0.0008±0.07 p=0.90	**R=0.28 p=0.0005**
RVFWS	Age 0.01±0.07 Sex - 0.09±0.07					

	BMI 0.001±0.07 SBP - 0.05±0.07					

*Standardized β coefficients, R (multiple correlation coefficient), † p<0.05 †† p<0.001 ††† p<0.0001
LV (left ventricle); RV (right ventricle); BSA (body surface area); BMI (body mass index); SBP (systolic blood pressure); RA (right atrium); RV E' (early diastolic annular velocity); RV A' (late diastolic velocity); RV S' (systolic ejection velocity); TAPSE (tricuspid annular plane systolic excursion); FAC (fractional area change); IVC (inferior vena cava), RV free wall strain (RVFWS

Figures

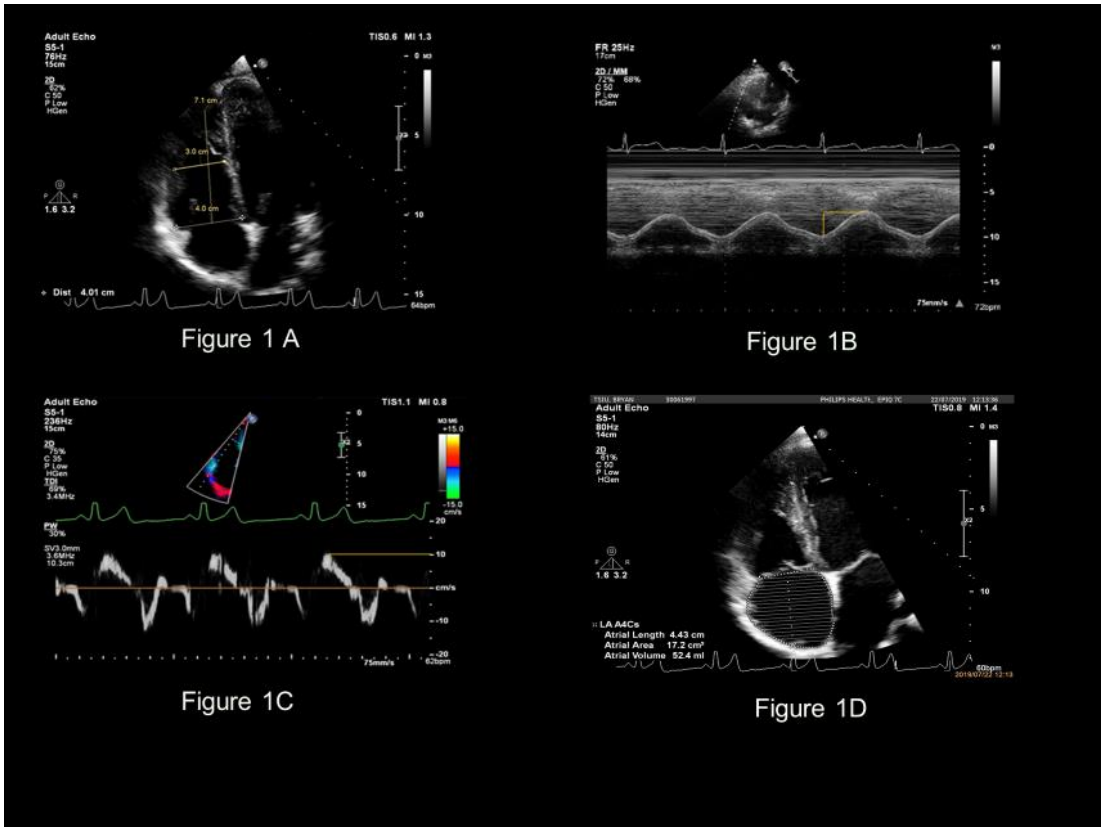

Figure 1A: RV basal, RV mid cavity and the RV length measured at end diastole.

Figure 1B: TAPSE (Tricuspid Annular Plane Systolic Excursion) measurement.

Figure 1C: RV S' (systolic ejection velocity) measurement.

Figure 1D: RA (Right atrial) volume at end systole.

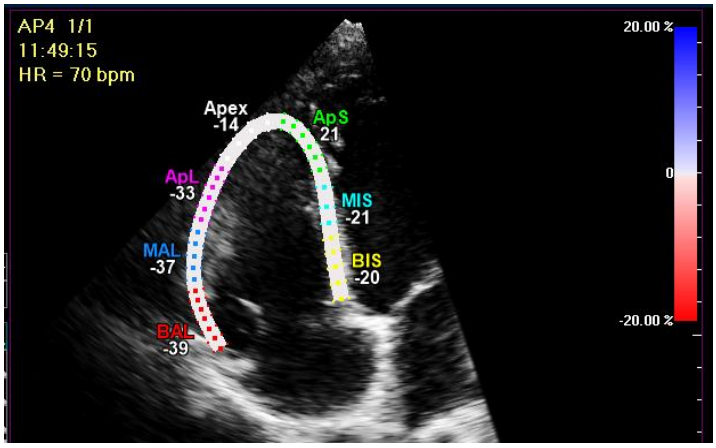

Figure 2: RV free wall strain which utilizes the values of the three segments of the free wall depicted in red, blue and purple.

Chapter 3: Paper 2

Original Article

Prevalence and significance of isolated left ventricular non-compaction phenotype in normal black Africans using echocardiography

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Short title: Hypertrabeculation of left ventricle in normal sub-Saharan population
Word Count: 2,920
Subject code: Echocardiography
Non-standard abbreviations: CHBH, Chris Hani Baragwanath Hospital; ILVNC, isolated left ventricular noncompaction; IVSd, interventricular septal wall thickness in diastole; LVEDD, left ventricular end-diastolic diameter; NC/C, noncompacted to compacted; PWD, posterior wall thickness in diastole

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ABSTRACT

Background: Several large, prospective screening studies of predominantly Caucasian patients have suggested that hypertrabeculation may not necessarily be pathologic unless there is concomitant left ventricular (LV) dysfunction, LV dilatation, history of arrhythmia, family history, or characteristic gene mutations. This conundrum may be magnified in blacks, in whom hypertrabeculation and LV hypertrophy is more common. We therefore investigated the frequency of hypertrabeculation/isolated LV noncompaction (ILVNC) phenotype in normal black Africans and evaluated LV function using sensitive measures of deformation and twist.

Methods: Two hundred and fifty-three volunteers were recruited and evaluated according to strict inclusion and exclusion criteria. Their mean age was 36.3±12.2 years.

Results: Trabeculations were found in 12 (4.74%) participants. Three (1.2%) subjects had ≥4 LV trabeculations. The LV apex was the most common anatomical site for the location of trabeculations. Subjects with trabeculations were more likely to be males of a younger age, and had greater LV end-diastolic and end-systolic parameters and lateral e'. However, 0.8% of the population fulfilled the Stolberger criteria, and none fulfilled the Jenni, Milwaukee, or Baragwanath criteria. All subjects in this study had normal rotation patterns with no differences in rotational parameters or net twist.

*Conclusions***:** Trabeculations may be found as a normal variant in black Africans. Assessing trabeculations alone may infer ILVNC, however, utilizing the more comprehensive ILVNC criteria enables differentiation of a possible LVNC phenotype. Normal individuals with hypertrabeculation have normal LV function and normal rotation patterns, with no differences in rotational parameters or net twist.

Keywords: echocardiography; trabeculations, normals

1. Introduction

Two-dimensional (2D) echocardiography is the basis for identifying isolated left ventricular noncompaction (ILVNC). Currently there are several echocardiographic criteria used to diagnose ILVNC.[1] The major problems with utilising echocardiography for the diagnosis relate to the lack of a gold standard to compare

these criteria, the poor reproducibility when applying these criteria, and that in some instances the phenotype of ILVNC has been observed in clinical scenarios that may not imply disease, such as in athletes and pregnant women.[2,3,4] In patients with normal ejection fraction (EF), the differentiation of ILVNC from a normal variant can be challenging.

The potential impact of race on ILVNC diagnosis has been highlighted in several studies that suggest that trabeculations may be more common in individuals of African ancestry.[1,2,5,6,7] Among African individuals, it is possible to differentiate normal individuals from patients with ILVNC with a low EF by using a more comprehensive set of echocardiographic criteria (Baragwanath criteria), which we have utilised, that incorporates aspects of both the Jenni and Stollberger critieria.[8] In the real-world, however, it can be challenging to separate ILVNC phenotype from normality when confronted with individuals with a normal EF if not systematically studied. In clinical practice at Chris Hani Baragwanath Hospital (CHBH), we have utilised functional parameters such as tissue Doppler E' and left ventricular (LV) twist patterns (presence/absence of rigid body rotation) in conjunction with previously proposed comprehensive CHBH criteria to aid in this differentiation. This approach is feasible but remains untested.

A recent analysis of normal individuals suggested that racial differences were important reasons for variability in echocardiographic parameters of the LV.[9,10,11,12] Thus; there is the possibility that the previously observed frequency of trabeculations in individuals of African origin may represent racial variability. Hence, we undertook this study to determine what percentage of individuals satisfied the conventional echocardiographic criteria in current clinical use. A second aim was to determine whether individuals with a possible ILVNC phenotype have functional abnormality such as abnormal relaxation and abnormal LV twist patterns.

2. Methods

This prospective cross-sectional study was conducted at CHBH. Subjects were recruited from unrelated hospital staff and volunteers following an advertisement about this study. A total of 300 subjects were screened by clinical evaluation, electrocardiography (ECG), and echocardiography. Subjects were included in the study based on: 1) absence of cardiac-related symptoms, 2) normal blood pressure

(≤140/90 mmHg), 3) absence of cardiovascular/systemic disease based on clinical evaluation, and 4) presence of sinus rhythm (heart rate between 50-90 beats/min). Subjects were excluded based on: 1) use of any chronic medication, 2) abnormal 12-lead ECG, 3) abnormal findings on echocardiogram, or 4) suboptimal image quality on the echocardiogram. All subjects who fulfilled the inclusion and exclusion criteria were enrolled in the study after providing informed consent. The final sample comprised 253 individuals, who then underwent comprehensive echocardiography according to a standardised protocol. The study was approved by the University of the Witwatersrand ethics committee (M110204) and is in accordance with the principles outlined in the Declaration of Helsinki.

2.1 Echocardiography

All echocardiograms were obtained according to a standardised protocol on a Philips iE33 machine (Amsterdam, The Netherlands) equipped with an S5-1 transducer that transmits a frequency of 1.7 MHz and receives a frequency of 3.4 MHz. All data were transferred to an Xcelera workstation (Philips) and analysed offline.

All echocardiographic measurements were averaged from three heartbeats. Measurements relating to chamber size and function were performed in accordance with the American Society of Echocardiography (ASE) chamber quantification guidelines of 2015.[13] Parameters relating to LV diastolic function were measured using pulsed-wave Doppler and tissue Doppler and interpreted according to the consensus ASE/European Association of Echocardiography (EAE) guidelines for the evaluation of LV diastolic function by echocardiography.[14] LVEF was calculated using the modified Simpson's method.[14] LV mass was calculated using the formula:

$$\text{LV mass} = 0.8\times\{1.04\ [([\ \text{LVEDD} + \text{IVSd} + \text{PWd}]^3 - \text{LVEDD}^3)]\} + 0.6.$$

Relative wall thickness was calculated using the formula: (2 × PWd) ÷ LVEDD.

(LVEDD, LV end-diastolic diameter; IVSd, interventricular septal wall thickness in diastole; PWd, posterior wall thickness in diastole.)

2.2 Speckle-tracking analysis

The 2D speckle-tracking images were acquired at a frame rate of 50-80 frames per second, during sinus rhythm, with <10% variability in heart rate. Parasternal short-axis images at the level of the LV base, showing the tips of the mitral valve leaflets, and a short-axis image at the apical LV level were used to assess LV rotation. The tracking points were placed on an end-diastolic frame in each parasternal short-axis image. In areas of hypertrabeculation, the tracking points were placed in the compacted part of the muscle. Tracking points were separated about 60 degrees from one another to fit the total LV circumference. After positioning these points, the program tracked them. In keeping with the standard ASE/EAE consensus document on myocardial deformation, counter-clockwise rotation was assigned a positive value and clockwise rotation a negative value.[13] The peak systolic rotation was measured at the apex. Thereafter, the basal rotation at a time isochronous to that of the peak apical rotation was measured. Net instantaneous twist was then calculated as peak apical rotation minus basal rotation.[1] In addition to quantifying apical and basal rotation, we analysed the direction of rotation during the ejection phase of systole and identified rotation as either normal or having evidence of rigid body rotation, which was either entirely counterclockwise or clockwise at both the base and apex during the ejection phase of systole.

2.3 Echocardiographic assessment for established ILVNC criteria in the normal population

The presence or absence of trabeculations was documented by analysing the short-axis and apical long-axis views of the LV. An abnormal trabeculation was identified if it occurred distal to the papillary muscles, did not have any attachment to the interventricular septum, and was seen in both apical and short-axis views. Thereafter, the presence of bilayered myocardium was documented and the noncompacted dimension and compacted dimension were measured in systole and diastole using short-axis images. The ratio of noncompacted to compacted (NC/C) endocardium was then calculated in systole and diastole. An analysis using the Jenni, Stollberger, and Milwaukee criteria was performed.[1] In addition; we applied the comprehensive published criteria used previously at CHBH, which has been named the Baragwanath criteria, to differentiate ILVNC from normal individuals.[8]

I. Baragwanath criteria

(1) Ratio of NC/C measured at end systole >2.

(2) Presence of ≥3 prominent trabeculations in the LV apex that did not originate from the septum.

(3) Deep intertrabecular recesses that filled with blood from the ventricular cavity as visualised on colour Doppler ultrasound.[8]

II. Jenni criteria

(1) Bilayered myocardium consisting of NC/C >2.

(2) Predominant location of the pathology is midlateral, midinferior, and apex.

(3) Evidence of intertrabecular recesses filled with blood from the LV cavity.

(4) Acquisition of short-axis image, with a measurement of the NC/C ratio performed at end-systole.[1]

III. Stollberger criteria

(1) Four or more trabeculations seen protruding from the LV wall, located apically to the papillary muscles and visible in one imaging plane.

(2) Trabeculations with the same echogenicity as the myocardium and synchronous movement with ventricular contractions.

(3) Perfusion of the intertrabecular recesses from the LV cavity.

(4) Differentiation between false chords, aberrant bands, and trabeculations in the apical four-chamber view, as well as atypical views to obtain the best image quality.[1,15]

IV. Milwaukee criteria

(1) Evaluation of the trabeculation sizes in multiple imaging windows, at different ventricular levels, throughout the cardiac cycle.

(2) Identification of the bilayered myocardium (C and NC) in the short-axis views, the mid and apical levels, the apical two- and four-chamber views, and the apical long-axis view.

(3) Measurement of NC/C >2 in diastole in the short-axis view.[1]

Intertrabecular spaces were defined as deep myocardial recesses that communicate with the ventricular cavity only, and not with the coronary circulation [16]. False

tendons were defined as linear fibromuscular structures, <3 mm, seen across the LV cavity, usually inserting into a papillary muscle and without attachment to the mitral valve (Fig. 1).[17,18] LV membranes or LV bands were identified as discrete fibromuscular structures, also seen across the LV cavity without insertion into a papillary muscle (Figs. 2, 3).[19]

2.4 Statistics

Statistical analyses were performed using a Dell statistical program, Statistica 13.0. Results are presented as means ± standard deviations for continuous variables or frequencies and percentages for categorical variables. Differences between the two groups were assessed using the independent t-test or Mann-Whitney test if variables were not normally distributed. Categorical data were compared with a Fisher's exact test. Probability (P) value <0.05 was considered statistically significant.

3. Results

The clinical and echocardiographic characteristics of the study population, as well as a comparison by sex, are presented in Table 1. The mean age of the 253 participants was 36.3 ± 12.2 years, with 150 (59.3%) female participants. All patients had diastolic pulsed-wave and tissue Doppler measurements within the normal accepted guideline range. Males had higher systolic blood pressure, body surface area, end-diastolic and end-systolic dimensions and volumes, LV mass, left atrial volumes, and lateral E'.

3.1 LV trabeculations

Trabeculations were found in 12 (4.74%) participants (Table 2). Nine of the 12 participants with trabeculations were male. Three (1.2%) subjects had ≥4 LV trabeculations. The LV apex was the most common anatomical site for the location of trabeculations. False tendons were identified in 22 (8.7%) subjects (Fig. 1), and a further 19 (7.5%) subjects had LV membranes/bands (Figs. 2, 3). A comparison between subjects with trabeculations and those without trabeculations revealed that the subjects with trabeculations were of a younger age, and had greater LV end-diastolic and end-systolic diameters and lateral E'. LV mass indexed to body surface area and LV volumes indexed to body surface area were no different between the two groups (Table 3).

3.2 ILVNC criteria

No subjects fulfilled the Jenni, Milwaukee, or Baragwanath criteria, and only 2 (0.8%)

fulfilled the Stollberger criteria. The two participants satisfying the Stollberger criteria had ≥4 trabeculations identified in the apical three-chamber view. Nine of the 12 individuals with trabeculations had a systolic compacta thickness ≤8 mm. The two participants satisfying the Stollberger criteria had compacta thicknesses of 8.1 mm and 8.6 mm. From the group of participants with trabeculations, the overall mean NC/C systolic ratio was 1.5 ± 0.4 and the mean NC/C diastolic ratio was 2.7 ± 0.1.

3.3 LV rotation patterns

Of the 253 subjects, 37 could not be analysed for rotation patterns due to technical difficulties such as suboptimal images and off-axis imaging. All remaining subjects in this study whose images could be analysed had normal twist patterns in systole with the base moving clockwise and the apex counterclockwise. The LV apical and basal rotation and net twist were not different between those with trabeculations and those without trabeculations (Table 4).

4. Discussion

The main findings of this study were as follows: 1) trabeculations were found in 4.74% of participants, 2) no subjects fulfilled the Jenni, Milwaukee, or Baragwanath criteria, and only 2 (0.8%) fulfilled the Stollberger criteria, and 3) there were no differences in rotation patterns, quantitative LV rotation parameters, or LV twist between subjects with and without trabeculations.

In this normal cohort of African patients, almost 20% had a combination of trabeculations, false tendons, and LV bands. However, true trabeculations as defined in this study occurred in only 4.74% of patients. Gati *et al.* found that in their control group, which comprised both Caucasian and Afro-Caribbean subjects, 7% of subjects had trabeculations.[2] In contrast, Tamborini *et al*. used echocardiography in a Caucasian population and found in their normals that 40.8% with abnormal images had a combination of false tendons and trabeculation.[19] Our finding of 4.74% having ≥4 trabeculations is concordant with the findings of Boyd *et al*., who at pathology found that 4% of normal individuals had ≥4 trabeculations.[20] At autopsy in hearts free of cardiac disease, Boyd *et al*. found prominent LV trabeculae in 323 of 474 (68%) specimens. “Prominent trabeculation” was defined as “discrete muscle bundles more than 2 mm in diameter.”[20]

In this study, patients with trabeculations did not differ from those without

trabeculations with regard to sex or body surface area. Subjects with trabeculations appeared to have a trend suggesting greater LV dilation (trend toward larger LVEDD and LVEDV) and higher LV mass. This may suggest that some degree of difference in LV volume overload was present in the group with trabeculation. However, all subjects with trabeculation had normal diastolic and systolic function and LV rotation patterns. Thus, subjects with a potentially abnormal or variant phenotype in this study had no functional abnormality. This implies that trabeculations may represent a normal anatomical variant and should be interpreted as a normal finding on echocardiography when associated with normal LV function.

We previously showed that in 54 normal controls no individuals satisfied the Baragwaneth criteria for ILVNC.[8] A major finding of that study of normal African individuals was that some individuals may have morphological features very suggestive of LVNC phenotype if the Stollberger criteria are used whereas no individuals satisfied the other criteria tested. Gati *et al.* found that none of their controls of African descent had LVNC.[2] In contradistinction, Kohli *et al.* showed that more black individuals in their control groups fulfilled echocardiographic criteria for noncompaction than Caucasian individuals (13.3% vs. 3.3%).[7] There are several factors that may relate to these diverse findings. Firstly, the study of individuals of African descent may differ because the African population is not a homogenous population and may vary with regard to genetics, body surface area, and even variability of echocardiographic parameters.[10] The latter was demonstrated in the Echocardiographic Normal Ranges Meta-Analysis of the Left Heart (EchoNoRMAL) study, in which left atrial diameters were greater in Afro-Caribbean and lesser in African subjects.[10]

A second reason for the variability of results is the non-uniformity of LVNC criteria used. Not only do the studies mentioned vary with regard to the criteria used, but, since the publication of Kohli *et al.* in 2008, the individual criterion themselves have been modified—including those utilised by Jenni *et al.* and Stollberger *et al*.[5,16,17,18,21] Thus, the current criteria are more similar, more encompassing, and stricter. A third reason for the discrepancy relates to echocardiography technique, which may differ with regard to protocols and imaging. In this study, all short-axis imaging was performed on axis using x-plane imaging, whereas, as acknowledged by the authors, Kohli *et al.,* in their retrospective analysis, collected all echocardiographic data

without a focus on LVNC.[7] As a result, there was the potential for short-axis views to be more oblique, increasing the likelihood of a diagnosis of LVNC. Finally, there are several other well-recognised impediments to accurate LVNC echocardiographic diagnosis, including analysis in varying imaging planes and different phases in the cardiac cycle as well as the lack of reproducibility of criteria.[22]

From the aforementioned discussion, it is evident that abnormal LV phenotype with either increased trabeculation or even a phenotypic mimicker of LVNC cardiomyopathy exists in normal individuals. We propose the following approach to the diagnosis of possible LVNC in Africans using echocardiography.[2,11,13,23,24] Firstly, exclude adaptive (athletes and pregnancy) and pathological states (bicuspid aortic valve and sickle cell anaemia) in which LVEF may be normal. Secondly, establish that the patient truly is normal using ASE reference values for LV size, geometry, and systolic and diastolic function. In this manner, cardiomyopathy associated with LVNC phenotype, such as hypertrophic cardiomyopathy or Fabry disease, can be excluded. Thereafter, critical echocardiographic analysis of images in long- and short-axis views should be performed employing simultaneous biplane imaging to ensure that the short axis is minimally oblique. If trabeculations do exist, ensure that they are not mimickers such as false tendons and then apply either the Jenni or CHBH criteria. If the technology is available, ensure that the LV twist pattern is normal. Normality may be proposed if the individual has some phenotypic features consistent with LVNC but does not fulfill the proposed echocardiographic criteria and has normal functional parameters. In those who do fulfill the echocardiographic criteria but have normal functional parameters and no family history of LVNC, serial observation is required even though this probably represents normality.

4.1 Limitations

There are several limitations to our study that may be overcome in future studies. Firstly**,** older individuals (>65) were underrepresented owing to difficulty recruiting normal healthy older individuals in a peri-urban African environment; therefore, the results may only pertain to individuals between the ages of 20 and 60. Furthermore, recruitment was on an ad hoc basis and thus resulted in an uneven age and sex distribution. A second important limitation is that subclinical disease was not excluded because haemoglobin, thyroid hormone, glucose, and lipid levels were not assessed. A third limitation was that demographic data that may be associated with being overweight or obese, such as smoking, education level, and degree of physical

activity, were not systematically recorded. No systematic data were collected about the degree of exercise performed by individuals, but there were no elite/competitive athletes. Lastly, absolute LV rotation and twist values may vary between vendors, and as a result, the quantitative values used in this study may not be applicable to other vendor technology.

5. Conclusion

The results of this study suggest that although hypertrabeculation is common, all current diagnostic criteria are useful in excluding the diagnosis of ILVNC. The presence of normal measures of systolic and diastolic function also indicate that hypertrabeculation itself is unlikely to represent a pathologic state.

Declarations of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

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Table 1

Clinical and echocardiographic characteristics of the overall population, and males vs. female.

Variables	Overall (n=253)	Females (n=150)	Males (n=103)	P values
Clinical parameters				
Age, years	36.3±12.2	37.1±12.5	35.0±11.6	0.23
Systolic blood pressure, mm Hg	121±12	119±12	124±11	**0.001**
Diastolic blood pressure, mm Hg	76±10	75±10	77±9	0.17
Pulse, bpm	76±12	79±11	72±12	**<0.0001**
BSA, m^2	1.8±0.2	1.8±0.2	1.9±0.2	**0.0002**
Body mass index, kg/m^2	27.9±6.2	29.6±6.4	25.5±5.0	**<0.0001**
Two-dimensional LV measurements				
LV end-diastolic diameter, mm	43.0±4.5	41.9±4.4	44.5±4.3	**<0.0001**
LV end-systolic diameter, mm	28.2±3.9	27.2±3.4	29.1±3.7	**0.0001**
Septal wall thickness, mm	8.9±1.5	8.8±1.5	9.1±1.5	0.06
Posterior wall thickness, mm	8.7±1.3	8.6±1.4	9.0±1.3	**0.008**
Relative wall thickness, ratio	0.40±0.83	0.37±0.09	0.37±0.81	0.83
End-diastolic volume, mL	88.5±23.6	85.0±21.9	93.6±25.2	**0.002**
End-diastolic volume indexed to BSA, m^2	48.6±12.2	47.7±11.8	50.7±12.1	**0.03**
End-systolic volume, mL	33.8±9.9	31.9±8.9	36.6±10.8	**0.0002**
End-systolic volume indexed to BSA, m^2	18.6±5.1	17.9±4.6	19.7±5.5	**0.0049**

Ejection fraction, %	62.3±5.7	62.7±5.7	61.7±5.6	0.13
Left atrial volume indexed to BSA, m^2	18.1±5.5	31.9±8.9	36.6±10.8	**0.009**
LV mass, grams	124.3±32.5	117.1±30.7	134.8±32.3	**<0.0001**
LV mass/BSA index, kg/m^2	68.2±15.9	65.5±15.4	72.1±15.9	**0.002**
LV diastolic parameters				
E peak, m/s	80.5±16.9	81.9±17.9	78.6±15.3	0.09
A peak, m/s	57.4±14.5	59.6±15.5	54.2±12.3	**0.003**
E/A, ratio	1.5±0.4	1.4±0.4	1.5±0.44	0.49
Deceleration time, ms	155.7±80.5	160.6±92.9	148.7±57.6	0.70
Medial E', m/s	10.0±6.6	10.1±8.3	9.9±2.4	0.44
Medial A', m/s	8.0±1.9	8.0±1.9	8.1±1.9	0.73
Lateral E', m/s	14.2±3.4	13.8±3.6	14.7±3.1	**0.04**
Lateral A', m/s	7.8±2.2	7.9±2.4	7.7±2.0	0.47

Data presented as mean ± standard deviation or number (percentage).

Bold represents statistical significance.

*LV diastolic parameters were measurable in only 149 females and 102 males.

BSA, body surface area; LV, left ventricular; E', late diastolic velocity; A', early diastolic velocity.

Table 2
Subjects with left ventricular trabeculations.

Trabeculations (n=12)	**n (%)**
≥4	3 (1.18%)
3	6 (2.37%)
2	2 (0.79%)
1	1 (0.39%)
Predominant location of trabeculations	
Apex, only	9 (3.56%)
Mid-lateral wall, only	1 (0.39%)
Mid-inferior wall, only	0 (0%)
Dual segments	
Apex/mid-lateral walls	1 (0.39%)
Apex/mid-inferior walls	1 (0.39%)

Table 3

Clinical and echocardiographic characteristics of participants with LV trabeculations vs. non-trabeculation LV.

Variables	Trabeculations (n=12)	Non-trabeculation (n=241)	P value
Clinical parameters			
Age, years	25.1±8.5	36.8±12.1	**<0.001**
Gender, %	10 (3.9%)	93 (38.6%)	1.00
Systolic blood pressure, mm Hg	123±11	121±13	0.66
Diastolic blood pressure, mm Hg	71±10	76±10	0.05
Pulse, bpm	71±12	77±12	0.08
BSA, m^2	1.7±0.14	1.8±0.2	0.23
Body mass index, kg/m^2	25.3±5.2	28.1±6.2	0.09
Two-dimensional LV parameters			
LV end-diastolic diameter, mm	45.6±4.0	42.8±4.5	**0.04**
LV end-systolic diameter, mm	30.6±3.4	27.9±3.9	**0.02**
Septal wall thickness, mm	9.2±1.4	8.9±1.4	0.43
Posterior wall thickness, mm	8.8±1.4	8.8±1.3	0.99
Relative wall thickness, ratio	0.4±0.1	0.4±0.1	0.15
End-diastolic volume, mL	92.5±14.4	88.3±24.0	0.38
End-diastolic volume indexed to BSA, m^2	53.2±8.9	48.7±12.1	0.11
End-systolic volume, mL	34.2±8.3	33.8±10.1	0.78
End-systolic volume indexed to BSA, m^2	19.7±4.9	18.5±5.1	0.43
Ejection fraction, %	63.6±6.8	62.2±5.6	0.54
Left atrial volume, mL	35.6±9.5	32.6±10.3	0.33

Left atrial volume indexed to BSA, m^2	20.4±5.3	17.9±5.5	0.13
LV mass, grams	141.2±32.2	123.4±32.3	**0.002**
LV mass indexed to BSA, m^2	75.0±20.1	65.4±16.4	0.12
LV diastolic parameters			
E peak, m/s	87.9±13.0	80.1±17.0	0.08
A peak, m/s	54.2±14.9	57.6±14.4	0.39
E/A, ratio	1.7±0.44	1.5±0.44	0.05
Deceleration time, ms	178.4±106.7	153.9±79.6	0.27
Medial E', m/s	10.8±1.7	9.9±6.7	0.08
Medial A', m/s	7.2±1.9	8.1±1.9	0.16
Lateral E', m/s	16.9±2.7	14.0±3.4	**<0.01**
Lateral A', m/s	8.0±2.5	7.8±2.2	0.79

Data presented as mean ± standard deviation or number (percentage).

Bold indicates statistical significance.

BSA, body surface area; LV, left ventricular.

Table 4

Rotation patterns.

Variables	Overall *(n=216)	Trabeculated (n=12)	Non-trabeculated (n=204)	P value
Apical rotation	5.99º±3.12º	5.55º±2.17º	6.02º±3.17º	0.61
Basal rotation	-5.19º±3.14º	-5.91º±2.97º	-5.15º±3.15º	0.41
Net twist	11.24º±4.25º	11.45º±3.46º	11.23º±4.30º	0.86

*Of the 253 patients recruited, rotation patterns were measurable in only 216 patients

Figure Legends

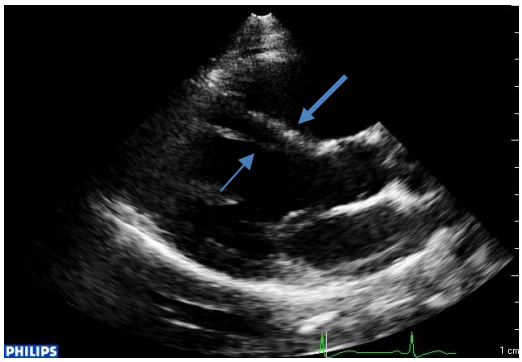

Fig. 1. False tendon in parasternal long axis view

Parasternal long-axis view demonstrating a false tendon adjacent to the left ventricular septal wall (bold arrow, interventricular septum; thin arrow, false tendon).

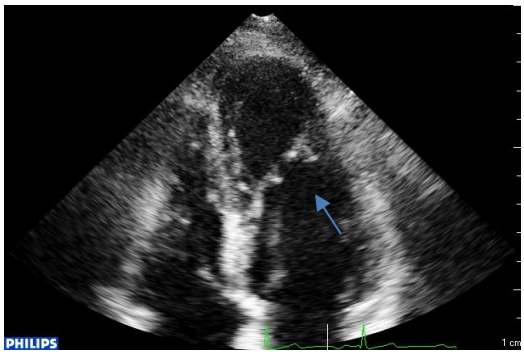

Fig. 2. Ventricular band in apical four-chamber view

Four-chamber view demonstrating a left ventricular band (arrow).

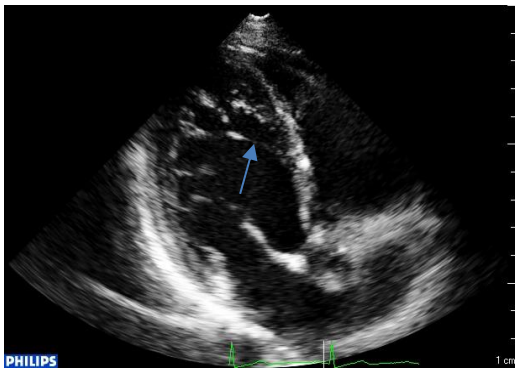

Fig. 3. Ventricular membrane in apical three-chamber view

Three-chamber view demonstrating left ventricular membranes (arrow) extending from the septum to the inferolateral wall.

Chapter 4: Paper 3

Original Article

Right Ventricular function in Isolated Left Ventricular Noncompaction and Idiopathic Dilated Cardiomyopathy

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Abstract

Background While right ventricular (RV) dysfunction may occur in Isolated left ventricular noncompaction (ILVNC) and Idiopathic dilated cardiomyopathy (IDCMO), a comparison of the prevalence and predictors of RV dysfunction between these two patient populations has not been previously studied. The aims of this study therefore was to estimate the prevalence of RV dysfunction and predictors of RV dysfunction, using echocardiography, in ILVNC, and IDCMO patients.

Methods and results 98 patients, 49 with ILVNC and 49 with IDCMO were enrolled in a prospective cross-sectional study at Chris Hani Baragwanath Academic Hospital. The prevalence of RV dysfunction was more common in ILVNC (TAPSE – 32.7%, Tricuspid S' – 44.9%, FAC - 61.2%), compared to IDCMO (TAPSE – 18.4%, Tricuspid S' – 20.4%, FAC – 18.4%). The independent predictors of RV dysfunction following stepwise multiple regression were LV ejection fraction ($p < 0.0001$) and LV end systolic diameter ($p< 0.0001$).

Conclusion

Right ventricular dysfunction was more prevalent in ILVNC compared to IDCMO patients, but varied depending on the echocardiographic technique utilized. LVEF was the most important predictors of RV dysfunction in both groups of patients.

Keywords Isolated left ventricular noncompaction ● Isolated dilated cardiomyopathy ● Right ventricular dysfunction

Introduction

Assessment of right ventricular (RV) function using echocardiography is technically challenging but has emerged as an important prognostic factor in a variety of diseases, such as heart failure, RV myocardial infarction and congenital heart disease.[1-4] Right ventricular dysfunction has been described in patients with isolated left ventricular noncompaction (ILVNC) and occurs in up to 61% of ILVNC cases.[1,3,5,6] This dysfunction may be related to intrinsic RV myocardial abnormality or be a consequence of left ventricular (LV) dysfunction. [7]

In a recent study using cardiac magnetic resonance imaging (CMR), significant RV dysfunction was thought to be a marker of advanced ILVNC and was associated with a worse prognosis.[5] Similarly, Nucifora et al. identified ILVNC associated with LV dysfunction as the most important predictor of RV dysfunction in another CMR study.[6] A limitation of these two CMR studies is that they did not evaluate three important contributors to right-sided abnormality: LV diastolic dysfunction, mitral regurgitation and pulmonary hypertension. Our hypothesis was that the degree of LV abnormality is the sole contributing determinant of RV dysfunction in ILVNC without right ventricular noncompaction (RVNC), and that this is not dissimilar to what occurs in patients with idiopathic dilated cardiomyopathy (IDCMO). Therefore, the aims of this study were 1) to estimate the prevalence of RV dysfunction, using echocardiography, in ILVNC patients without RVNC, and in IDCMO patients, and 2)

to determine the independent factors associated with RV dysfunction in patients with ILVNC and IDCMO, using echocardiography.

Methods

This prospective cross-sectional study was conducted at Chris Hani Baragwanath Academic Hospital, Cardiomyopathy Clinic. A total of 98 patients, 49 with ILVNC and 49 with IDCMO, were recruited over 32 months. All patients who fulfilled the inclusion criteria and provided voluntary consent were enrolled in either the IDCMO or ILVNC registries and included in the analysis.

Echocardiography

All echocardiograms were obtained according to a standardized protocol on either a Phillips iE 33 machine (Amsterdam, The Netherlands) equipped with an S5-1 transducer that transmits a frequency of 1.7 MHz and receives a frequency of 3.4 MHz, or a GE Healthcare Vivid q machine equipped with a phased-array transducer that transmits a frequency of 1.5-3.6 MHz. All data were transferred to an Xcelera workstation, (Philips) or an Echopac V.8 (GE Healthcare) and analyzed offline. Measurements relating to chamber size and function were performed in accordance with the American Society of Echocardiography (ASE) chamber quantification guidelines of 2015 and the 2010 ASE guidelines on right heart assessment.[8,9,10,11] Parameters relating to LV diastolic function were measured and interpreted according to the consensus ASE/European Association of Echocardiography (EAE) guidelines for the evaluation of LV diastolic function by echocardiography.[12] The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method.[8, 9] Global longitudinal strain, a parameter that longitudinal shortening, was derived from speckle tracking. The degree of mitral and tricuspid regurgitation was classified as mild, moderate or severe using an integrated assessment in accordance with the ASE guidelines on valvar regurgitation.[13, 14] Pulmonary artery pressure was measured using tricuspid regurgitation, and considered elevated above 25mmHg. In addition, no patients had uncontrolled hypertension or significant anemia (hemoglobin <10 g/dl) at the time of echocardiography. The RV S' was measured in the RV focused view and a value of < 9.5 was used to identify abnormal RV function.[10, 11] All right sided parameters were measured at end diastole on a right ventricular focused apical 4-chamber view according to the chamber guidelines of

2015. RV systolic function was evaluated by measuring fractional area change (FAC) (calculated as diastolic area – systolic area / diastolic area), (FAC <35% was used to identify abnormal RV function), tricuspid annular plane systolic excursion (TAPSE) determined by m-mode across the RV free wall annulus (TAPSE <17mm was used to identify abnormal RV function), and lastly and tricuspid annular peak systolic velocity (RVS') determined with tissue Doppler imaging.[10, 11]

Isolated left ventricular noncompaction

A combination of the Oechslin et al. and Stöllberger criteria which we have previously reported on was used to diagnose ILVNC.[15,16,17] All four of the following criteria were required for a diagnosis of ILVNC:

1. A ratio of noncompacted to compacted myocardium >2 when measured at end systole;
2. Presence of more than three prominent trabeculations in the LV apex that did not originate from the septum;
3. Deep intertrabecular recesses that filled with blood from the ventricular cavity as visualized on color Doppler ultrasound; and
4. No evidence of congenital or acquired heart disease.

All echocardiograms of patients with ILVNC and IDCMO were separately analyzed by a cardiologist (F.P) experienced in the diagnosis of ILVNC to determine if they fulfilled the proposed ILVNC criteria. No patients with IDCMO fulfilled the comprehensive criteria for diagnosis of ILVNC.

Isolated dilated cardiomyopathy

IDCMO was previously defined in a large prospective registry from Baragwanath Academic Hospital. [18] Inclusion criteria were ejection fraction of ≤45% and end diastolic dimension of >55 mm. The exclusion criteria for both ILNVC and IDCMO were documented hypertension (past or present), known coronary artery disease (past or present), echocardiographic features suggestive of organic valvular disease (e.g. moderate or severe aortic regurgitation), clinical criteria for peripartum cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy, any systemic illness (e.g, human immunodeficiency virus), thyroid disease or any primary organ failure (e.g. chronic renal failure).

Statistics

Statistical analysis was performed with Statistica v14.0.015, TIBCO Software Inc, and SAS v9.4, SAS Institute Inc, Cary, NC, USA. Descriptive data for the continuous variables were presented as mean ± standard deviation or median (IQR) if distribution was non-normal. Independent T- tests and Mann Whitney test were used for comparisons between the ILVNC and IDCMO. Categorical variables were summarized as frequencies, percentages, and comparisons performed with Chi-square and Fischer's exact tests as appropriate. Univariate and multiple - linear regression analyses were performed to determine the independent markers of RV dysfunction (RV S'). Multivariate models to predict RV S' were selected in a stepwise multiple linear regression analysis. Statistical calculations were two-sided. Probability (P) value <0.05, two-sided, was considered statistically significant.

Results

Patients with ILVNC had significantly greater LV dilatation, higher LV mass, lower EF and lower GLS (Table 1). LV diastolic parameters in ILVNC patients, such as greater LA volumes, higher E/A ratios and E/E', were suggestive of higher LV filling pressure, and worse diastolic dysfunction, in comparison to DCMO patients. Similarly, moderate or severe functional MR was more prevalent in ILVNC (26.5%), than IDMO (8.2%) patients.

An analysis of right heart parameters revealed that patients with ILVNC had significantly greater RV dilatation than DCMO patients (Table 2). All three parameters of RV systolic function-TAPSE, RV S' and RV FAC were lower in ILVNC vs IDCMO. Using the three techniques of RV systolic function, RV dysfunction was identified by TAPSE- ILVNC (32.7%) vs IDCMO (18.4%) p=0.006, Tricuspid S' – ILVNC (44.9%) vs IDCMO (20.4%) p=0.04, and FAC-ILVNC (61.2%) vs IDCMO (18.4%) p<0.0001. RV E' a surrogate of myocardial relaxation was lower in ILVNC vs IDCMO. The prevalence of moderate/severe TR was similar. The pulmonary artery pressure was higher in ILVNC vs IDCMO. Similarly, RA volume was higher in ILVNC vs IDCMO.

Univariate linear regression analysis (Table 3) revealed that pathology (ILVNC), LV end systolic diameter, end systolic volume, ejection fraction, deceleration time, medial and lateral E' velocities, LV systolic sphericity index and LV diastolic

sphericity index were independently associated with increased RV function (RV S') (Figs 1 and 2). However, when a multiple stepwise linear regression analysis was performed, LV ejection fraction ($p < 0.0001$), LV end systolic diameter ($p< 0.013$) were the predictors of RV dysfunction. (Table 4)

Discussion

The prevalence of RV dysfunction was higher in patients with ILVNC compared to patients with IDCMO in the present study, and most likely varied depending on the imaging technique used. The echocardiographic parameters however, that proved to be independent predictors of RV dysfunction were LVEF, and LV end-systolic diameter.

Prior ILVNC studies have described the prevalence of RV dysfunction ranging between 16% to 61%.[1,5,6,19,20] This variation is likely based on the clinical profile of the sample studied and the imaging modality used to determine RV dysfunction.[20, 21, 22] In a Sub-Saharan population of ILVNC with moderate or severe LV dysfunction, the prevalence of RV dysfunction in the present study was 58.2%, very similar to a study by Peters et al. who described the prevalence of RV dysfunction to be as high as 61% using echocardiography.[1] Nucifora et al, however, using cardiac magnetic resonance imaging (CMR), found a much lower prevalence of RV dysfunction in ILVNC (16%).[6] The CMR definition of RV dysfunction is also important in accounting for differences in prevalence because a CMR study by Leung et al. found RV dysfunction in almost half their patients using a definition of RV ejection fraction <35%.[5] This contrast may be due to differences in the patient profile studied. In contrast, the patients with ILVNC included in the current study, had chronic heart failure and a low EF. Furthermore, the RV dysfunction observed in our population was not associated with right ventricular noncompaction, which may be a factor contributing to intrinsic RV dysfunction.

Our study confirmed that despite several factors predicting RV dysfunction by univariate analysis, multiple regression analysis revealed that LVEF was the most important independent variable that predicted RV dysfunction by stepwise analysis in several models. This finding is not unexpected but highlights the fact that the LV abnormality and its functional consequences, such as mitral regurgitation, diastolic

dysfunction and elevated LV filling pressures, may account for the RV dysfunction noted irrespective of pathology.

An additional consideration relating to RV dysfunction in patients with chronic left heart failure, such as those in our cohort, are the numerous potential biochemical factors at play. In heart failure, excessive adverse sympathetic activity and neurohumoral factors, such as the renin-angiotensin-aldosterone system, natriuretic peptides, endothelin system and cytokines, have been reported to play a role in adverse RV remodeling similar to that observed in LV failure.[4,23,24] Remodeling of a failing right ventricle may be adversely affected by excessive sympathetic adrenergic stimulation.[23,24] Patients with similar EF, irrespective of pathology and perhaps independent of hemodynamic factors, may have varying degrees of RV functional abnormality even if they are on similar heart failure therapy due to these biochemical differences, which are driven initially by the left-sided pathology and may subsequently be driven secondarily by the failing right ventricle.

This study has some important limitations. The population comprised of patients referred for further evaluation of heart failure; therefore, it is possible that we have described the prevalence of RV dysfunction in advanced disease. RV dysfunction was defined using an echocardiographic parameter and not CMR, which is the criterion standard. RV dysfunction may be affected by RV loading conditions as well as technical difficulties, thereby affecting the accuracy of the parameters included. Longitudinal follow-up and biochemistry analysis are needed to imply causality.

Conclusions

The prevalence of right ventricular dysfunction was more prevalent in ILVNC compared to IDCMO patients, but varied depending on the echocardiographic technique utilized. The most important echocardiographic predictor determining RV dysfunction was LVEF, independent of contributing hemodynamic factors such as mitral regurgitation, and diastolic function.

Funding: none

Conflict of interest: None declared.

Table 1: Clinical and echocardiographic characteristics of participants with IDCMO versus ILVNC

Variables	IDCMO (n=49)	ILVNC (n=49)	p- value
Clinical parameters			
Age, y	40.3 ± 12.0	43.6 ± 14.6	0.24
*Male sex, n (%)	22 (44.9)	22 (44.9)	1.00
Systolic blood pressure, mmHg	121 ± 15	**114 ± 15**	**0.02**
Diastolic blood pressure, mmHg	78 ± 12	73 ± 13	0.051
Heart rate, bpm	73 ± 11	77 ± 17	0.16
BSA, m^2	1.79 ± 0.2	1.78 ± 0.2	0.25
Body mass index, kg/m^2	27.9 ± 6.7	26.0 ± 6.7	0.12
Two-dimensional LV parameters			
LV end-diastolic diameter, mm	**58.1 ± 9.7**	**64.6 ± 9.9**	**<0.01**
LV end-systolic diameter, mm	**49.4 ± 9.8**	**56.1 ± 10.3**	**<0.01**
Septal wall thickness, mm	10.0 ± 1.9	9.9 ± 1.6	0.78
Posterior wall thickness, mm	9.8 ± 1.6	10.1 ± 1.8	0.31
Relative wall thickness, ratio	**0.39 ± 0.08**	**0.32 ± 0.07**	**<0.001**
****EDV, mL**	**151.0 (83.0)**	**201.5 (106.9)**	**0.017**

****EDV indexed to BSA, ratio**	**80.9 (40.6)**	**109.3 (66.0)**	**<0.001**
****ESV, mL**	**106.0 (66.9)**	**149.0 (94.0)**	**0.008**
****ESV indexed to BSA, ratio**	**53.7 (39.5)**	**79.7 (53.7)**	**<0.001**
Ejection fraction, %	**32.2 ± 8.9**	**26.4 ± 9.6**	**<0.01**
LV systolic sphericity index, ratio	1.4 ± 0.3	1.4 ± 0.2	0.99
LV diastolic sphericity index, ratio	1.3 ± 0.2	1.3 ± 0.2	0.88
****LA volume, mL/m^2**	**38.0 (24.8)**	**73.0 (61.3)**	**<0.001**
****LA volume indexed to BSA, ratio**	**21.6 (10.9)**	**42.8 (33.2)**	**<0.0001**
****LV mass, g**	**214.0 (109.0)**	**263.0 (113.0)**	**0.006**
****LV mass indexed to BSA, ratio**	**116.3 (58.4)**	**154.0 (68.6)**	**0.002**
*Mitral regurgitation: n,(%)			
Mild	14 (28.6)	6 (12.2)	
Moderate	2 (4.1)	8 (16.3)	**0.02**
Severe	2 (4.1)	5 (10.2)	

LV diastolic parameters

E peak, m/s	**73.2 ± 21.2**	**92.9 ± 35.3**	**0.001**
**A peak, m/s	56.3 (18.2)	47.7 (1.8)	0.09
****E/A, ratio**	**1.3 (0.6)**	**1.8 (1.8)**	**0.002**
Deceleration time, ms	**136.1 ± 39.1**	**110.9 ± 42.3**	**0.003**
Medial E', m/s	**8.2 ± 2.7**	**5.7 ± 2.6**	**<0.001**
Medial A', m/s	**7.4 ± 2.4**	**5.4 ± 2.2**	**<0.001**
Lateral E', m/s	**11.7 ± 4.0**	**8.2 ± 3.3**	**<0.001**
Lateral A', m/s	**7.5 ± 2.8**	**5.8 ± 2.8**	**0.003**
E/E', ms	**7.4 (2.8)**	**13.3 (10.0)**	**<0.0001**
Strain Parameters			
LV GLS	**-11.00 ± 4.36**	**-7.23 ± 3.22**	**<0.001**

Bold parameters indicates statistical significance. Data presented as mean ± standard deviation.*Data presented as number (percentages). **Data presented as median and interquartile range. IDCMO: 10 patients and ILVNC: 10 patients (EDV, ESV, ESV indexed to BSA, LA volume, LA volume indexed to BSA, LV mass, LV mass indexed to BSA, A peak and E/A ratio)
RWT, LVEDV, LVESV, A peak, E/A ratio, medial A' measured in 47 and 48 ILVNC patients respectively
MR, measured in 18 IDCMO, and 19 ILVNC patients.
BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrial; LV, left ventricular;; LV GLS, Left ventricular Global Longitudinal Strain

Table 2: Right heart parameters of participants with IDCMO versus ILVNC

Variables	IDCMO (n=49)	ILVNC (n=49)	p- value
RV base, mm	**33.6 ± 4.6**	**40.3 ± 8.1**	**<0.0001**
Mid RV, mm	**25.0 ± 4.4**	**28.4 ± 7.1**	**0.005**
TAPSE, mm	**19.4 ± 4.3**	**16.9 ± 3.9**	**0.006**
FAC, %	**39.6 ± 7.6**	**29.8 ± 10.8**	**<0.0001**
****RA volume, ml**	**32.0 (13.6)**	**43.3 (38.8)**	**<0.001**

****PAP, mmHg**	**23.0 (7.0)**	**34.0 (20.0)**	**<0.001**
*Tricuspid regurgitation: n,(%)			
Mild	16 (32.7)	16 (32.7)	
Moderate	0 (0)	2 (4.1)	0.24
Severe	0 (0)	2 (4.1)	
RV diastolic parameters			
RV E', m/s	10.2 ± 4.1	8.6 ± 3.1	**0.03**
RV S', m/s	11.3 ± 2.3	10.1 ± 3.5	**0.04**

Bold parameters indicates statistical significance Data presented as mean ± standard deviation.*Data presented as number (percentages). **Data presented as median and interquartile range.
IDCMO: 2 patients and ILVNC: 2 patients (RA volume and PAP), PAP, measured in 29 IDCMO and 37 ILVNC patients. TR, measured in 16 IDCMO and 20 ILVNC patients. RV, right ventricle, RA, right atrium; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; PAP, pulmonary artery pressure, S', systolic annular motion, TAPSE(<17mm), measured in 9 IDCMO, 16 ILVNC, FAC (<35%), measured in 9 IDCMO, 30 ILVNC; RVS'(<9.5m/s), measured in 10 IDCMO, 22 ILVNC

Table 3: Univariate linear regression of RV dysfunction (RVS')

Variables	**Beta-coefficient ± standard error**	***P*-value**
Age, years*	-0.11 ± 0.09	0.22
Pathology : ILVNC	0.40 ± 0.10	<0.0001
Female sex, no. (%)	-0.13 ± 0.11	0.22
LV end-diastolic diameter, mm*	-0.21 ± 0.10	0.038
LV end-systolic diameter, mm*	-0.44 ± 0.10	<0.0001

End-diastolic volume, mL	-0.33 ± 0.10	0.002
End-systolic volume, mL	-0.44 ± 0.10	<0.0001
Ejection fraction, %	0.51 ± 0.10	<0.0001
Left atrial volume, mL	-0.33 ± 0.10	0.002
Pulmonary artery pressure, mmHg*	-0.23 ± 0.13	0.069
RV base	-0.05 ± 0.03	0.15
E peak, m/s	-0.10 ± 0.11	0.35
A peak, m/s	-0.08 ± 0.11	0.48
E/A ratio	-0.28 ± 0.11	0.012
Deceleration time, ms	0.35 ± 0.10	0.001
Medial E', m/s	0.26 ± 0.10	0.013
Medial E/E', m/s	-0.34 ± 0.10	0.002
Lateral E', m/s	0.29 ± 0.70	0.006
Lateral E/E', m/s	-0.34 ± 0.10	0.002
LV systolic sphericity index, ratio	0.43 ± 0.14	0.004
LV diastolic sphericity index, ratio	0.51 ± 0.13	<0.0001
Mitral regurgitation:		
Mild	- 0.14 ± 0.13	0.26≈
Moderate		
Severe		

LV, left ventricular; RV, right ventricular; S', systolic annular motion, medial E', peak E' medial wall velocity; lateral E', peak E' lateral wall velocity. IDCMO: 33 patients and ILVNC: 24 patients

≈p values refer to the combined mild, moderate and severe MR

Table 4 Multiple linear regression analysis for RV dysfunction (RV S')

Variables	Beta-coefficient ± standard error	*P*-value
MODEL 1 (n=86; Stepwise R^2 = 0.294)		
Age	0.09 ± 0.10	0.38
Male sex	-0.07 ± 0.10	0.45
Pathology: ILVNC	0.12 ± 0.09	0.21
Ejection fraction	0.39 ± 0.10	<0.001
Deceleration time	0.25 ± 0.10	0.014
LV systolic index	0.10 ± 0.10	0.32
MODEL 2 (n=86; Stepwise R^2 =0.320		
.		
Age	0.016 ± 0.018	0.39
Male sex	-0.390 ± 0.493	0.43
Pathology: ILVNC	0.639 ± 0.475	0.43
Ejection fraction	0.088 ± 0.022	0.0001
Deceleration time	0.009 ± 0.004	0.014
LV diastolic index	0.872 ± 1.309	0.51
MODEL 3 (n=91; Stepwise R^2 = 0.122)		
Age	0.03 ± 0.11	0.81
Male sex	-0.06 ± 0.11	0.57
Pathology: ILVNC	0.17 ± 0.10	0.134

LV end-systolic diameter	-0.29 ± 0.11	0.013
MODEL 5 (n=91; Stepwise R^2 = 0.236)		
Age	0.10 ± 0.13	0.55
Male sex	0.10 ± 0.13	0.93
Pathology: ILVNC	0.07 ± 0.12	0.55
Ejection fraction	0.41 ± 0.13	0.002
Mitral regurgitation	-0.12 ± 0.12	0.33
MODEL 6 (n=91; Stepwise R^2 = 0.236)		
Age	0.10 ± 0.12	0.42
Male sex	-0.02 ± 0.13	0.91
Pathology: ILVNC	0.09 ± 0.13	0.51
Ejection fraction	0.41 ± 0.12	0.002
Mitral regurgitation	-0.10 ± 0.13	0.43
Left atrial volume index	-0.04 ± 0.14	0.76

R^2 = multiple regression coefficient.
LV, left ventricular; ILVNC, Isolated left ventricular noncompaction; RV, right ventricular; S', systolic annular motion lateral E', peak E' lateral wall velocity.

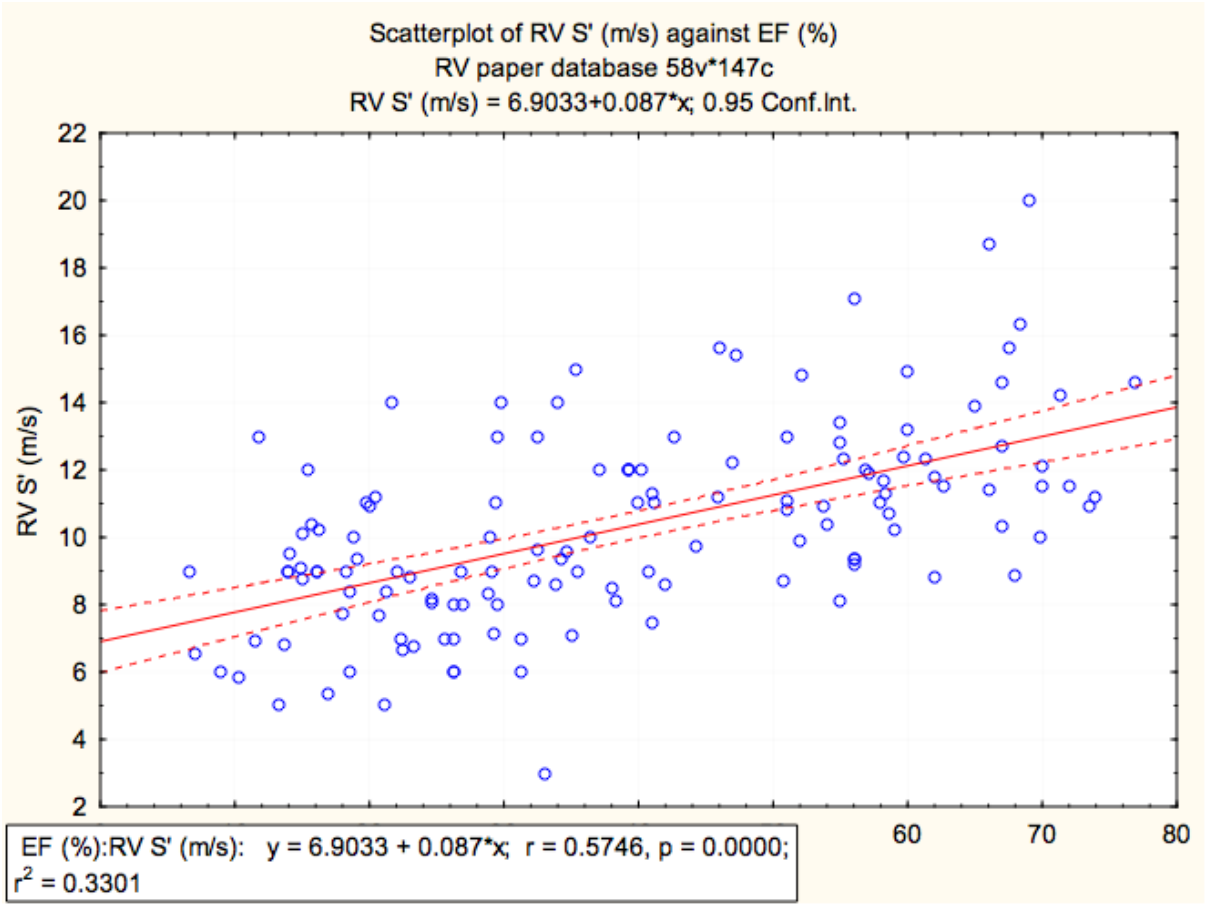

Figure 1: Univariate linear regression of RV dysfunction (RVS') vs LV ejection fraction (EF)

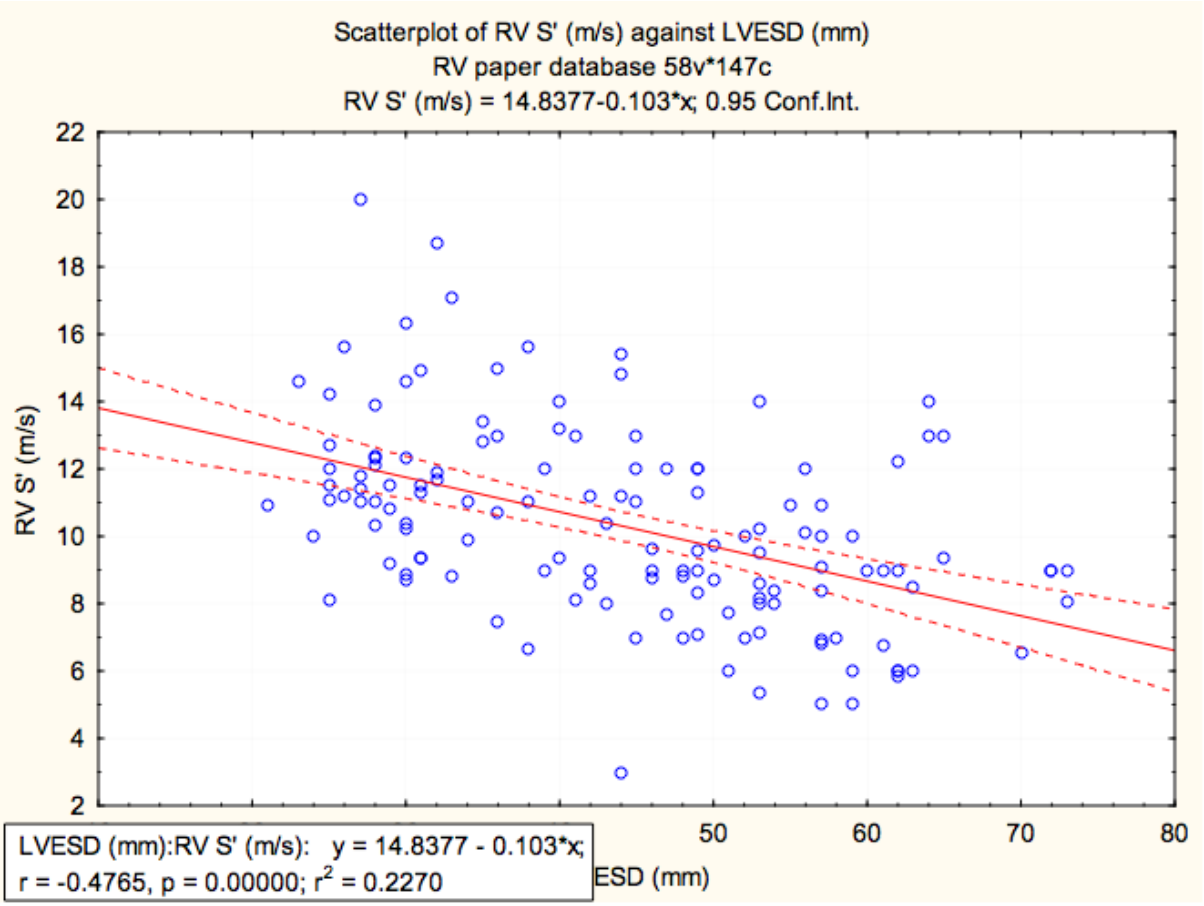

Figure 2: Univariate linear regression of RV dysfunction (RVS') vs left ventricular end systolic diameter (LVESD)

Chapter 5: Paper 4

Original Article

Serum Biomarkers and Ventricular Remodeling: An Analysis of Isolated Left Ventricular Non-compaction versus Idiopathic Dilated Cardiomyopathy in a Black African Sample

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Abstract

Background Despite several similar morphological and functional similarities, Isolated left ventricular noncompaction (ILVNC) and idiopathic dilated cardiomyopathy (IDCMO) may differ with regard to abnormalities of myocardial mechanics. No prior study has compared differences between ILVNC and IDCMO in a Sub-Saharan population .Therefore, the aim of this study was to assess whether myocardial mechanics and ventricular remodeling biomarkers differ between ILVNC and IDCMO (Idiopathic dilated cardiomyopathy) in a Black South African sample.

Methods and results. From an established Cardiomyopathy Registry, at Chris Hani Baragwanath Academic Hospital, a subgroup of 26 ILVNC and 26 IDCMO were selected for biomarker assessment. No patients with IDCMO fulfilled the comprehensive morphological criteria to diagnose ILVNC. Our results showed that patients with ILVNC had more adverse remodeling, evidenced by increased LV dilatation (66.4 ± 10.1 vs 56.1 ± 10.3), LV mass (295.0 (143.0) vs 234.0 (140.0), atrial volumes, and lower EF (ejection fraction) (28.5 ± 9.0 vs 33.3 ± 7.7), when compared to IDCMO. Rigid body rotation and regional longitudinal strain was not statistically significant different between both groups. No differences were noted between the two groups with regard to Procollagen-1 (procollagen type 1), MMP1 (matrix metalloproteinase), TIMP1 (tissue inhibitor of matrix metalloproteinase) and Fas/APO-1 (apoptosis antigen-1).

Conclusion Despite differences in the pathology and, perhaps, the pathogenesis of LV dysfunction in these two groups of patients, we found no differences in regional LV strain, RBR or biomarker concentrations between IDCMO and ILVNC.
Keywords Isolated left ventricular noncompaction ● Isolated dilated cardiomyopathy ●Biomarkers

Introduction

The differentiation of Isolated left ventricular noncompaction (ILVNC) with the dilated phenotype and a reduced ejection fraction from Idiopathic dilated cardiomyopathy (IDCM) can be challenging.[1] In both scenarios there may be several common morphological and functional abnormalities. [2] The presence of trabeculation is found in both conditions, which sometimes makes the differentiation difficult. [1,3,4]

The use of echocardiographic and cardiac magnetic resonance (CMR) criteria for the detection of the LVNC phenotype is one way to differentiate these conditions. A recent French multi-centre study suggested that the distinction between ILVNC and IDCMO is best made on echocardiography using the Jenni criteria, and on CMR imaging by using the Peterson criteria.[5] In addition to morphological based analysis, Paterick and Tajik proposed that functional abnormalities such as the use of left ventricular twist analysis abnormality should be considered as additional criteria to diagnose ILVNC. [6]

Initial reports from Kohli et al who studied Afrocaribean individuals suggested that hypertrabeculation may be a normal finding in black subjects.[7] They asserted that the findings of hypertrabeculation may even be more unreliable in black individuals with the dilated cardiomyopathy phenotype.[7] We recently demonstrated that in a normal black Sub-Saharan population that no individual satisfied any of the existing proposed morphological criteria. [8]

Peters et al described the first prospective large cohort of Sub Sahara patients with ILVNC who were differentiated from a normal control group by the morphologically based Jenni criteria. [9] This study demonstrated that patients with ILVNC and systolic impairment could be distinguished from a normal control population. [9] However, no study in a Sub-Saharan population has been conducted to compare ILVNC and IDCM. We postulated that in addition to the morphology criteria that ILVNC may differ with regard to certain functional and remodeling factors, from patients with IDCMO and ILVNC. The aims of this study was firstly, to compare myocardial mechanics between IDCMO and ILVNC patients. Secondly, to compare surrogates of adverse ventricular remodeling (Procollagen 1, TIMP, MMP and Fas/APO-1) between IDCMO and ILVNC.

Methods

This prospective cross-sectional study was conducted at Chris Hani Baragwanath Academic Hospital, after receiving approval from the University of the Witwatersrand Ethics Committee (clearance number M120271).

Patients were randomly selected from a dedicated cardiomyopathy clinic. Twenty-six patients who satisfied the echocardiographic criteria for ILVNC diagnosis and 26 patients with IDCMO diagnosis were included in the study. Exclusion criteria for both ILNVC and IDCMO were documented hypertension (past or present), known coronary artery disease (past or present), echocardiographic features suggestive of organic valvular disease (e.g. moderate or severe aortic regurgitation), clinical criteria for peripartum cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy, any systemic illness (e.g., human immunodeficiency virus), thyroid disease or any primary organ failure (e.g. chronic renal failure) and significant anemia (hemoglobin <10 g/dl)

Echocardiography

All echocardiograms were obtained according to a standardized protocol, on a Phillips iE 33 machine (Amsterdam, The Netherlands) equipped with an S5-1 transducer that transmits a frequency of 1.7 MHz and receives a frequency of 3.4 MH. All data were transferred to a Philips Xcelera workstation, and analyzed offline.

A combination of the Jenni and Stollberger criteria were utilized for the diagnosis of ILVNC.[10,11,12,13,14] We have recently demonstrated that in a cohort of normal individuals that, none satisfied these criteria.[8] These criteria are 1) a ratio of noncompacted to compacted myocardium >2 when measured at end systole; 2) presence of more than three prominent trabeculations in the 3) LV apex that did not originate from the septum; 4) deep intertrabecular recesses that filled with blood from the ventricular cavity as visualized on color Doppler ultrasound; and 5) no evidence of congenital or acquired heart disease.[10,11,12] IDCMO was defined per Sliwa et al,published in 2008 Patients with IDCMO were defined as having an ejection fraction of ≤45% and end diastolic dimension of >55 mm, which was also used to describe adverse remodelling.[15,16]

Measurements relating to chamber size and function were performed in accordance with the American Society of Echocardiography (ASE) chamber quantification guidelines of 2015 and the 2010 ASE guidelines on right heart assessment.[17,18] Parameters relating to LV diastolic function were measured and interpreted using pulsed-wave Doppler and tissue Doppler according to the consensus ASE/European Association of Cardiovascular Imaging (EAVCI) guidelines for the evaluation of LV diastolic function by echocardiography.[19] Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method.[18] The LV sphericity index was calculated by dividing the left ventricle's maximal long-axis internal dimension by its maximal short-axis dimension at end diastole.[18] The degree of mitral and tricuspid regurgitation was classified as mild, moderate or severe using an integrated assessment in accordance with the EAVCI guidelines on valvular regurgitation.[20] All echocardiograms of patients with ILVNC and IDCMO were separately analysed by an experienced cardiologist (F.P).

Speckle-tracking analysis

The 2D speckle-tracking images were acquired at a frame rate of 50-80 frames per second, during sinus rhythm, with <10% variability in heart rate. Parasternal short-axis images at the level of the LV base, showing the tips of the mitral valve leaflets, and a short-axis image at the apical LV level were used to assess LV rotation. The tracking points were placed on an end-diastolic frame in each parasternal short-axis image. In areas of hypertrabeculation, the tracking points were placed in the compacted part of the muscle. Tracking points were separated about 60 degrees from one another to fit the total LV circumference. After positioning these points, the program tracked them. In keeping with the standard ASE/EACVI consensus document on myocardial deformation, counter-clockwise rotation was assigned a positive value and clockwise rotation a negative value.[21] The peak systolic rotation was measured at the apex. Thereafter, the basal rotation at a time isochronous to that of the peak apical rotation was measured. Net instantaneous twist was then calculated as peak apical rotation minus basal rotation.[21] In addition to quantifying apical and basal rotation, we analysed the direction of rotation during the ejection phase of systole and identified rotation as either normal or having evidence of rigid body rotation, which was either entirely counterclockwise or clockwise at both the

base and apex during the ejection phase of systole.[22] Patients with rigid body rotation of the LV were not included in the rotation pattern analysis.
Global longitudinal strain (GLS) was measured in the apical 3-chamber, apical 4-chamber and apical 2-chamber sequentially, at frame rates >50fps, and a stable ECG recording. GLS was of the LV was averaged from the 16 LV segments.[22]
Basal, mid and apical longitudinal strain were averaged from 6 segments, and analyzed separately.[22]
All echocardiographic measurements were averaged from three heartbeats.

Biomarkers of fibrosis and apoptosis

All patients provided written consent to having blood biomarkers of fibrosis and apoptosis measured. Blood was drawn via Venesection, collected in BD (Becton Dickson) vacutainer tubes and centrifuged for 15 minutes at 3200 G. Aspirated serum was aliquoted into 1.5ml Eppendorf tubes (Hamburg, Germany), and stored at -80ºC. Measures of the serum for MMP-1, TIMP-1 and Fas/APO-1, were performed with a Magnetic Luminex Screening Assay kit, and concentrations automatically generated using Bio-Plex Manager software, Version 5.0 (Hercules, USA). Measures of Procollagen 1 was performed using a sandwich based enzyme-linked immunosorbent assay kit (Texas, USA), and concentrations generated on an ELx800 microplate reader (USA).

Statistics

STATA v16.0, STATACorp LLC, Texas, USA and Statistica v14.0.015, TIBCO Software Inc, were used to analyse the data. Descriptive data for the continuous variables are presented as mean ± standard deviation or median or interquartile range (IQR) if not normal distribution. Categorical data are summarized as frequencies and percentages. Continuous and normal distributed parameters were compared between ILVNC and IDCMO with independent t-test otherwise, Mann Whitney test was used. Chi-square and Fischer's exact test were performed as appropriate. Probability (P) value <0.05, two-sided, was considered statistically significant.

Results

A comparison of the clinical and echocardiographic characteristics revealed that patients with ILVNC had a greater degree of LV dilatation, higher LV mass, lower EF, and larger LA volumes (Table 1). LV diastolic function was worse in LVNC than in IDCMO, evidenced by E/E', vs 12.8(6.2 ms) vs 8.6(2.2) ms, p=0.007. Moderate and severe functional versus mild MR was more common in ILVNC versus IDCMO (50%vs 15.4%, p=0.02). With exception of RV base in ILVNC (39.1 ± 8.2 mm vs 34.9 ± 5.4 mm in IDCMO, p=0.03), there were no differences in chamber sizes or functional surrogates of RV function. Rigid body rotation was found in 11.5% of LVNC patients and 15.4% of DCMO patients (p>0.05).

In those with measureable rotation patterns, no differences were noted in basal and apical rotation, whereas net twist was higher in IDCMO, 6.5º (3.0º) versus 5.4º (4.6º), p=0.03 (Table 2). A possible trend where GLS was higher in IDCMO than ILVNC was noted (p=0.11). However, there were no differences with regard to regional variation in longitudinal strain from the base to the apex in either group.

Biomarkers relating to collagen metabolism and apoptosis showed no differences between the two groups with regard to procollagen 1, MMP1, TIMP1 and Fas/APO-1 (Table 3).

Discussion

The findings in our study revealed that patients with ILVNC had more adverse LV remodeling, evidenced by a greater degree of LV dilatation, LV mass, and lower EF (ejection fraction), when compared to IDCMO. While LV twist and LGS was lower in ILVNC, no statistical differences between the prevalence of RBR and the presence of a base to apical longitudinal strain gradient were found between the two groups. Lastly, no differences were noted between the two groups with regard to procollagen 1, MMP1, TIMP1 and Fas/APO-1.

ILVNC appears to be a heterogeneous disease with multiple possible phenotypes. Jeffries has proposed a nine phenotype model of ILVNC with the dilated phenotype constituting the third phenotype.[23] The dilated form of ILVNC clinically mimics IDCMO, but may have a more adverse outcome.[23] In addition, the risk of thromboembolism and ventricular arrhythmias is estimated to be similar in patients

with IDCMO, although patients with ILVNC have a higher incidence of heart failure hospitalization. [23,24]

Based on the increased incidence of a more adverse outcome of LV remodeling in our study, this may be translated into higher LV filling pressures and a trend towards increased pulmonary hypertension, tricuspid regurgitation (TR) and therefore adverse right ventricular (RV) remodeling. Thus, the findings of a trend towards lower global longitudinal strain (GLS) and significantly, lower net twist in patients with ILVNC is not unexpected and is in keeping with the increased adverse ventricular remodeling in patients with ILVNC.[3]

Normally, compaction progresses from epicardium to the endocardium and from the base towards the apex of the heart.[26] This pattern of reduced apical function compared to basal segments in patients with non-compaction is possibly attributed to embryogenic theory which states that compaction of myocardium occurs from epicardium to endocardium and from base to the apex.[26] An arrest in embryogenesis may result in a morphologically abnormal apical structure in ILVNC, and impacts on ventricular function, resulting in RBR, decreased apical function and decreased strain.[26] In our study, there was no difference in regional longitudinal strain between ILVNC and IDCM. In contradistinction, Tarando et al found that longitudinal shortening was greater in the non-compacted segments when compared to the compacted segments.[3] According to Tarando, a mid-wall strain base-apex gradient had 88.4 % sensitivity and 66.7 % specificity in distinguishing LVNC from DCM (AUC = 0.83; cut-off of -23 or |0.23|%).[3] In addition, in a multivariable model, the base-apex mid-wall gradient in an apical 4-chamber view was the only independent echocardiographic criteria (OR = 0.76, CI 95 % [0.66; 0.90], p = 0.0010) allowing for the distinction between LVNC and DCM.[3]

Prior studies of ILVNC have found a much higher prevalence of RBR. Van Dalen found RBR in 88% of ILVNC, whereas Peters found RBR in 53.3% of ILVNC.[22,25] The lower prevalence of RBR most likely reflects our smaller sample size with possible selection bias as the methodology used to measure the rotation parameters and the vendor software were the same.

Further, large multi-centre cohorts are required to reevaluate these discrepant data on the base to apex longitudinal strain gradient and RBR.

In lieu of the more adverse remodeling noted in subjects with ILVNC compared to IDCM in this study, it would be expected that factors contributing to adverse remodeling might be more prevalent in ILVNC than in IDCM. However, we found that there was no difference in procollagen 1, MMP/TIMP1 ratios or in a surrogate of apoptosis- Fas/APO-1. The former markers of fibrosis have been documented as abnormal in another disease such as hypertensive heart failure with low EF.[26] Fas/APO-1 has been previously studied in peripartum cardiomyopathy and was found to be generally elevated in cardiomyopathies.[27] In the present study the markers were not statistically significant different between ILVNC and IDCMO, implying that the remodeling process results in a similar impairment in both groups of patients.

The more adverse remodeling process in LVNC may be affected by other factors not measured in this study such as indices of wall stress, surrogates of oxidative stress and neurohumoral factors and maybe different to that observed in DCM.[23] Oechslin et al, have postulated that in LVNC genomic factors, such as common and rare genetic variants, probably interacting with nongenetic (e.g., hemodynamic, environmental) factors, determine the final phenotype of the myocardium which may in turn influence the remodeling process.[28]

An important feature not assessed in this study related to myocardial perfusion of the LV is hypoperfusion of the left ventricle in ILVNC, resulting in sub-endocardial microvascular abnormalities seen on positron emission tomography.[29] Some authors have postulated that in this clinical scenario, intramural perfusion could be adversely affected by the prominent trabeculations and intertrabecular recesses, particularly in the sub-endocardium, causing sub-endocardial ischemia.[29] Complex endomyocardial morphology and sub-endocardial ischemia and fibrosis might also lead to the development of myocardial dysfunction and influence remodeling.[29,30,31]

Limitations

This was a small single centre cross- sectional study. A Selection bias in determining biomarkers might have occurred due to the reduced number of patients in the both groups. The sample comprised of patients referred for further evaluation of heart failure; therefore, it is possible that the described prevalence of ventricular dysfunction and ventricular remodeling referred to advanced disease. Although current guidelines recommend testing B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP), this biomarker was not measured in this study. Conclusion on the findings of the serum biomarkers have to be read with caution and should be considered as preliminary results. Longitudinal follow-up and additional biochemistry analyses are needed in order to draw more robust inferences to the population.

Conclusions

The present study despite differences in LV remodeling, found no differences between myocardial mechanics and the biomarkers studied in ILVNC and IDCM. We postulate that, the pathogenesis of LV with dysfunction together secondary remodeling of the LV are factors that may result in similar functional LV impairment in both ILVNC and IDCMO patients and which requires future more detailed study.

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Conflict of interest: None declared.

Tables

Table 1: Clinical and echocardiographic characteristics of participants with IDCMO and ILVNC

Variables	IDCMO (n=26)	ILVNC (n=26)	p- value
Clinical parameters			
Age, y	44.4 ± 10.7	44.0 ± 14.7	0.91

Male sex, n (%)	16 (61.5)	13 (50)	0.40
Systolic blood pressure, mmHg	120 ± 18	115 ± 16	0.30
Diastolic blood pressure, mmHg	78 ± 14	73 ± 13	0.12
Heart rate, bpm	73 ± 11	71 ± 2	0.78
BSA, m^2	1.83 ± 0.17	1.76 ± 0.16	0.12
Body mass index, kg/m^2	28.6 ± 6.9	25.6 ± 5.6	0.09
LV parameters			
LV end-diastolic diameter, mm	**56.1 ± 10.3**	**66.4 ± 10.1**	**<0.001**
LV end-systolic diameter, mm	**47.6 ± 10.9**	**56.6 ± 10.5**	**<0.001**
Septal wall thickness, mm	10.9 ± 1.7	10.4 ± 1.6	0.71
Posterior wall thickness, mm	10.6±1.4	10.2 ± 1.8	0.39
Relative wall thickness, ratio	**0.39 ± 0.1**	**0.32 ± 0.1**	**<0.01**
***EDV, mL**	136.0(82.5)	**183.0 (105.0)**	**0.02**
***ESV, mL**	**88.0 (60.5)**	**127.5 (86.0)**	**0.02**
Ejection fraction, %	**33.3 ± 7.7**	**28.5 ± 9.0**	**0.04**
***LA volume, mL/m^2**	**46.1 (36.6)**	**63.8 (48.0)**	**0.036**
***LA volume indexed to BSA, ratio**	**24.5 (16.5)**	**37.9 (24.5)**	<0.01
***LV mass, g**	**234.0 (140.0)**	**295.0 (143.0)**	**0.018**
LV systolic index, ratio	1.8 ± 0.3	1.7 ± 0.3	0.12
LV diastolic index ratio	1.6 ± 0.3	1.5 ± 0.2	0.09

Mitral regurgitation: n (%)			
Mild	14 (53.8)	6 (23.1)	
Moderate	2 (7.7)	8 (30.8)	
Severe	2 (7.7)	5 (19.2)	**0.02**
LV diastolic parameters			
E peak, m/s	**69.7 ± 24.7**	**86.3 ± 31.8**	**0.04**
*A peak, m/s	60.8 (24.4)	51.8 (25.2)	0.27
***E/A, ratio**	**1.1 (0.5)**	**1.6 (1.4)**	**<0.01**
Deceleration time, ms	125.7 ± 33.0	115.5 ± 41.9	0.34
Medial E', m/s	6.8 ± 2.4	6.1 ± 2.4	0.33
Medial A', m/s	**6.8 ± 2.4**	**5.5 ± 1.9**	**0.03**
Lateral E', m/s	9.4 ± 3.4	8.1 ± 3.2	0.17
Lateral A', m/s	7.1 ± 2.9	6.1 ± 2.4	0.19
***E/E', ms**	**8.6 (2.2)**	**12.8 (6.2)**	**0.007**
RV parameters			
RV base, mm	**34.9 ± 5.4**	**39.1 ± 8.2**	**0.03**
***RA volume, ml	35.5 (16.2)	42.7 (27.0)	0.09
RV diastolic parameters			
RV S', m/s	10.6 ± 2.7	10.2 ± 2.6	0.59

Bold parameters indicates statistical significance. .

Data presented as mean ± standard deviation *Data presented as median and interquartile range.

RWT, LVEDV, LVESV, A peak, E/A ratio, medial A' measured in 26 DCMO and 26 LVNC patients respectively

Mitral Regurgitation, measured in 18 DCMO, and 19 LVNC patients.

BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; RV, right ventricle, RA, right atrium; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; E/E', mitral annular early diastolic velocity; RVS', RV free wall strain

Table 2: LV Myocardial Mechanics in IDCMO versus ILVNC

Variables	DCMO (n=26)	LVNC (n=26)	P value
Longitudinal Strain Patterns			
LV GLS	-9.92±3.67	-8.17±3.29	0.11
Basal LS	-10.4 ± 3.5	-9.9 ± 3.8	0.48
Mid LS	-10.1 ± 5.1	-8.0 ± 4.0	0.25
Apical LS	-9.9 ± 4.9	-8.5 ± 4.2	0.38
Rotation Patterns			
*Apical Rotation	3.0º (2.3º)	3.0º (2.7º)	0.46
*Basal Rotation	-3.1º (2.8º)	-2.4º (2.9º)	0.10
***Net Twist**	**6.5º (3.0º)**	**5.4º (4.6º)**	**0.03**

*Data presented as median and interquartile range.
LV GLS, Left ventricular Global Longitudinal Strain; LS, Longitudinal Strain
Longitudinal strain patterns were measured in 18 ILVNC and 26 IDCMO patients.
Rotation patterns were measured in 22 DCMO patients and 23 LVNC patients.

Table 3: Biomarkers of inflammation and fibrosis of participants with IDCMO versus ILVNC

Variables	IDCMO (n=26)	ILVNC (n=26)	P value
* Fas/APO-1	6316 (2435)	6307 (2432)	0.68

Log Fas/APO-1	8.83 ± 0.42	8.73 ± 0.27	0.33
*MMP1	3662 (2757)	4167 (2131)	0.55
logMMP1	8.22 ± 0.64	8.27 ± 0.56	0.79
*TIMP1	175493 (47790)	185531 (81746)	0.92
Log TIMP1	12.12 ± 0.20	12.17 ± 0.27	0.38
MMP1/TIMP1 ratio	0.024 ± 0.017	0.023 ± 0.012	0.78
Log MMP1/TIMP1	-3.89 ± 0.60	-3.90 ± 0.59	0.94
*Pro Collagen 1	15739 (11926)	15995 (8726)	0.80
Log Pro-collagen 1	9.56± 0.80	9.50 ± 0.88	0.79

Data presented as mean ± standard deviation. *Data presented as median and interquartile range.
Procollagen-1 (procollagen type 1), MMP1 (matrix metalloproteinase), TIMP1 (tissue inhibitor of matrix metalloproteinase) and Fas/APO-1 (apoptosis antigen-1). Pro Collagen 1 measured in 24 DCMO patients.

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Appendices

Appendix 1: Ethics clearance certificate

Biomarkers ethics clearance 2015

R14/49 Ms Samantha Nel

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140937

NAME: (Principal Investigator)	Ms Samantha Nel
DEPARTMENT:	Cardiology Chris Hani Baragwanath Academic Hospital Advanced Echocardiographic Research Laboratory
PROJECT TITLE:	Left Ventricular Noncompaction - Insights into the Pathophysiological mechanisms and consequences of the Left Ventricular Dysfunction
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Elena Libhaber, Prof Rafique Essop and Dr Ferande Peters
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/02/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2: Ethics extension certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Ms S Nel

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M2009207

NAME: (Principal Investigator)	Ms S Nel
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine - Cardioliogy Medical School University
PROJECT TITLE:	Left ventricular non-compaction - insights into pathophysiological mechanisms and consequences of Left Ventricular Dysfunction
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Renewal of M140937
SUPERVISOR:	Professors F Peters and E Libhaber
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/10/23

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore reports and re-certification will be due early in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

Appendix 3: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Samantha Nel (Student number: 1021713) am a student registered for the degree of PhD in the academic year 2022.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 23 March 2022

1

Appendix 4: Plagiarism letter

Johannesburg, 31 March 2022

RE: Plagiarism Report from Turn-it-in

Please see attached the plagiarism report received from Turn-it-in, 31/03/2022. The similarity percentage was 27%. Reviewing the text, which was highlighted for similarity, it referred to terminology, nomenclature, description of pathology, and largely the methods used to make the diagnosis of idiopathic left venrtricular noncompaction (ILVNC) and idiopathic dilated cardiomyopathy (IDCMO) regarding to both criteria and techniques.

Kind Regards

Samantha Nel

(student 1021713)

Supervisor1: Prof Ferande Peters Libhaber

Supervisor 2: Prof Elena

Appendix 5: Turn-it-in Report

TITLE: Left ventricular noncompaction – insights into the pathophysiological mechanisms and consequences of

Abstract

is distinct anatomical phenotype. It is detected by imaging in a variety of clinical scenarios. These clinical scenarios include congenital heart disease, neuromuscular diseases, valvular disease, pregnancy, sickle cell anemia and other cardiomyopathies such as hypertrophic cardiomyopathy. The within accompanied by two layered structure in which a thin compacta has an overlying prominent trabeculation with an adjacent intertrabecular space that is in direct communication with the blood pool is the distinct phenotypic hallmark.

Several controversies have emerged in recent years with regard to whether left ventricular noncompaction is a distinct pathological entity or a remodelling epiphenomenon, whether it is a distinct genetic disorder, whether the imaging criteria used are accurate and whether it is should be considered a normal variant in certain patient populations. One such population are individuals of African descent in whom it has been postulated by some authors that hypertrabeculation is a normal variant .The consequence is that some normal individuals and those with the phenotype of dilated cardiomyopathy may satisfy current imaging . Exactly what the phenotype in these clinical scenarios means has not been systematically studied until recently. The aforementioned controversies and questions are the key issues that were studied in this thesis.

Therefore, this thesis firstly evaluated normal echocardiographic ventricular South study revealed that there was a direct correlation between age, .468 .431) there was no correlation between BMI and RV linear measurements, however ' increase . Secondly, large South 4.7% trabeculations were found, no subjects fulfilled all four criteria for the diagnosis of ILVNC and similar rotation patterns,

quantitative LV rotation patterns and net twist were shown in both individuals with and without trabeculations

Thirdly, the prevalence and predictors dysfunction ILVNC dilated cardiomyopathy (IDCMO) were evaluated using echocardiography. The main findings indicate that ILVNC had more RV dilatation than IDCMO and that - RV S' FAC were decreased compared to IDCMO. In most relevant RV dysfunction, followed by LVESD (p=0.0001) and LVEDD (p=0.003).

Lastly, the question that was explored was whether ILVNC with low ejection fraction differed from IDCMO with regard to myocardial mechanics and biomarkers of LV remodeling. The results showed that patients with ILVNC had more adverse remodeling, evidenced by increased LV dilatation (66.4 ± 10.1 vs 56.1 ± 10.3), LV mass (295.0 (143.0) vs 234.0 (140.0) and lower EF (ejection fraction) (28.5 ± 9.0 vs 33.3 ± 7.7), when compared to IDCMO.Net twist was higher in IDCMO group vs ILVNC [6.5 (3.0) vs 5.4 (4.6)].

Rigid body rotation and regional longitudinal strain was different both are found between the biomarkers of LV remodeling (Procollagen 1, MMP1, TIMP1, and Fas/APO-1), These results should be considered as preliminary, due to the reduced sample size in both groups.

This thesis has provided key normal reference ranges for several echocardiographic parameters that may define normality in this population group using echocardiography. Furthermore this thesis highlights that normal individuals in this population group do not satisfy current used echocardiographic left ventricular non-compaction criteria and will have normal left ventricular rotational parameters.

With regard to a comparison between ILVNC with the dilated phenotype and a reduced EF and IDCMO, it appears that more adverse left ventricular remodeling and its ensuing functional abnormality are more common in ILVNC. The consequence is that right ventricular dysfunction is more prevalent in ILVNC and that in both instances; the LVEF was the most important predictor of right ventricular dysfunction. This thesis did not find any significant differences with regard to

abnormal rotation patterns or regional longitudinal strain between ILVNC and DCM or with regard to the biomarkers studied.

The strength of the thesis is that it provides guidance to clinicians with regard to identifying normality in individuals from this population group. Overall, the thesis has unraveled some of the controversies, but several issues remain unresolved with regard to the comparison of ILVNC with IDCMO. This may require future larger studies to address different aspects of ILVNC such as genetic analysis, more extensive biomarkers of heart failure in addition to speckle tracking parameters.

Chapter 1: Integrated Narrative

1.1 Background

The normal myocardial structure of the left ventricle (LV) has two layers, a thin endocardial trabecular layer with an underlying prominent compacted layer.[1] The endocardial trabecular layer usually develops into less than four prominent trabecular.[1] At autopsy, at least three trabeculae have been observed in approximately 4% of the normal population.[1]

Grant et al reported the first observation of an abnormality of the myocardium, characterised by increased trabeculation, with abnormal embryonal sinusoids.[2] Thereafter, in the 1960's, some [25] were found to abnormal myocardial phenotype, which was identified on either angiography or autopsy, and described as persistent intra-myocardial sinusoids or spongy myocardium.[3,4]

Two decades later, Engberding et al, with the use of two dimensional echocardiography reported on a myocardial phenotype similar to persistent myocardial sinusoids, in the absence of any other recognised cardiac disorders.[5] In 1990, Chin et al. described their case series using echocardiography which demonstrated the presence of abnormal trabeculae with an underlying thin compacted layer and coined the term 'noncompaction'.[6] These authors proposed that this was most likely a disorder of endomyocardial morphogenesis. Subsequently the term left ventricular noncompaction (LVNC) has been used, although Stollberger et al. utilised the term left ventricular hypertrabeculation.[7]

ILVNC was considered to be a rare cardiac abnormality, however with a combination of increased awareness and advancements in diagnostic imaging, there has been an increased rate of detection of this disease. [28] ILVNC :5000 individuals in general , and 3 to 4% in patients diagnosed with heart failure.[8] In recent years more publications related to ILVNC, with an increasing divergence of opinion relating to several controversies have emerged.

1.2 Disorders associated with ILVNC

ILVNC may occur if there is associated congenital heart disease, myocardial diseases such as hypertrophic cardiomyopathy and myocarditis, or in families where known genetic mutations have been identified, and have revealed other myocardial pathologies.[9,10] LVNC has also been reported in several medical disorders which include several neuromuscular abnormalities, sickle cell anemia, chronic kidney disease, hypertension and Chagas disease.[11,12,13,14] Physiological states where the ILVNC phenotype has been described also includes pregnancy and athletes.[15,16]

1.3 The characteristic phenotype of ILVNC

The hallmark of the phenotype of ILVNC is characterised by three key features. [2] Firstly, there should be prominent left trabeculations which are not connected to the interventricular septum.[2] Second, is the presence of adjacent accompanying deep inter-trabecular recesses which are perfused by blood within the left ventricular cavity, with no connection to the coronary circulation. [2] Third, is that overlying trabeculations should be a thin compacted layer of myocardium. [2] These three key features create a unique two-layered phenotypic appearance which is found more commonly in certain areas of the myocardium, with the apex, apical lateral and mid lateral walls being the most common affected ventricular walls.[2]

1.4 Controversies relating to ILVNC

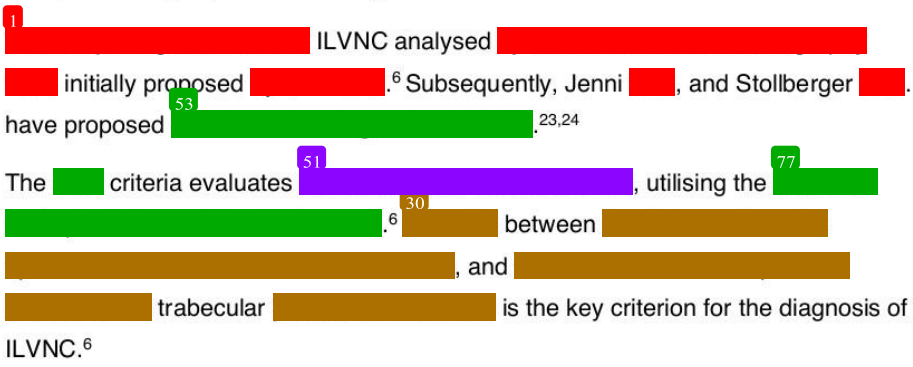
There are several controversies relating to ILVNC which include the possibility of ILVNC being a genetic disorder, or perhaps merely a remodelling phenomenon. ILVNC is characterised [15], whereas European Cardiac Society (ECS) refers to ILVNC as an unclassified cardiomyopathy.[17,18]

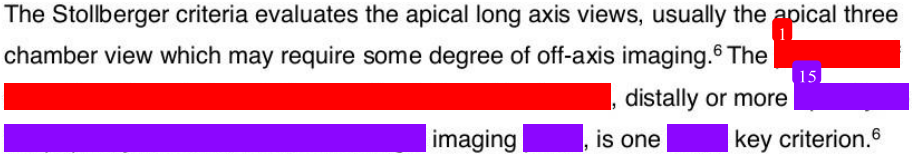
A second major controversy is whether this process occurs exclusively as an arrest during embryological development or perhaps post-natal factors such as volume overload may cause the development of the ILVNC phenotype. The documentation of the presence of this phenotype, its reversal in patients with myocarditis and a

normal pregnancy suggest that the embryological theory may not fully explain the development of the ILVNC phenotype.[16,19] The presence of documented ILVNC in athletes and patients with sickle cell anemia have led to postulate that volume overload results in adaptive left ventricular remodelling, which may also result in the ILVNC phenotype.[15]

A third controversy relates to the identification of the ILVNC phenotype with imaging. Several issues arise regarding which imaging technique is the gold standard between echocardiography and Cardiac Magnetic Resonance (CMR). Can the established echocardiographic criteria identifying ILVNC be used as the gold standard, over the CMR criteria?

Echocardiography is often the main investigation used to diagnose ILVNC.[20] This diagnostic imaging tool has in recent years become increasingly widely available, and remains more cost effective than CMR, with improved technology in spatial resolution. [20] The main disadvantage of CMR is its technical feasibility. [20,21,22] CMR has limitations in certain individuals because of poor spatial resolution in certain anatomical area, in particular the left lateral ventricular wall. [20,21,22] Furthermore, it is highly operator dependent, and may lead to under diagnosis of ILVNC, especially if suboptimal images, or off-axis images are obtained. [20,21,22]



The Stollberger criteria evaluates the apical long axis views, usually the apical three chamber view which may require some degree of off-axis imaging.[6] The 

The presence of perfusion by colour flow Doppler within the inter-trabecular spaces between the aforementioned trabecular is a second key criteria.[6]

The Jenni criteria is the most widely used echocardiographic criteria. This criteria evaluates imaging .[23] A myocardium greater than two is diagnostic of ILVNC.[23] The Jenni criteria was validated initially at autopsy, and subsequently applied to differentiate ILVNC in hypertensive individuals and in subjects with valvular heart disease.[24,25]

An additional criteria has been .[2] 'Milwaukee' criteria which also suggests that a noncompacted two.[2] This measurement is .[2] Paterick et al, proposed that this criteria , however, no prospective have been conducted .[2] These criteria are known to differ in several ways, and thus are not unexpectedly have a low agreement when studied.[2]

A fourth controversy on the identification of the phenotype of ILVNC, which refers to a possible manifestation of a normal variant in certain populations, particularly individuals who normal clinical status individuals identified with this ILVNC phenotype on imaging, varies from being asymptomatic to displaying life threatening cardiac manifestations such as heart failure, arrhythmias, systemic emboli or sudden cardiac death.[2,26] Thus misdiagnosis of pathology in a normal individual who may be asymptomatic but who may be uncertain of their future clinical course may have serious biological, social, economic and psychological consequences to an individual.

1.5 Is ILVNC a normal morphological variant in Black Africans?

Kohli, et al studied the three main echocardiographic criteria in as a .[27] They found that .[27] In 30% , all three were satisfied.[27] Furthermore, 8.3% of normal individuals satisfied criteria for ILVNC.[27] In their conclusion, Kohli, et al. expressed a concern that over diagnosis of ILVNC may occur, especially in black individuals.[27] This study's findings have been cited

numerous times as evidence that ILVNC may be a normal variant in black individuals.[26,28,29]

Further evidence supporting the observation of Kohli, et al. arose from a study of African athletes which [redacted] ILVNC.[26] [redacted] ILVNC [redacted].[27,30]

1.6 Differentiating the normal individual from ILVNC with normal LVEF

The differentiation of a normal heart with increased trabeculation from ILVNC with a normal EF is a key consideration. While merely relying on the traditional echocardiographic criteria may aid in most cases, this remains problematic as some normal cases may satisfy criteria, particularly highlighted by Kohli et al in some black individuals and as previously mentioned by studies of Afro-Caribbean athletes.[27,30] To improve the diagnostic discriminatory power, some authors suggested that either a family history or myocardial mechanics be utilized in combination with echocardiographic criteria.[2] Utilizing the presence of a family history is useful, but will not account for sporadic cases of ILVNC. Furthermore, the feasibility of performing family screening amongst individuals where the index case has an equivocal diagnosis may not be feasible and may potentially cause unnecessary added emotional stress in some circumstances.[31]

Thus utilizing myocardial mechanics as a potential additional complementary diagnostic tool is worthy of consideration.[32,33] The left ventricle during systole undergoes four major changes which results in the net contractile action which results in the efficient ejection of blood.[32,33] Myocardial fibers [redacted] a [redacted] direction, [redacted] a [redacted] direction while simultaneously the left ventricle undergoes a rotational deformation, that resembles the wringing of a towel, termed left ventricular twist. [32,33] In the normal individual, [redacted] net consequence [redacted] basal left ventricular [redacted] and [redacted] predominant apical counter clockwise rotation. [32,33]

1.7 The potential link between LVNC and abnormal myocardial mechanics

During embryological development the normal progression of myocardial compaction proceeds [6] .[34,35] Some postulates relating to the genetics and epigenetics of ILVNC may suggest that perhaps an arrest in embryogenesis or a partial arrest in this process potentiated by post-natal factors occurs.[36] The consequences of this is phenotypically the ILVNC phenotype which is most commonly seen to afflict the left ventricular apex, apical-lateral and apical-inferior walls in clinical series.[29,37] The functional consequences of ILVNC is best understood from evidence in patients with low EF and the dilated phenotype. In several studies, the [10] did correlate with extent LV noncompaction.[6,38,39]

One key plausible factor related [9] development ILVNC low EF is documentation of subendocardial ischemia in ILVNC. [18] LVNC both and nuclear scintigraphic techniques such as positron emission and thallium, in the absence of epicardial coronary stenosis.[40,41,42] Jenni et al, demonstrated that [62] was present .[40] Junga et al have postulated that reduced subendocardial [18] ILVNC a few potential factors which includes, a mismatch of the coronary circulation with increased [18] .[41]This predisposition to subendocardial dysfunction will predominantly affect the function of subendocardial fibers and may manifest as reduced longitudinal strain and reduced basal clockwise rotation.[40,41,42] The apex is almost exclusively involved and thus apical dysfunction may manifest in potentially greater apical longitudinal strain dysfunction or apical rotation abnormality.[40,41,42]

1.8 Abnormality of global and regional LV function

Longitudinal strain or dysfunction of rotational parameters may thus identify sub-clinical left ventricular contractile dysfunction in individuals with normal EF and the

ILVNC phenotype.[32,33,45] Using speckle tracking this may represent a feasible diagnostic technique that requires more detailed study to determine whether additional functional criteria may emerge that may more accurately distinguish normal individuals from pathologic ILVNC with a normal LVEF.[43] Bellavia et al were the first to document in a small cohort using speckle tracking that [39] ILVNC with normal EF versus normal controls.[43] Furthermore they found that left ventricular rotation [26] with normal .[43] preliminary findings requires more definitive study since discrepant findings using tissue Doppler imaging were found when comparing ILVNC with normal LVEF versus normal controls.[43] Tufekcioglu and coworkers found abnormal systolic pulse wave tissue Doppler imaging [26] versus controls whereas Bellavia et al, did not find any differences in peak velocity of systolic annular motion (S') between [26] >50% .[43,44] discrepant findings may represent inconsistencies with the technique of tissue Doppler rather than true abnormality .

Thus, based on the aforementioned issues, we thought it would be prudent to study a large normal, healthy Sub-Saharan black African cohort to determine to whether the conventional clinically utilized echocardiographic criteria would be satisfied by this population. Furthermore, we postulated that normal individuals would have normal myocardial mechanics. A fundamental issue however, would be to firstly determine if a clinically normal individual has a structurally and functionally normal heart. Current limitations of normal echocardiographic reference parameters in the 2015 [8] provides reference echocardiographic clinical practice.[31] However, these normative values are based on meta-analysis of data from studies emanating predominantly from the United States. [45]

The established reference ranges may not be accurate in some populations since reports from [8] Iran "normal" individuals from have echocardiographic values that are smaller than that reported from American and European studies.[34,35,36,45] An additional factor

that contributes to variation of measurements is the lack of standardization of measurement techniques between studies. These differences were addressed [34,35]. This study found that echocardiographic [34,35].

Prior studies on black individuals such as the Dallas heart study have suggested that black individuals have a greater tendency to have greater LV mass.[46] As mentioned previously, it seems that black individuals may have greater LV trabeculations.[27,30] A key question that emanates from these observations is whether these findings may differ between black individuals from North America, Afro Caribbean individuals and Sub-Saharan individuals. The WASE study included a Nigerian [34,35] postulated a large echocardiographic black would firstly define normal echocardiographic reference ranges, and secondly, would allow us trabeculation population. Accordingly, undertook a study firstly echocardiographic parameters – both left and right heart parameters. Thereafter, we systematically evaluated all studies with regard to defining to what extent a normal black Sub-Saharan population would satisfy conventional clinically utilized echocardiographic criteria for the diagnosis of ILVNC.

1.9 Can myocardial mechanics be used as an additional functional criteria to distinguish DCMO from LVNC with a reduced EF?

Prominent left ventricular trabeculations may be found in both ILVNC and IDCM which may make the differentiation of these two entities difficult. While patients with IDCM do not satisfy the comprehensive echocardiographic criteria this has not been systematically studied in all populations. The utilization of standard trans thoracic left ventricular echocardiographic parameters has not yielded any robust differentiation between these two conditions in several prior studies.[47,48] However, Nieman et al described a striking difference in regional longitudinal strain in patients with LVNC when using tissue Doppler imaging.[48] They observed that despite a decrement in EF and global longitudinal strain, the basal left ventricular strain was greater than the

mid segment strain which in turn was greater than that documented at the apex. This base to apex gradient was strikingly different to DCM where the strain was equally depressed in all regions.[48] They postulated that left ventricular apical function is more adversely affected than the basal regions because embryological which leads to greater apical non compaction and consequently more abnormal function compared to the basal regions.[48] This theory may account for the findings of rigid body rotation that was first described by Van Dalen et al in individuals with LVNC.[49] Van Dalen et al found in their 2012 study that no patients with DCM had Rigid body rotation in comparison to 88% of LNVC patients who had RBR.[49]

Ashwal et al in their study utilized speckle tracking and LVNC depressed GLS normal .[50] In addition they found that the strain was depressed to a greater degree in the apex compared to the base of the left ventricle.[50] Furthermore, they found RBR in 50% of their population.[50] In contradistinction Huttin et al .[51]

In lieu of these diametrically opposed findings, further work is accuracy and . Furthermore, no direct comparison has been conducted in a between DCM LVNC regard to standard echocardiographic parameters, myocardial mechanics and biomarkers that may relate to the remodeling process. Thus, we decided to study the aforementioned issues in patients with LVNC and DCM.

1.10 Findings of the thesis with clinical relevance

This thesis addresses the following key questions

(1) Are trabeculations in the left ventricle a normal phenomenon or is there a distinct pathological phenotype that can be used to differentiate normality from pathology in normal black Africans?

(2) Are echocardiographic criteria for the diagnosis of LVNC too sensitive, thus resulting in an overdiagnosis?

(3) Are echocardiograpghic criteria for ILVNC satisfied in normal individuals of Sub-Saharan African decent?

(4)Does ILVNC with reduced EF differ from IDCMO with regard to myocardial mechanics and biomarkers of LV remodeling?

(5)What is [47] right ventricular dysfunction IDCMO and ILVNC reduced EF?

1.10.1 The value of this research

Paper 1: [2] .

This is largest and the first echocardiographic study to define normal echocardiographic parameters using the ASE 2015 chamber quantification guidelines [2]. It highlights what reference range for a Black Sub-Saharan population may be.

Paper 2: [16] African .

It is the first study to evaluate the application of all ILVNC criteria [2] normal Sub-Saharan represents largest Sub-Saharan population studied, which is more than four times larger than the control group of Kohli, et al. This is the first study to prospectively evaluate the Paterick/Milwakee criteria.

The two papers listed above confirm that it is not normal for normal black Sub-Saharan individuals to satisfy ILVNC echocardiographic criteria. These findings do not apply to individuals with anemia, athletes or pregnancy woman, since these specific populations were excluded from our study. The application of this research to clinical practice is useful when, and if, an individual has a trabeculated left ventricle, but does not satisfy echocardiographic criteria, has normal tissue Doppler parameters and normal LV twist, the individual should therefore be deemed as

normal. The addition of regional and global strain to LV rotation may further prove to be useful, as a discriminating factor that would however require future validation.

Paper 3: [redacted] function [redacted].

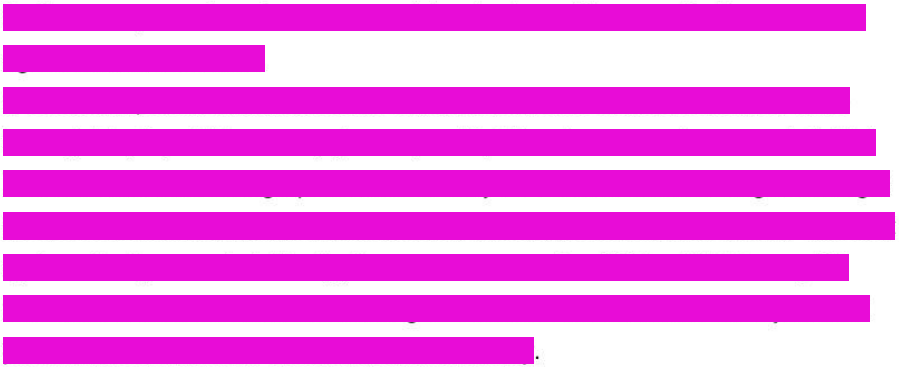
This is one of the first studies to make a comparison between ILVNC with reduced EF versus IDCMO, in a Black Sub-Saharan population, [redacted] standard echocardiographic [redacted] parameters, [redacted] right ventricular parameters. This study found evidence of more adverse LV remodeling in ILVNC. The most important predictor of RV dysfunction was LV dysfunction. These differences in LV remodeling is at variance with other studies and does require a larger study to be undertaken to further study these differences. The addition of genetic analysis may be useful to understand the differences between these two patient populations.

Paper 4: Serum Biomarkers and ventricular remodeling: an analysis of [redacted] versus [redacted] in a black African population.

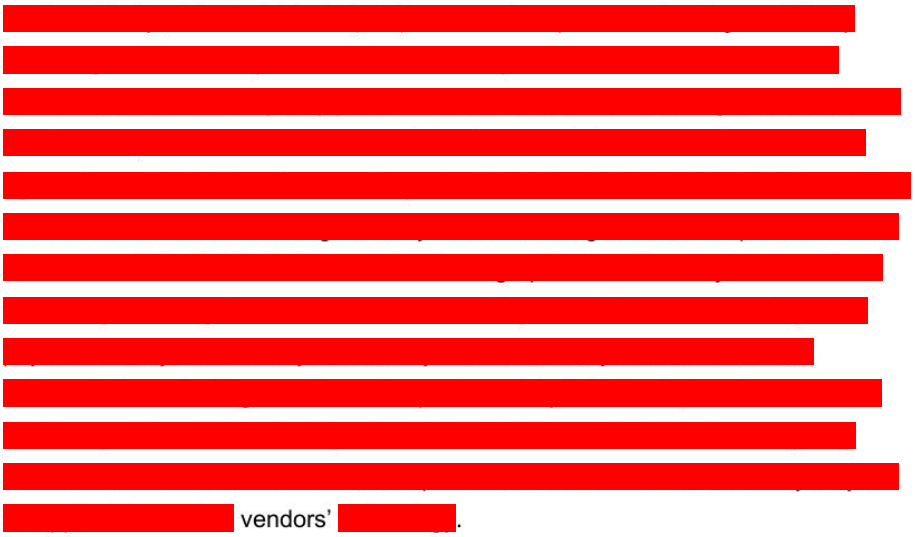
This is the first study to evaluate a comparison of myocardial mechanics and biomarkers of left ventricular remodeling in ILVNC versus IDCMO. This study found no significant differences between the biomarkers measured (Procollagen 1, TIMP/MMP ratio, Fas/APO -1) [redacted] two [redacted]. Furthermore, [redacted] was [redacted] regional strain or [redacted] detection of rigid body rotation. This study was limited by the small sample size, which may have contributed to a sample bias, since the overall population registry of the ILVNC clinic at Chris Hani Baragwanath Academic Hospital was over 120 cases during the study period, and a IDCMO registry of over 800 cases. We consider these findings preliminary and a larger study size is required together with additional biomarker analyses relating to LV remodelling.

1.11 Study Limitations

Paper 1: [redacted]



Paper 2: [1]



vendors' .

Paper 3: population comprised patients [11]

; therefore [27] prevalence RV dysfunction in . RV dysfunction was defined using an echocardiographic parameter and not CMR, which is the criterion standard. RV dysfunction may be affected by RV loading conditions as well as technical difficulties, thereby affecting the accuracy of the parameters included. No invasive data on

[25] and were available. Longitudinal [25] biochemistry are imply causality.

Paper 4: [13] small . A Selection bias in determining biomarkers might have occurred [4] reduced the both sample comprised patients referred for further evaluation of heart failure; therefore it is possible that the described prevalence of ventricular dysfunction and ventricular remodeling referred to advanced disease. Although [24]), this biomarker was not measured in this study. Conclusion on the findings of the serum biomarkers have to be read with caution and should be considered as preliminary results.

1.12 Future research: Remaining controversies to be investigated

What is the potential of additional echocardiographic mechanics or mechanical criteria in distinguishing between IDCMO and ILVNC, and could this be useful as a method of distinguishing between the two pathologies.

Would Black professional athletes in Sub-Saharan Africa display similar ILVNC phenotypes as documented in Western counterparts.

1.13 Conclusion

This is the largest and the first echocardiographic study to define normal echocardiographic parameters using the ASE 2015 chamber quantification guidelines in a Black African population.

It is the first study to evaluate the application of all LVNC criteria to a normal Black African Sub-Saharan population, and represents the largest Sub-Saharan population studied, which is more than four times larger than the normal control group of Kohli et al.

Chapter 4: Paper 3

Original Article

function

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Abstract

Background While right ventricular (RV) dysfunction may occur in (ILVNC) (IDCMO), a comparison of between these two patient populations has not been previously studied. The therefore was of RV dysfunction

56 98 , 49 ILVNC 49 IDCMO in 37 . The 4 more common (TAPSE – 32.7%, Tricuspid S' – 44.9%, FAC - 61.2%), compared to IDCMO (TAPSE – 18.4%, Tricuspid S' – 20.4%, FAC – 18.4%). The independent predictors of RV dysfunction following stepwise multiple regression were LV 19 .0001), LV .003), LV .0001) lateral E/E' (.034).

Conclusion

Right ventricular dysfunction was more prevalent in ILVNC compared to IDCMO patients, but varied depending on the echocardiographic technique utilized. LVEF was the most important predictors of RV dysfunction in both groups of patients.

Keywords 4 • Isolated

• Right ventricular dysfunction

Introduction

is technically challenging but has emerged as an important , RV myocardial infarction .[1-4] Right ventricular patients (ILVNC) and occurs in up to 61% of ILVNC cases.[1,3,5,6] This dysfunction may be related to intrinsic RV myocardial abnormality or be a consequence .[7] a recent study using was thought to be a marker of advanced ILVNC and was associated with a worse prognosis.[5] Similarly, Nucifora et al. identified ILVNC associated with LV dysfunction as the most important predictor of RV dysfunction in another CMR study.[6] A limitation of these two CMR studies is that they did not evaluate three : LV . Our hypothesis was that the degree of LV abnormality contributing determinant in ILVNC without right ventricular noncompaction (RVNC), and that this is not dissimilar to what occurs in (IDCMO). , the 1) patients without RVNC, in , and 2) independent dysfunction ILVNC and IDCMO, using echocardiography.

cross-sectional Academic 98 patients, 49 with ILVNC and 49 with IDCMO, were recruited over 32 months. All patients inclusion in either the IDCMO or ILVNC registries and included in the analysis.

Echocardiography

All either

, or Healthcare phased-array .5-3.6) or an Echopac V.8 (GE analyzed 2015 ,[10,11] . modified 's .[8, 9] degree of mitral and tricuspid regurgitation using an integrated assessment valvar .[13, 14] In addition, no patients had uncontrolled hypertension or significant anemia (hemoglobin <10 g/dl) at the time of echocardiography. The RV S' a value of < 9.5 abnormal .[10, 11] All right sided a right ventricular 4- .), (FAC <35% abnormal),) determined across RV annulus (TAPSE <17mm abnormal), and lastly and (RVS') with .[10, 11]

Isolated left ventricular noncompaction

A combination of the Oechslin et al. and Stöllberger criteria which we have previously reported on was used to diagnose ILVNC.[15,16,17] All four of the following criteria were required for a diagnosis of ILVNC:

1. myocardium > ;
2. ;

3. color ; and
4. .

All echocardiograms patients with ILVNC and IDCMO were separately) experienced in the diagnosis of ILVNC to determine if they fulfilled the proposed ILVNC criteria. No patients with IDCMO fulfilled the comprehensive criteria for diagnosis of ILVNC.

Isolated dilated cardiomyopathy

IDCMO was previously defined in a large prospective registry from Baragwanath Academic Hospital. [18] Inclusion criteria were of ≤ >55 mm.The exclusion criteria for both ILNVC and IDCMO present), . moderate or severe aortic regurgitation), clinical criteria for peripartum cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy,).

Statistics

Statistica 13. SAS 9.4 v. Descriptive the) if distribution was non-normal. Independent T- tests and comparison between ILVNC IDCMO. summarized frequencies comparisons performed with 's determine independent markers RV dysfunction (RV S'). Multivariate RV S' selected stepwise .

with ILVNC had significantly greater LV dilatation, higher LV mass, lower EF and lower GLS (diastolic parameters ILVNC , such

greater LA volumes, higher E/A ratios and E/E', were suggestive of higher LV filling pressure, and worse diastolic dysfunction, in comparison to DCMO patients. Similarly, moderate or severe functional MR was more prevalent in ILVNC (26.5%), than IDMO (8.2%) patients.

An analysis of right heart parameters revealed that patients with ILVNC had significantly greater RV dilatation than DCMO patients (Table 2). All 3 ' and FAC were lower in ILVNC vs IDCMO. Using the three techniques of RV systolic function, RV dysfunction was identified by: TAPSE- ILVNC (32.7%) vs IDCMO (18.4%) p=0.006, Tricuspid S' – ILVNC (44.9%) vs IDCMO (20.4%) p=0.04, and FAC-ILVNC (61.2%) vs IDCMO (18.4%) p<0.0001. RV E' a surrogate of myocardial relaxation was lower in ILVNC vs IDCMO. The prevalence of moderate/severe TR was similar. The pulmonary artery pressure was higher in ILVNC vs IDCMO. Similarly, RA volume was higher in ILVNC vs IDCMO. Univariate linear regression analysis (Table 3) revealed that pathology (ILVNC), LV , deceleration time, medial and lateral E' velocities, and were independently associated with increased RV function (RV S') (Figs 1- 3). stepwise linear .0001), LV .003) and LV .0001) lateral E/E' (.034) were predictors of RV dysfunction. (Table 4)

Discussion

The prevalence of RV dysfunction was ILVNC IDCMO the present study, and most likely varied depending on the imaging technique used. The echocardiographic parameters however, that proved independent predictors of RV dysfunction were .

Prior ILVNC studies have described the prevalence of RV dysfunction ranging between 16% to 61%.[1,5,6,19,20] This variation is likely based on the clinical profile of the sample studied and the imaging modality used to determine RV dysfunction.[20, 21, 22] In a Sub-Saharan population of ILVNC with LV prevalence dysfunction present study 58.2%, very

Peters described the prevalence of RV dysfunction to be as high as 61% using echocardiography.[1] Nucifora et al, however, using cardiac magnetic resonance imaging (CMR), found a much lower prevalence of RV dysfunction in ILVNC (16%).[6] The CMR definition of RV dysfunction is also important in accounting for differences in prevalence because a CMR study by Leung et al. found RV dysfunction in almost half their patients using a definition of RV ejection fraction <35%.[5] This contrast may be due to differences in the patient profile studied. In contrast, ILVNC current a EF, and considerable percentage of these patients had secondary pulmonary hypertension, which may result in a greater degree of RV dysfunction. Furthermore, the RV dysfunction observed in our population was not associated with right ventricular non compaction, which may be a factor contributing to intrinsic RV dysfunction.

Our study confirmed that despite several factors predicting RV dysfunction by univariate analysis, multiple regression LVEF independent variable that predicted RV dysfunction by stepwise analysis in several models. This finding is not unexpected but highlights the fact that the LV abnormality and its functional consequences, such as mitral regurgitation, diastolic dysfunction and elevated LV filling pressures, drive the secondary pulmonary hypertension, which may account for the RV dysfunction noted irrespective of pathology.

An additional consideration relating to RV dysfunction left , such as those our cohort, are the numerous potential biochemical factors at play. In heart failure, excessive adverse sympathetic activity and neurohumoral factors, such as the , have been reported play a role in adverse RV remodeling similar to that observed in LV failure.[4,23,24] Remodeling of a failing right ventricle may be adversely affected by excessive sympathetic adrenergic stimulation.[23,24] Patients with similar EF, irrespective of pathology and perhaps independent of hemodynamic factors, may have varying degrees of RV functional abnormality even if they are on similar heart failure therapy due to these biochemical

differences, which are driven initially by the left-sided pathology and may subsequently be driven secondarily by the failing right ventricle.

11 . The population comprised of patients 11 ; therefore, 27 prevalence RV dysfunction in . RV dysfunction was defined using an echocardiographic parameter and not CMR, which is the criterion standard. RV dysfunction may be affected by RV loading conditions as well as technical difficulties, thereby affecting the accuracy of the parameters included. No invasive data on 25 and were available. Longitudinal 25 biochemistry are imply causality.

Conclusions

The prevalence of right ventricular dysfunction was more prevalent in ILVNC compared to IDCMO patients, but varied depending on the echocardiographic technique utilized. The most important echocardiographic predictor determining RV dysfunction was LVEF, independent of contributing hemodynamic factors such as mitral regurgitation, diastolic function and pulmonary hypertension.

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Conflict of interest: None declared.

participants IDCMO versus ILVNC

Variables	IDCMO (n=49)	ILVNC (n=49)	p- value
Clinical parameters			
Age, y	40.3 ± 12.0	43.6 ± 14.6	0.24
*Male sex, n (%)	22 (44.9)	22 (44.9)	1.00
	121 ± 15	**114 ± 15**	**0.02**
	78 ± 12	73 ± 13	0.051
	73 ± 11	77 ± 17	0.16
BSA,	1.79 ± 0.2	1.78 ± 0.2	0.25
	27.9 ± 6.7	26.0 ± 6.7	0.12
Two-dimensional parameters			
	58.1 ± 9.7	**64.6 ± 9.9**	**<0.01**
	49.4 ± 9.8	**56.1 ± 10.3**	**<0.01**
	10.0 ± 1.9	9.9 ± 1.6	0.78
	9.8 ± 1.6	10.1 ± 1.8	0.31
, ratio	**0.39 ± 0.08**	**0.32 ± 0.07**	**<0.001**
****EDV, mL**	**151.0 (83.0)**	**201.5 (106.9)**	**0.017**
****EDV indexed to BSA, ratio**	**80.9 (40.6)**	**109.3 (66.0)**	**<0.001**

****ESV, mL**	**106.0 (66.9)**	**149.0 (94.0)**	**0.008**
****ESV indexed to BSA, ratio**	**53.7 (39.5)**	**79.7 (53.7)**	**<0.001**
Ejection fraction, %	**32.2 ± 8.9**	**26.4 ± 9.6**	**<0.01**
[redacted], ratio	1.4 ± 0.3	1.4 ± 0.2	0.99
[redacted], ratio	1.3 ± 0.2	1.3 ± 0.2	0.88
****[redacted]/m²**	**38.0 (24.8)**	**73.0 (61.3)**	**<0.001**
****[redacted], ratio**	**21.6 (10.9)**	**42.8 (33.2)**	**<0.0001**
****[redacted]**	**214.0 (109.0)**	**263.0 (113.0)**	**0.006**
[redacted], ratio	**116.3 (58.4)**	**154.0 (68.6)**	**0.002**
*Mitral regurgitation: n, (%)			
Mild	14 (28.6)	6 (12.2)	
Moderate	2 (4.1)	8 (16.3)	**0.02**
Severe	2 (4.1)	5 (10.2)	

LV diastolic parameters

	73.2 ± 21.2	**92.9 ± 35.3**	**0.001**
	56.3 (18.2)	47.7 (1.8)	0.09
	1.3 (0.6)	**1.8 (1.8)**	**0.002**
Deceleration time, ms	**136.1 ± 39.1**	**110.9 ± 42.3**	**0.003**
Medial	**8.2 ± 2.7**	**5.7 ± 2.6**	**<0.001**
Medial A',	**7.4 ± 2.4**	**5.4 ± 2.2**	**<0.001**
Lateral	**11.7 ± 4.0**	**8.2 ± 3.3**	**<0.001**
Lateral	**7.5 ± 2.8**	**5.8 ± 2.8**	**0.003**
', ms	**7.4 (2.8)**	**13.3 (10.0)**	**<0.0001**
Strain Parameters			
LV GLS	**-11.00 ± 4.36**	**-7.23 ± 3.22**	**<0.001**

Bold parameters indicates statistical significance. number (percentages).
**Data and . IDCMO: 10 patients ILVNC: 10 patients (EDV, ESV, ESV indexed to BSA, LA volume, LA volume , LV mass , A peak E/A ratio)
RWT, LVEDV, LVESV, A peak, E/A ratio, medial A' measured in 47 and 48 ILVNC patients respectively
, measured in 18 IDCMO, and 19 ILVNC patients.

2: Right heart parameters of participants with IDCMO versus ILVNC

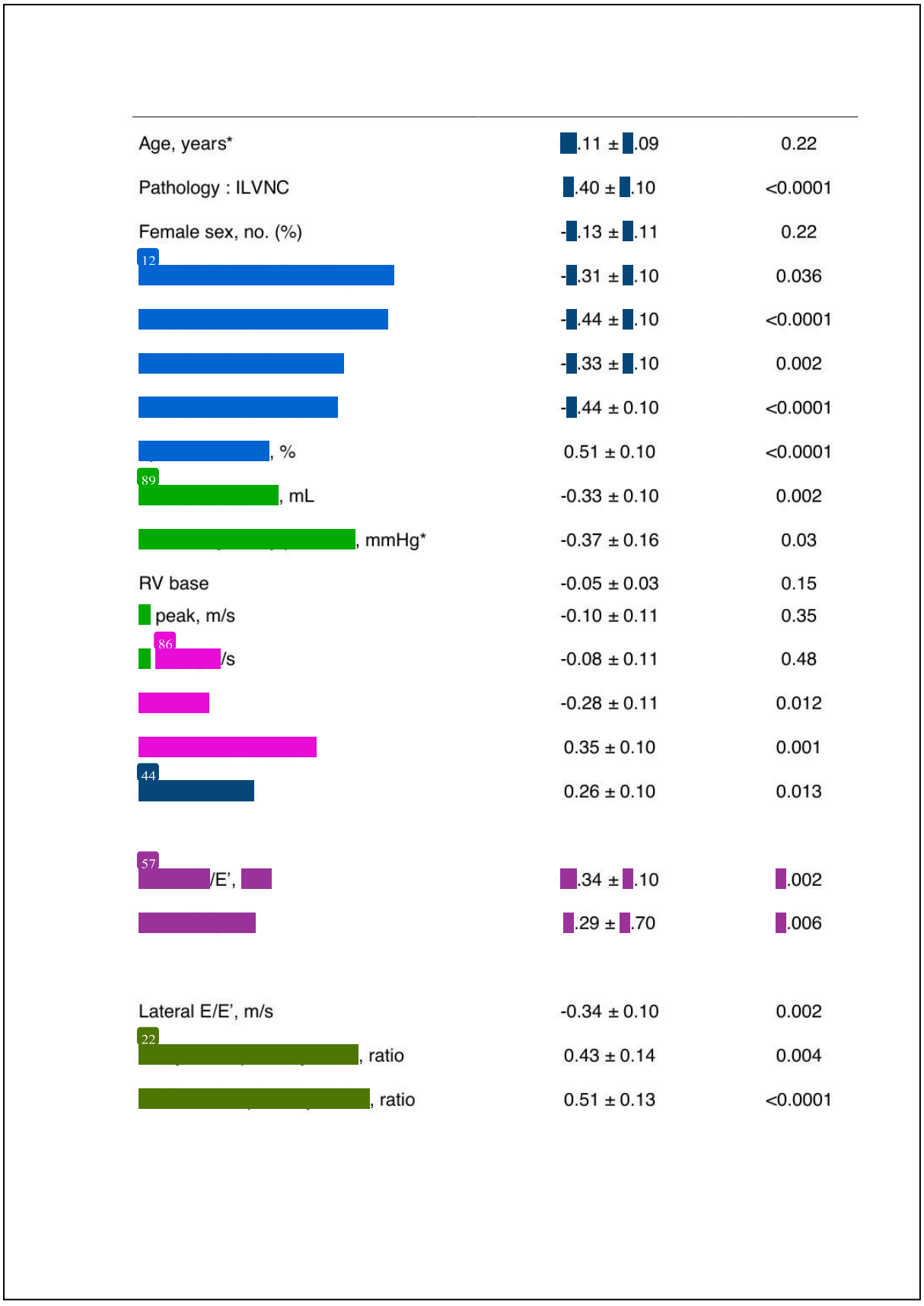
Variables	IDCMO (n=49)	ILVNC (n=49)	p- value
RV base, mm	**33.6 ± 4.6**	**40.3 ± 8.1**	**<0.0001**
Mid RV, mm	**25.0 ± 4.4**	**28.4 ± 7.1**	**0.005**

TAPSE, mm	**19.4 ± 4.3**	**16.9 ± 3.9**	**0.006**
FAC, %	**39.6 ± 7.6**	**29.8 ± 10.8**	**<0.0001**
****RA volume, ml**	**32.0 (13.6)**	**43.3 (38.8)**	**<0.001**
****PAP, mmHg**	**23.0 (7.0)**	**34.0 (20.0)**	**<0.001**
Tricuspid regurgitation: n, (%)			
Mild	16 (32.7)	16 (32.7)	
Moderate	0 (0)	2 (4.1)	0.24
Severe	0 (0)	2 (4.1)	
RV diastolic parameters			
RV E', m/s	10.2 ± 4.1	8.6 ± 3.1	**0.03**
RV S', m/s	11.3 ± 2.3	10.1 ± 3.5	**0.04**

Bold parameters indicates statistical significance. Data presented as mean ± standard deviation.*Data presented as number (percentages).
**Data presented as median and interquartile range. IDCMO: 2 patients and ILVNC: 2 patients (RA volume and PAP)
PAP, measured in 29 IDCMO and 37 ILVNC patients.
TR, measured in 16 IDCMO and 20 ILVNC patients.
RV, right ventricle, RA, right atrium; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; PAP, pulmonary artery pressure, S', systolic annular motion, TAPSE(<17mm), measured in 9 IDCMO, 16 ILVNC
FAC (<35%), measured in 9 IDCMO, 30 ILVNC
RVS'(<9.5m/s), measured in 10 IDCMO, 22 ILVNC

Table 3 Univariate linear regression analysis of RV dysfunction (RV S')

Variables	**Beta-coefficient ± standard error**	***P*-value**


Age, years*
.11 ± .09
0.22
Pathology : ILVNC
.40 ± .10
<0.0001
Female sex, no. (%)
-.13 ± .11
0.22
12
-.31 ± .10
0.036
-.44 ± .10
<0.0001
-.33 ± .10
0.002
-.44 ± 0.10
<0.0001
, %
0.51 ± 0.10
<0.0001
89
, mL
-0.33 ± 0.10
0.002
, mmHg*
-0.37 ± 0.16
0.03
RV base
-0.05 ± 0.03
0.15
peak, m/s
-0.10 ± 0.11
0.35
86
/s
-0.08 ± 0.11
0.48
-0.28 ± 0.11
0.012
0.35 ± 0.10
0.001
44
0.26 ± 0.10
0.013
57
/E',
.34 ± .10
.002
.29 ± .70
.006
Lateral E/E', m/s
-0.34 ± 0.10
0.002
22
, ratio
0.43 ± 0.14
0.004
, ratio
0.51 ± 0.13
<0.0001

Mitral regurgitation:		
Mild	- 0.14 ± 0.13	0.26≈
Moderate		
Severe		

LV, left ventricular; RV, right ventricular; S', systolic annular motion, medial E', [redacted]; lateral E', [redacted]. IDCMO: 33 patients and ILVNC: 24 patients

≈p values refer to the combined mild, moderate and severe MR

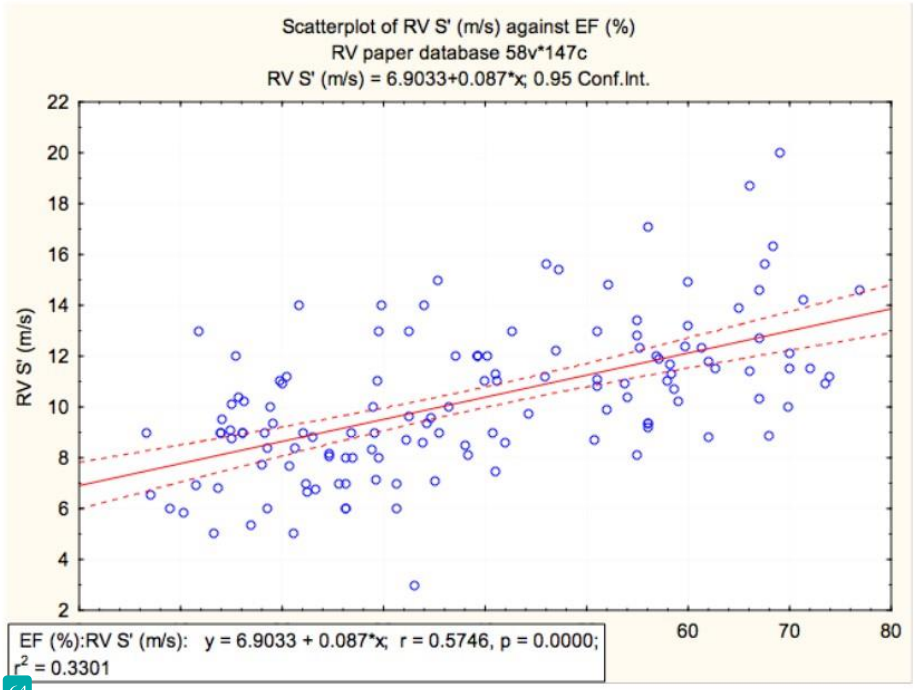
Table 4 Multiple linear regression analysis for RV dysfunction (RV S')

Variables	**Beta-coefficient ± standard error**	***P*-value**
MODEL 1 (n=86; Stepwise R^2 = 0.294)		
Age	0.09 ± 0.10	0.38
Male sex	-0.07 ± 0.10	0.45
Pathology: ILVNC	0.12 ± 0.09	0.21
Ejection fraction	0.39 ± 0.10	<0.001
Deceleration time	0.25 ± 0.10	0.014

LV systolic index	0.10 ± 0.10	0.32
MODEL 2 (n=86; Stepwise R^2 =0.320		
Age	0.016 ± 0.018	0.39
Male sex	-0.390 ± 0.493	0.43
Pathology: ILVNC	0.639 ± 0.475	0.43
Ejection fraction	0.088 ± 0.022	0.0001
Deceleration time	0.009 ± 0.004	0.014
LV diastolic index	0.872 ± 1.309	0.51
MODEL 3 (n=91; Stepwise R^2 = 0.134)		
Age	0.06 ± 0.10	0.58
Male sex	0.03 ± 0.10	0.73
Pathology: ILVNC	1.11 ± 0.53	0.039
[redacted]	-0.89 ± 0.29	0.003
[redacted]	-1.33 ± 0.38	<0.001
MODEL 5 (n=91; Stepwise R^2 = 0.236)		
Age	0.10 ± 0.13	0.55
Male sex	0.10 ± 0.13	0.93
Pathology: ILVNC	0.07 ± 0.12	0.55
Ejection fraction	0.41 ± 0.13	0.002
Mitral regurgitation	-0.12 ± 0.12	0.33
MODEL 6 (n=91; Stepwise R^2 = 0.236)		
Age	0.10 ± 0.12	0.42
Male sex	-0.02 ± 0.13	0.91

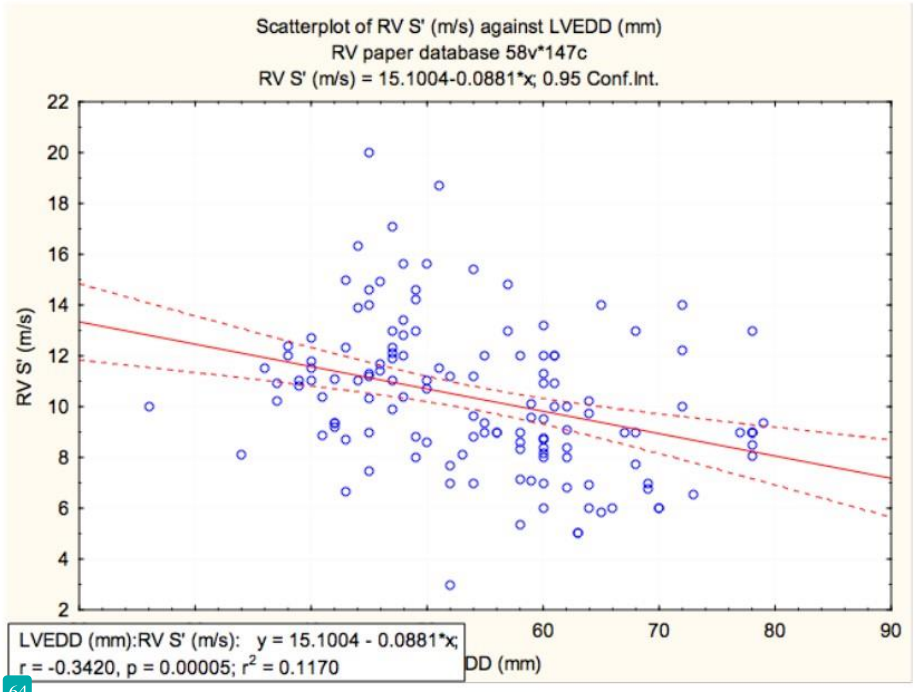
Pathology: ILVNC	.09 ± .13	.51
Ejection fraction	.41 ± .12	.002
Mitral regurgitation	-.10 ± .13	0.43
58	-.04 ± .14	0.76

R^2 = multiple regression coefficient.
46 ; ILVNC, Isolated noncompaction; ; S', systolic motion lateral E', peak E' lateral wall velocity.

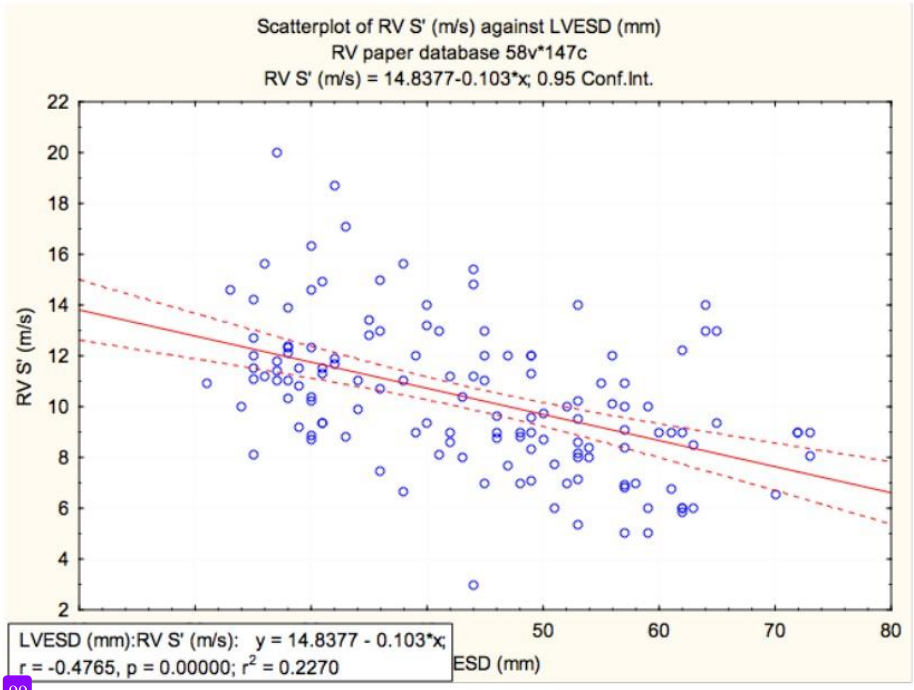


64

RV dysfunction (RVS') vs ejection fraction (EF)



64 **RV dysfunction (RVS') vs left ventricular end diastolic diameter (LVEDD)**



99 **RV dysfunction (RVS') vs left ventricular end systolic diameter (LVESD)**

Chapter 5: Paper 4

Original Article

Serum Biomarkers and Ventricular Remodeling: An Analysis Non-compaction in a Black African Sample

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Abstract

Background Despite several similar morphological and functional similarities, Isolated (ILVNC) (IDCMO) may differ with regard to abnormalities of myocardial mechanics. No prior study has compared differences between ILVNC and IDCMO in a Sub-Saharan population . whether myocardial mechanics, ventricular remodeling biomarkers differ between ILVNC and IDCMO (Idiopathic dilated cardiomyopathy) in a Black South African sample.

Methods and results From an established Cardiomyopathy Registry, at Chris Hani Baragwanath Academic Hospital, a subgroup of 26 ILVNC and 26 IDCMO were selected for biomarker assessment. No patients with IDCMO fulfilled the comprehensive morphological criteria to diagnose ILVNC. Our results showed that patients with ILVNC had more adverse remodeling, evidenced by increased LV dilatation (66.4 ± 10.1 vs 56.1 ± 10.3), LV mass (295.0 (143.0) vs 234.0 (140.0), atrial volumes, and lower EF (ejection fraction) (28.5 ± 9.0 vs 33.3 ± 7.7), when compared to IDCMO. Rigid body rotation and regional longitudinal strain 10 different both . No 45 noted Procollagen-1 (procollagen type 1), 7) and Fas/APO-1 (apoptosis antigen-1).

10 pathology and, perhaps, pathogenesis of LV dysfunction in these two groups of patients, we found no differences in regional LV strain, RBR or biomarker concentrations between IDCMO and ILVNC.

Keywords 4 ● Isolated ●Biomarkers

Introduction

The differentiation of [4]) with dilated phenotype a reduced ejection fraction from Idiopathic dilated cardiomyopathy (IDCM) can be challenging.[1] In both scenarios there may be several common morphological and functional abnormalities. [2] The presence of trabeculation is found in both conditions, which sometimes makes the differentiation difficult. [1,3,4]

The use of [68] detection the phenotype is one way to differentiate these conditions. A recent French multi-center study suggested that the distinction between ILVNC and IDCMO is best made on echocardiography using the Jenni criteria, and on CMR imaging by using the Peterson criteria.[5] In addition to morphological based analysis, Paterick and Tajik proposed that functional abnormalities such as the use of left ventricular twist analysis abnormality should be considered as additional criteria to diagnose ILVNC. [6]

Initial reports from Kohli et al who studied Afro-Caribbean individuals suggested that hypertrabeculation may be a normal finding in black subjects.[7] They asserted that the findings of hypertrabeculation may even be more unreliable in black individuals with the dilated cardiomyopathy phenotype.[7] We recently demonstrated that in a normal black Sub-Saharan population that no individual satisfied any of the existing proposed morphological criteria. [8]

Peters et al described the first prospective large cohort of Sub Sahara patients with ILVNC who were differentiated from a normal control group by the morphologically based Jenni criteria. [9] This study demonstrated that patients with ILVNC and systolic impairment could be distinguished from a normal control population. [9] However, no study in a Sub-Saharan population has been conducted to compare ILVNC and IDCM. We postulated that in addition to the morphology criteria that ILVNC may differ with regard to certain functional and remodeling factors, from patients with IDCMO and ILVNC. [87] was firstly, myocardial mechanics IDCMO and ILVNC patients. Secondly, to compare surrogates of adverse ventricular remodeling (Procollagen 1, TIMP, MMP and Fas/APO-1) between IDCMO and ILVNC.

Methods

This [redacted] was conducted [redacted], [redacted] (clearance number M120271).

Patients were randomly selected from a dedicated cardiomyopathy clinic. Twenty six [redacted] ILVNC [redacted] and 26 patients with IDCMO diagnosis were included in the study. Exclusion criteria for both ILNVC and IDCMO [redacted] present), [redacted]. moderate or severe aortic regurgitation), clinical criteria for peripartum cardiomyopathy, restrictive cardiomyopathy, hypertrophic cardiomyopathy, [redacted]) and significant anemia (hemoglobin <10 g/dl)

Echocardiography

All [redacted] MH. [redacted].

A combination of [redacted] Jenni and Stollberger criteria were utilized for the diagnosis of ILVNC.[10,11,12,13,14] We have recently demonstrated that [redacted], none satisfied these criteria.[8] These criteria are [redacted] myocardium >[redacted]; 2) [redacted] 3) [redacted]; 4) [redacted] color [redacted]; and 5) [redacted].[10,11,12] IDCMO was defined per Silwa et al, published in 2008 Patients with IDCMO were defined as having [redacted] of ≤[redacted] >55 mm.[15,16]

Measurements relating to [2] [redacted] .[17,18] [1] [redacted] .[19] [3] [redacted] modified [redacted] 's [redacted] .[18] [redacted] [3] [redacted] .[18] The degree [redacted] mitral and tricuspid regurgitation was classified [97] [redacted] an integrated assessment [7] [redacted] EAE [redacted] .[20]

An experienced cardiologist (F.P) separately analyzed all echocardiograms of patients with ILVNC and IDCMO.

[55] [redacted] [1] 50- [redacted], with < [redacted] .[21] [redacted] .[21] [redacted]

.[22] of the LV not included in the rotation pattern analysis.

the sequentially, rates >50fps, and a stable ECG recording. GLS was of the LV was averaged from the 16 LV segments.[22] Basal, mid and apical longitudinal strain were averaged from 6 segments, and analyzed separately.[22]

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Biomarkers fibrosis and apoptosis

All patients provided written consent to having blood biomarkers of fibrosis and apoptosis measured. Blood was drawn via Venesection, collected in BD (Becton Dickson) vacutainer tubes and centrifuged for 15 minutes at 3200 G. Aspirated serum was aliquoted into 1.5ml Eppendorf tubes (Hamburg, Germany), and stored at -80°C. Measures of the serum for MMP-1, TIMP-1 and Fas/APO-1, were performed with a Magnetic Luminex Screening Assay kit, and concentrations automatically generated , USA). Measures of Procollagen 1 was performed using a sandwich based enzyme-linked immunosorbent assay kit (Texas, USA), and concentrations generated on an ELx800 microplate reader (USA).

Statistics

STATA v16.0 and Statistica 13.0 were used to analyse the data. Descriptive data for the presented or) if not summarized frequencies and . Continuous and normal distributed parameters were compared between ILVNC and IDCMO with independent otherwise was used. and performed as appropriate. Probability (P) value <

A comparison of echocardiographic revealed that ILVNC had a greater degree of LV dilatation, higher LV mass, lower EF,

and larger LA volumes (Table 1). LV diastolic function was worse in LVNC than in IDCMO, evidenced by E/E', vs 12.8(6.2 8.(2. .007. Moderate and severe functional versus mild MR was more common in ILVNC versus IDCMO (50%vs 15.4%, p=0.02). With exception of RV base in ILVNC (39.1 ± 8.2 .4 in IDCMO, .03), there were no differences in chamber sizes or functional surrogates of RV function. 11.5% LVNC and 15.4% of DCMO patients (p>0.05).

In those with measureable rotation patterns, no differences were noted in basal and apical rotation, whereas net twist was higher in IDCMO, 6.5° (3.0°) versus 5.4° (4.6°), p=0.03 (Table 2). A possible trend where GLS was higher in IDCMO than ILVNC was noted (p=0.11). However, there were no differences with regard to regional variation strain in either group.

Biomarkers relating to collagen metabolism and apoptosis showed no procollagen 1, MMP1, TIMP1 and Fas/APO-1 (Table 3).

Discussion

The findings in our study revealed that ILVNC , evidenced by greater degree LV dilatation, LV mass, and lower EF (ejection fraction), when compared to IDCMO. While LV twist and LGS was lower in ILVNC, no statistical differences between the prevalence of RBR or the presence of a base to apical longitudinal strain gradient were found . Lastly, noted with regard to procollagen 1, MMP1, TIMP1 and Fas/APO-1.

ILVNC appears to be a heterogeneous disease with multiple possible phenotypes. Jeffries has proposed a nine phenotype model of ILVNC with the dilated phenotype constituting the third phenotype.[23] The dilated form of ILVNC clinically mimics IDCMO, but may have a more adverse outcome.[23] In addition, the risk of thromboembolism and ventricular arrhythmias is estimated IDCMO, although ILVNC have a higher incidence of heart failure hospitalization.[23,24]

Based on the increased incidence of a more adverse outcome of LV remodeling in our study, this may be translated into higher LV filling pressures and a trend towards increased pulmonary hypertension, tricuspid regurgitation (TR) and therefore adverse right ventricular (RV) remodeling. Thus, the findings of a trend towards lower [45]) and , lower net twist ILVNC is not unexpected and is in keeping with the increased adverse ventricular remodeling in patients with ILVNC.[3]

[6]
.[26] [6]
.[26] An arrest in embryogenesis may result in a morphologically abnormal apical structure in ILVNC, and impacts on ventricular function, resulting in RBR, decreased apical function and decreased strain.[26] In our study, [21] regional ILVNC IDCM. In contradistinction, Tarando et al found that [5] when compared to segments.[3] According to Tarando, [5] !%).[3] addition, in for .[3]

Prior studies of ILVNC have found a much higher prevalence of RBR. Van Dalen found RBR in 88% of ILVNC, whereas Peters found RBR in 53.3% of ILVNC.[22,25] The lower prevalence of RBR most likely reflects our smaller sample size with possible selection bias as the methodology used to measure the rotation parameters and the vendor software were the same.

Further, large multi-center cohorts are required to reevaluate these discrepant data on the base to apex longitudinal strain gradient and RBR.

In lieu of the more adverse remodeling noted in subjects with ILVNC compared to IDCM in this study, it would be expected that factors contributing to adverse remodeling may be more prevalent in ILVNC than in IDCM. However we found that there was no difference in procollagen 1, MMP/TIMP1 ratios or in a surrogate of apoptosis- Fas/APO-1. The former ~~are~~ markers of fibrosis have been documented as abnormal in another disease condition such as hypertensive heart failure with low EF.[26] Fas/APO-1 has been previously studied in peripartum cardiomyopathy and was found to be generally elevated in cardiomyopathies.[27] In the present study the markers were not statistically significant different between ILVNC and IDCMO,implying that the remodeling process results in a similar impairment in both groups of patients.

The more adverse remodeling process in LVNC may be affected by other factors not measured in this study such as indices of wall stress, surrogates of oxidative stress and neurohumoral factors and maybe different to that observed in DCM.[23] Oechslin et al, have postulated that in LVNC [29] which in turn influence the remodeling process.[28]

An important feature not assessed in this study related to myocardial perfusion of the LV is hypoperfusion of the left ventricle in ILVNC, resulting in subendocardial microvascular abnormalities seen on positron emission tomography.[29] Some authors have postulated that in this clinical scenario, [29] also the myocardial dysfunction influence remodeling.[29,30,31]

Limitations

[7] small . A Selection bias in determining biomarkers might have occurred [4] reduced the both sample comprised patients referred for further evaluation of heart failure; therefore it is possible that the described prevalence of ventricular

dysfunction and ventricular remodeling referred to advanced disease. Although [redacted]), this biomarker was not measured in this study. Conclusion on the findings of the serum biomarkers have to be read with caution and should be considered as preliminary results. Longitudinal follow-up and additional biochemistry analyses are needed in order to draw more robust inferences to the population.

Conclusions

The present study despite differences in LV remodeling, found no differences between myocardial mechanics and the biomarkers studied in ILVNC and IDCM. We postulate that, the pathogenesis of LV with dysfunction together secondary remodeling of the LV are factors that may result in similar functional LV impairment in both ILVNC and IDCMO patients and which requires future more detailed study.

Acknowledgements

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[redacted].

Tables

participants with IDCMO ILVNC

	IDCMO (n=26)	ILVNC (n=26)	p- value
Clinical parameters			
Age, y	44.4 ± 10.7	44.0 ± 14.7	0.91
Male sex, n (%)	16 (61.5)	13 (50)	0.40
	120 ± 18	115 ± 16	0.30
	78 ± 14	73 ± 13	0.12
	73 ± 11	71 ± 2	0.78
BSA,	1.83 ± 0.17	1.76 ± 0.16	0.12
	28.6 ± 6.9	25.6 ± 5.6	0.09
parameters			
	56.1 ± 10.3	**66.4 ± 10.1**	**<0.001**
	47.6 ± 10.9	**56.6 ± 10.5**	**<0.001**
	10.9 ± 1.7	10.4 ± 1.6	0.71
	10.6±1.4	10.2 ± 1.8	0.39
, ratio	**0.39 ± 0.1**	**0.32 ± 0.1**	**<0.01**
***EDV, mL**	136.0(82.5)	**183.0 (105.0)**	**0.02**
***ESV, mL**	**88.0 (60.5)**	**127.5 (86.0)**	**0.02**

Ejection fraction, %	**33.3 ± 7.7**	**28.5 ± 9.0**	**0.04**
***[redacted]/m²**	**46.1 (36.6)**	**63.8 (48.0)**	**0.036**
***[redacted],**	**24.5 (16.5)**	**37.9 (24.5)**	<0.01
ratio			
***[redacted]**	**234.0 (140.0)**	**295.0 (143.0)**	**0.018**
[redacted], ratio	1.8 ± 0.3	1.7 ± 0.3	0.12
[redacted] ratio	1.6 ± 0.3	1.5 ± 0.2	0.09
Mitral regurgitation: n (%)			
Mild	14 (53.8)	6 (23.1)	
Moderate	2 (7.7)	8 (30.8)	
Severe	2 (7.7)	5 (19.2)	**0.02**
LV diastolic parameters			
[redacted]	**69.7 ± 24.7**	**86.3 ± 31.8**	**0.04**
[redacted]	60.8 (24.4)	51.8 (25.2)	0.27
[redacted]	**1.1 (0.5)**	**1.6 (1.4)**	**<0.01**
Deceleration time, ms	125.7 ± 33.0	115.5 ± 41.9	0.34
Medial [redacted]	6.8 ± 2.4	6.1 ± 2.4	0.33
Medial A',	**6.8 ± 2.4**	**5.5 ± 1.9**	**0.03**
Lateral [redacted]	9.4 ± 3.4	8.1 ± 3.2	0.17
Lateral [redacted]	7.1 ± 2.9	6.1 ± 2.4	0.19
[redacted]', ms	**8.6 (2.2)**	**12.8 (6.2)**	**0.007**
RV parameters			
RV base, mm	**34.9 ± 5.4**	**39.1 ± 8.2**	**0.03**
*RA volume, ml	35.5 (16.2)	42.7 (27.0)	0.09

RV diastolic parameters			
RV S', m/s	10.6 ± 2.7	10.2 ± 2.6	0.59

Bold parameters indicates statistical significance. .

23 and .

RWT, LVEDV, LVESV, A peak, E/A ratio, medial A' measured in 26 DCMO and 26 LVNC patients respectively

Mitral Regurgitation, measured in 18 DCMO, and 19 LVNC patients.

40 66 atrial; ventricular; RV, right ; FAC, /E', annular early diastolic ; RVS', RV free wall strain

Table 2: LV Myocardial Mechanics in IDCMO versus ILVNC

Variables	DCMO (n=26)	LVNC (n=26)	P value
Longitudinal Strain Patterns			
LV GLS	-9.92±3.67	-8.17±3.29	0.11
Basal LS	-10.4 ± 3.5	-9.9 ± 3.8	0.48
Mid LS	-10.1 ± 5.1	-8.0 ± 4.0	0.25
Apical LS	-9.9 ± 4.9	-8.5 ± 4.2	0.38
Rotation Patterns			
*Apical Rotation	3.0° (2.3°)	3.0° (2.7°)	0.46

*Basal Rotation	-3.1° (2.8°)	-2.4° (2.9°)	0.10
***Net Twist**	**6.5° (3.0°)**	**5.4° (4.6°)**	**0.03**

*Data presented as median and interquartile range.

70

Longitudinal patterns were measured in 18 ILVNC and 26 IDCMO patients. Rotation patterns were measured in 22 DCMO patients and 23 LVNC patients.

Table 3: Biomarkers of inflammation and fibrosis of participants with IDCMO versus ILVNC

Variables	IDCMO (n=26)	ILVNC (n=26)	P value
* Fas/APO-1	6316 (2435)	6307 (2432)	0.68
Log Fas/APO-1	8.83 ± 0.42	8.73 ± 0.27	0.33
*MMP1	3662 (2757)	4167 (2131)	0.55
logMMP1	8.22 ± 0.64	8.27 ± 0.56	0.79
*TIMP1	175493 (47790)	185531 (81746)	0.92
Log TIMP1	12.12 ± 0.20	12.17 ± 0.27	0.38
MMP1/TIMP1 ratio	0.024 ± 0.017	0.023 ± 0.012	0.78
Log MMP1/TIMP1	-3.89 ± 0.60	-3.90 ± 0.59	0.94
*Pro Collagen 1	15739 (11926)	15995 (8726)	0.80
Log Pro-collagen 1	9.56± 0.80	9.50 ± 0.88	0.79

23

and .

Procollagen-1 (procollagen type 1),)

and Fas/APO-1 (apoptosis antigen-1). Pro Collagen 1 measured in 24 DCMO patients.

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Appendix 6: Certificate of submission for examination

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Full name	Samantha Heidi Nel		
Student number	1021713		
Title of submitted Research Project: Left ventricular noncompaction – insights into the pathophysiological mechanisms and mechanisms and consequences of LV dysfunction *NB: If this title is different to your previously approved title, no further action can be taken by the Faculty Office un a change of title has been approved.*			
Contact no	0728843294	E-mail	Samantha.nel@wits.ac.za

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6. I understand that I may not graduate unless my University fees have been paid in full.
7. My Supervisor(s) names, departments, telephone numbers and email addresses are as follows:

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Telephone	0837120094	E-mail	dressop@mweb.com

List all publications, which you have published in peer-reviewed journals from your postgraduate research report/dissertation/thesis during the course of your studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

Echocardiographic indices of the left and right heart in a normal black african population
Journal name, year, volume and page numbers: JASE 2020, 33:358-367

Prevalence and significance of Isolated left ventricular non-compaction phenotype in normal black Africans using echocardiography
Journal name, year, volume and page numbers: IJC Heart and Vasculature 2020, 30:100585

Signature of candidate:  Date: 31 March 2022

Appendix 7: Publication 1

Echocardiographic Indices of the Left and Right Heart in a Normal Black African Population

Samantha Nel, Mmed, Petros Nihoyannopoulos, MD, FACC, FESC, FRCP, Elena Libhaber, MSc, PhD, Mohammed R. Essop, MD, FACC, FRCP, Claudia Ferreira dos Santos, Mmed, Hiral Matioda, BSc, Claire Waterworth, MD, Sacha Grinter, BA-Hons, BSE, Ruchika Meel, MD, PhD, and Ferande Peters, MD, FACC, FRCP, *Johannesburg, South Africa; and London, United Kingdom*

Background: It is unknown whether ethnic differences occur with regard to right heart echocardiographic parameters. The aim of this study therefore was to establish normative values of left and right heart parameters in a black African population and to evaluate the effect of age and body mass index (BMI) on specific right ventricle (RV) parameters.

Methods: Two hundred fifty-three normal subjects were prospectively studied. A standardized echocardiographic examination was conducted with the RV focused view used to derive RV measurements. All left and right heart measurements were made in accordance with the American Society of Echocardiography 2015 chamber guideline recommendations. Right ventricle free wall strain was assessed using an RV focused apical four-chamber view.

Results: The average age was 36.3 ± 12.2 years, and 59% of patients were female. The mean left ventricular ejection fraction was 62.3% ± 5.7%. The RV linear measurements (RV base, 31.0 ± 4.5 mm; midcavity, 26.3 ± 5.8 mm) were not associated with sex, age, or BMI except for the RV length (64.6 ± 8.9 mm), which was greater in male patients. Tricuspid annular plane systolic excursion (TAPSE) was 21.7 ± 2.8 mm, fractional area change was 42.1% ± 5.5%, tricuspid annular peak systolic velocity RV S' was 12.1 ± 1.9 m/sec, and RV free wall strain was –31.5% ± 8.6%. Age and BMI were not associated with right atrial (RA) volumetric measurements, RV linear measurements, or any RV functional parameters except TAPSE and RV A', which increased with BMI.

Conclusions: This study establishes normal left and right heart parameters in a black African population. Aging was not associated with RA or RV parameters except for RV E' and A'. BMI does not affect RA/RV measurements but may cause variability in TAPSE and RV A'. (J Am Soc Echocardiogr 2020;33:358-67.)

Keywords: Echocardiography, Right ventricle, African, Normal

Echocardiographic assessment of the right ventricle (RV) is technically challenging. However, parameters reflecting right ventricular (RV) function have proven to be prognostically important in several diseases, including coronary disease, valvular disease, and heart failure.[1-5] Thus accurate assessment of RV function is crucial but may, like most echocardiographic parameters, be influenced by ethnicity, age, variations in body habitus, and sex.[6] Current guidelines provide reference values for parameters reflecting RV size and function but are limited in that they do not fully account for differences in body surface area (BSA) and ethnicity.[7-9]

Several studies of RV parameters are based predominantly on data from Caucasians.[8-10] A recent study by the ECHO normal collaboration highlighted that ethnic differences may occur with regard to certain echocardiographic parameters.[11] Ethnicity may cause variation in BSA and body mass index (BMI) and thus may directly influence echocardiographic measures.[11-13] However, in some instances, variability of some echocardiographic measurements may occur among different ethnic groups despite indexing for BMI and BSA. This may reflect differences in genetic factors that may impact cardiac chamber size and remodeling.

There is a paucity of data with regard to certain left heart echocardiographic parameters, and no prior studies have been conducted on right heart echocardiographic parameters in normal African populations.[14] Consequently, the applicability of current RV

From the Division of Cardiology, Chris Hani Baragwanath Academic Hospital (S.N., M.R.E., H.M., S.G., R.M., F.P.), School of Clinical Medicine (E.L.), and the Cardiovascular Pathophysiology and Genomics Research Unit (C.F.d.S., F.P.), University of the Witwatersrand, Johannesburg, South Africa; and Imperial College London, National Heart and Lung Institute, Hammersmith Hospital, London, United Kingdom (P.N., C.W.).

This study was funded by the Cardiology Division at Chris Hani Baragwanath Academic Hospital.

Conflicts of interest: None.

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Appendix 8: Publication 2

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Prevalence and significance of isolated left ventricular non-compaction phenotype in normal black Africans using echocardiography ☆

Samantha Nel [a], Bijoy K. Khandheria [b,*], Elena Libhaber [a], Ferande Peters [a,c], Claudia Ferreira dos Santos [a,c], Hiral Matioda [a], Sacha Grinter [a], Nirvathi Maharaj [a,c], Mohammed R. Essop [a]

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ABSTRACT

Background: Several large, prospective screening studies of predominantly Caucasian patients have suggested that hypertrabeculation may not necessarily be pathologic unless there is concomitant left ventricular (LV) dysfunction, LV dilatation, history of arrhythmia, family history, or characteristic gene mutations. This conundrum may be magnified in blacks, in whom hypertrabeculation and LV hypertrophy is more common. We therefore investigated the frequency of hypertrabeculation/isolated LV non-compaction (ILVNC) phenotype in normal black Africans and evaluated LV function using sensitive measures of deformation and twist.

Methods: Two hundred and fifty-three volunteers were recruited and evaluated according to strict inclusion and exclusion criteria. Their mean age was 36.3 ± 12.2 years.

Results: Trabeculations were found in 12 (4.74%) participants. Three (1.2%) subjects had ≥ 4 LV trabeculations. The LV apex was the most common anatomical site for the location of trabeculations. Subjects with trabeculations were more likely to be males of a younger age, and had greater LV end-diastolic and end-systolic parameters and lateral e'. However, 0.8% of the population fulfilled the Stollberger criteria, and none fulfilled the Jenni, Milwaukee, or Baragwanath criteria. All subjects in this study had normal rotation patterns with no differences in rotational parameters or net twist.

Conclusions: Trabeculations may be found as a normal variant in black Africans. Assessing trabeculations alone may infer ILVNC; however, utilizing the more comprehensive ILVNC criteria enables differentiation of a possible LVNC phenotype. Normal individuals with hypertrabeculation have normal LV function and normal rotation patterns, with no differences in rotational parameters or net twist.

1. Introduction

Two-dimensional (2D) echocardiography is the basis for identifying isolated left ventricular noncompaction (ILVNC). Currently there are several echocardiographic criteria used to diagnose ILVNC [1]. The major problems with utilising echocardiography for the diagnosis relate to the lack of a gold standard to compare these criteria, the poor reproducibility when applying these criteria, and that in some instances the phenotype of ILVNC has been observed in clinical scenarios that may not imply disease, such as in athletes and pregnant women [2–4]. In patients with normal ejection fraction (EF), the differentiation of ILVNC from a normal variant can be challenging.

The potential impact of race on ILVNC diagnosis has been highlighted in several studies that suggest that trabeculations may be more common in individuals of African ancestry [1,2,5–7]. Among African individuals, it is possible to differentiate normal individuals from patients with ILVNC with a low EF by using a more comprehensive set of echocardiographic criteria (Baragwanath criteria),

Abbreviations: CHBH, Chris Hani Baragwanath Hospital; ILVNC, isolated left ventricular noncompaction; IVSd, interventricular septal wall thickness in diastole; LVEDD, left ventricular end-diastolic diameter; NC/C, noncompacted to compacted; PWD, posterior wall thickness in diastole.

* All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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