EVALUATION OF THE LEFT VENTRICULAR EJECTION FRACTION POST RIGHT VENTRICULAR PACING AT INKOSI ALBERT LUTHULI CENTRAL HOSPITAL (IALCH), DURBAN, KWAZULU-NATAL (KZN)

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As the candidate's supervisor, I have approved this thesis for submission.

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I, Sherlina Kasipersad, declare that

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Executive Summary:

Since the implantation of the first artificial pacemaker in 1958, these devices have become the treatment of choice in bradycardias. Despite its widespread use, only a few studies have looked at the effects of single chamber right ventricular(RV) pacing on left ventricular(LV) function in patients with sinus node dysfunction or atrioventricular node dysfunction. In addition, these studies have produced conflicting results with no consensus reached. Furthermore, the limitation to these studies were the small sample sizes and the absence of sequential echocardiographic monitoring of LV function in each patient. To the best of the authors' knowledge, no such studies have been conducted in South Africa.

This study reviewed data collected from Inkosi Albert Luthuli Central Hospital (IALCH), which is a government hospital in Durban, KwaZulu-Natal (KZN), South Africa. The objective of the study was to evaluate the effects of RV pacing on LV function in a setting where the majority of patients requiring a permanent pacemaker receive single chamber RV apical pacing. The focus of this study was to assess the effect of RV pacing on LV function by assessing the ejection fraction(EF), on echocardiography, pre and post pacemaker insertion.

A retrospective chart review of 465 patients managed at the IALCH pacemaker clinic from 2003 up to 2012 was undertaken.

Adult patients 18 years and older with a documented EF at the time of insertion of a pacemaker were included in the study.

Patients were excluded from the study if they had coronary artery disease (CAD), unrepaired valvular heart disease, atrial fibrillation or dual chamber pacemakers.

After enforcing the exclusion criteria, 430 patients were excluded and only 35 patients were eligible for the study.

LV dysfunction was pre-defined as a left ventricular ejection fraction (LVEF) of < 50%.

This study showed that RV pacing did not have a statistically significant effect on LV function post pacemaker insertion, based on the assessment of EF.

The study was limited by the low number of eligible patients as it was a retrospective study and obtaining data was difficult as most patients who require a pacemaker do not routinely have a baseline echocardiograph done prior to insertion of the pacemaker. Another limiting factor in the study was that EF was the only modality of LV function that was assessed. Moreover, evaluation of the EF on echocardiography is subjective and user dependent. International studies have shown that the site of RV pacing has an impact on the degree of LV dyssynchrony and function. This factor could not be assessed in the current study as the site of RV pacing was not documented and was not standardised.

Pacing in the correct clinical context is a necessity and is lifesaving. Current literature shows that RV pacing is a safe, relatively simple, convenient procedure that is well tolerated and is effective. This study showed no deterioration in LV function in patients post RV pacemaker insertion, which is important as the RV remains the most common site of lead placement especially in the resource limited state sector. Some studies have reported that RV pacing is associated with LV dysfunction. However, since there is a paucity of level 1 evidence regarding this aspect of RV pacing, the need for prospective studies on the long-term effects of RV pacing on LV function is required. In addition, the impact of alternative pacing sites on LV function should be explored.

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Part 1: The Review of Literature

THE EFFECTS OF RIGHT VENTRICULAR PACING ON LEFT VENTRICULAR FUNCTION

1. Introduction:

More than 1 million pacemakers and approximately 400 000 implantable cardioverter defibrillators (ICDs) are implanted worldwide each year. Although there remains a preference for single chamber ventricular pacing in developing countries, 70% of pacemakers presently implanted worldwide are dual-chamber systems.[1]

Cardiac pacing is an effective treatment in the management of patients with bradyarrhythmias and tachyarrhythmias. It is the only effective treatment for patients with sick sinus syndrome and atrioventricular conduction disorders. Pacing of the right ventricle (RV) is a standard, widespread procedure because it is convenient, easily accessible, well-tolerated, effective and usually provides appropriate sensing and threshold parameters. [2,3] With the appearance of new indications for cardiac pacing which include patients with heart failure and left bundle branch block and the benefits of cardiac resynchronization therapy (CRT), the benefits of RV pacing has been questioned. There is increasing indirect evidence from international studies that RV pacing may have detrimental effects on (left ventricular) LV function.[1] LV dyssynchrony was found to be a critical factor in causing LV dysfunction. [4]

However, the effects of RV pacing on LV function in KwaZulu-Natal (KZN) remain unclear as no local studies have been done to establish the effect of RV pacing on LV function. This is a concern because the RV is the most common site of pacemaker insertion in the state sector due to the lack of resources and skilled staff.

This study set out to determine the effects of RV pacing on LV function by assessing the ejection fraction (EF) on echocardiography pre and post pacemaker insertion in the local South African context. A retrospective chart review of patients attending the Inkosi Albert Luthuli Central Hospital (IALCH) pacemaker clinic over a 10 year period was conducted.

In this paper we were able to show no statistically significant change in EF pre and post pacemaker insertion.

2. History of cardiac pacing:

In the 1920's and 1930's Dr Mark Lidwell of Australia and Dr Albert Hyman of the United States developed external cardiac pacemakers for clinical application. In 1958 the first internal cardiac pacemaker, designed by a Swedish team led by Ake Senning, a physician and Rune Elmqvist, an engineer was implanted in a patient with heart block. Over the next 3 decades a series of improvements and additions made the implantable devices more effective and reliable. In the early 1980's several advances were reported which included the creation of the dual chamber pacemaker and the development of rate responsive devices. This made a great improvement in the quality of life and life expectancy.[5]

3. Indications for cardiac pacing:

Initially pacing had an exclusively palliative role for patients with heart block and severe symptomatic bradycardia.[3] Current pacing practice is undergoing continuous and substantial changes. Cardiac pacing is now the treatment of choice in severe and symptomatic bradycardia.[6] Cardiac pacing remains the only effective therapy for patients with sick sinus disease despite the early recognition that the stimulation of this site leads to an abnormal contraction pattern by bypassing the physiological conduction system. [3] Numerous studies have shown symptomatic and functional improvement by cardiac pacing of patients with atrioventricular blocks and in patients with chronic, drug-refractory atrial fibrillation. Novel indications for cardiac pacing include drug-refractory heart failure and atrial fibrillation.[1,3]

With the appearance of novel pacing indications, the effect of the pacing site on cardiac function has become a critically important issue. It seems like the classical pacing site in the RV is no longer the gold standard because of the possible disadvantageous effects on cardiac function. [3]

4. Pathophysiology of RV pacing:

Pacing at virtually any ventricular site disturbs the natural pattern of activation and contraction because conduction of the electrical wave front takes place slowly through ventricular

myocardium rather than through the His-Purkinje system.[7]This results in the electrical wave front propagating more slowly and this induces heterogeneity in electrical activation of the myocardium, comparable to left bundle branch block. This is characterized by a single breakthrough of the electrical wave form at the interventricular septum and subsequent delayed activation at the infero-posterior base of the LV.[2,7]

Stimulation of the right ventricle leads to an abnormal electrical and mechanical activation pattern by bypassing the physiological conducting system. [3] It alters the electrical activation of the left ventricle and leads to dyssynchrony in left ventricular contraction, resulting in impaired haemodynamic function. [8]

Clinical and experimental studies examining RV pacing observed that this technique caused a prolonged QRS duration, left ventricle asymmetrical hypertrophy, dilatation, remodeling, mitral valve regurgitation, altered myocyte histology, reduced exercise capacity and coronary perfusion abnormalities. [4]

More than 80 years ago, it was shown that ventricular pacing results in adverse haemodynamic consequences in mammals. This finding has been replicated in numerous animal experiments and more recently in human patients. From these studies, the cause of the reduction in pump function was shown to be asynchronous electrical activation.[7]

The RV apex has become the most common site for placement of the pacemaker lead. The RV apex is convenient and easy for the implanter to reach and yields stable mechanical positions and stimulation thresholds.[7]

Similar to the changes in electrical activation of the ventricles, the mechanical activation pattern of the LV is changed during RV apical pacing. Importantly, it disrupts the onset and the pattern of mechanical contraction of the LV. Several animal studies have demonstrated that the early activated regions near the pacing site exhibit rapid early systolic shortening, resulting in pre-stretch of the late-activated regions. The affected regions exhibit an increase in (delayed) systolic shortening, imposing systolic stretch to the early activated regions exhibiting premature

relaxation. This abnormal contraction pattern of the various regions of the LV may result in a redistribution of myocardial strain and work and subsequent less effective contraction.[2]

Both the abnormal electrical and mechanical activation pattern of the ventricles can result in changes in cardiac metabolism and perfusion, remodeling, haemodynamics, and mechanical function. Even in the absence of coronary artery disease, myocardial perfusion defects may be present in up to 65% of the patients after long-term RV apical pacing and are mainly located near the pacing site.[2]

The table below taken from Laurens *et al* [2] summarises the effects of RV apical pacing.

Acute and Long-Term Effects of RV Apical Pacing [2]

Changes in electrical activation and mechanical activation
Metabolism/perfusion
Changes in regional perfusion
Changes in oxygen demand
Remodeling
Asymmetric hypertrophy
Histopathological changes
Ventricular dilation
Functional mitral regurgitation
Haemodynamics
Decreased cardiac output
Increased LV filling pressures
Mechanical function
Changes in myocardial strain
Interventricular mechanical dyssynchrony
Intraventricular mechanical dyssynchrony

5. Clinical Implications of RV pacing:

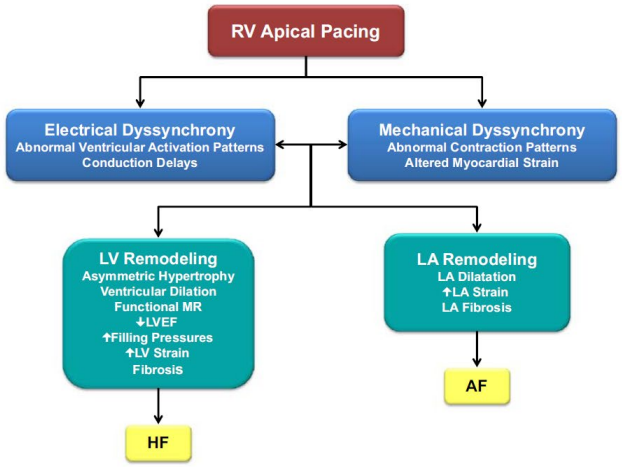

Figure 1. Mechanisms by which right ventricular (RV) apical pacing causes heart failure (HF) and atrial fibrillation (AF). LA indicates left atrial; and LVEF, left ventricular ejection fraction.

The above figure 1 taken from AM Gillis[1] highlights the mechanisms by which RV apical pacing causes heart failure and atrial fibrillation.

RV pacing has been shown to cause heart failure symptoms with and without previous systolic left ventricular dysfunction.[9] Unfortunately, the exact amount of RV apical pacing that negatively affects cardiac function remains unclear from the trials. A certain amount of ventricular pacing may actually be physiologically beneficial because it maintains atrio-ventricular conduction. At the same time, the negative effects of RV apical pacing may be more pronounced in certain patient populations. In particular, patients with underlying conduction disease and patients with ischaemic heart disease may be at risk. Furthermore, it has been suggested that patients who require pacing for a longer period of time and patients with depressed LV function at baseline are more susceptible to the deleterious effects of RV apical pacing. More studies are therefore needed to fully understand the beneficial and deleterious effects of RV apical pacing and to better identify the patients who are at risk for the detrimental effects of RV pacing.[2]

6. Pacing sites:

The effect of the pacing site on cardiac function has become a critically important issue and a subject of consideration since the appearance of new indications for cardiac pacing, which include heart failure and atrial fibrillation.[3] The ventricular pacing site has a major effect on LV function. The optimal pacing lead location for patients with a standard indication for ventricular pacing remains controversial.[4]From the larger pacing mode selection trials and the observational studies, there is a clear association between conventional right ventricular pacing and the risk of adverse events. However, in daily clinical practice not all patients who receive right ventricular pacing will experience adverse events. [2]

The RV apex is the preferred site of RV lead placement because of the ease of implantation and the low risk of lead dislodgement.[1] However, pacing of the RV apex can alter the electrical LV activation sequence and lead to dyssynchrony in LV contraction, resulting in impaired haemodynamic function.[8] There is growing evidence to support that LV free wall pacing and not RV apical pacing improves LV contraction in patients with heart failure and intraventricular conduction delays.[10]

The potential benefit of pacing from non-right ventricle apical sites that can theoretically closely simulate the normal cardiac electrical activation sequence needs to be explored further.[10] It is still unclear why some patients acutely develop ventricular dyssynchrony and others do not. This may be due to the subtle differences in the location of the pacing lead within the RV apex, and thus the proximity to the Purkinje system. Echocardiographic techniques used to assess ventricular dyssynchrony may not be sensitive enough to detect small changes in electromechanical activation. Therefore, larger and longer term clinical trials are needed to identify the optimal pacing site.[2]

Pacing from the right ventricle outflow tract, septal pacing and direct His bundle pacing have been suggested as alternative pacing sites as they are in closer proximity to the normal conduction system and may result in less electrical activation delay and less mechanical dyssynchrony. [2]

7. Important Clinical Trials:

The following supplementary table has been taken from AM Gillis [1]

Table 1:

Study	Patients	Design	Outcomes
DAVID[11]	506 patients with ICD indication	Prospective randomized DDDR lower rate 70bpm vs Backup VVI pacing lower rate 40bpm	1.61 increased relative risk of death or HF hospitalization
MOST Substudy[12]	1339 patients SND pacing indication QRS< 120ms	Retrospective analysis comparing DDDR vs VVIR pacing	Cumulative % VP > 40% in DDDR mode associated with 2.8 fold risk of HF hospitalization; cumulative % VP > 80% in VVIR mode associated with 2.5 fold risk of HF hospitalization; risk of developing AF increased by 0.7% or 1% for each 1% increment in cumulative % VP up to 80% in VVIR & DDDR groups respectively
SAVE PACe[13]	1065 patients SND pacing indication Normal QRS duration and AV conduction	Prospective randomized DDDR (AV delays 120-180ms) vs DDDR with algorithms to minimize ventricular pacing	Median % VP 9.1 vs 99% in DDDR with minimal VP algorithms vs conventional DDDR; 40% reduction in relative risk of AF in DDDR group with algorithms to reduce VP compared to conventional DDDR.
PACE[14]	177 patients Bradycardia pacing indication LVEF ≥ 45%	Prospective randomized BiV vs DDDR pacing	LVEF lower in DDDR vs BiV-pacing group 954.8+/-9.1% vs 62.2+/-7%, P<0.001) No difference in HF events
BLOCK HF[15]	691 patients High grade AV block pacing LVEF ≤ 50%	Prospective randomized BiV vs RV apical pacing (pacemaker or ICD based on clinical indications)	Significant reduction in primary outcome (composite endpoint of death, urgent HF visit requiring intravenous drug therapy or ≥ 15% increase in LVESV index) in BiV group compared to RV pacing group
MADIT[16]	567 ICD patients 65% RV paced ≤ 50%	Retrospective analyses	During late phase of extended follow-up mortality increased in patients with % RV pacing > 50% without baseline LBBB.

SND – sinus node disease

BiV – biventricular

LBBB – left bundle branch block

VP – ventricular pacing

It is important to emphasize that the adverse outcomes reported in the table have been dependent on a high cumulative percentage of RV pacing, generally more than 40%.[12,17,18] Furthermore, the increased risk of heart failure reported has been predominantly observed in those with pre-existing LV systolic dysfunction.[1]

The data that indicates that RV pacing causes heart failure over time in patients with a normal baseline LV function is extremely weak. [1] The Danish Multicenter Randomized Trial on Single Atrial Lead Pacing versus Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) study looked at patients with sinus node dysfunction and showed no correlation between the development of heart failure and RV pacing. Furthermore, although adverse LV remodelling characterized by LV chamber enlargement and reduction in LVEF has been described in some patients with congenital complete heart block after pacemaker implantation, the majority of these patients did not develop changes in systolic function nor did they develop symptomatic heart failure when followed up for prolonged periods of time.[1]

There is conflicting data regarding the differences between RV and biventricular pacing on the LV function.

The Preventing Ventricular Dysfunction in Pacemaker Patients without Advanced Heart Failure (PREVENT – HF) study was the first randomized controlled multi-centre trial comparing conventional RV versus biventricular pacing in patients with atrioventricular block who need bradycardia support. This study did not demonstrate significant LV volume differences between RV apical and biventricular pacing in patients who had been diagnosed with atrio-ventricular block and had been paced for more than 12 months.[19]

The Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization (BIOPACE) study concluded that there was a statistically insignificant difference between biventricular and RV pacing in patients with atrio-ventricular block who needed implantation of a permanent pacemaker.[20]

The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial randomised patients with atrio-ventricular block, New York Heart Association (NYHA) symptom class I-III heart failure, and LVEF ≤50% to biventricular or RV pacing. This study showed that cardiac structure and function improved with biventricular pacing for patients with atrio-ventricular block and LV systolic dysfunction. However, this trial was greatly limited by the inclusion of patients with EF of less than 30%.[20]

A sub-study of the Mode Selection Trial (MOST) demonstrated a strong association between right ventricular pacing and the risk of heart failure hospitalisation and atrial fibrillation in physiological pacing and ventricular pacing.[2]

It has been suggested that patients with moderate to severe LV dysfunction and a standard pacemaker indication may actually benefit from CRT instead of RV apical pacing alone.[2] A number of observational studies and randomized trials have performed a head-to-head comparison between the 2 pacing modes. These studies have been summarised in the table below.

Randomized Clinical Trials Comparing RV Apical Pacing Versus CRT [2]

Table 2:

Trial	n	Design	Inclusion Criteria	Primary End Point	Secondary End Point	Comment
MUSTIC [21]	43	Crossover	Chronic heart failure LV systolic	6MWT	Peak Vo_2 QOL Heart failure	CRT modestly superior over RV pacing for 6MWT and peak Vo_2

Trial	n	Design	Inclusion Criteria	Primary End Point	Secondary End Point	Comment
			dysfunction Persistent AF Ventricular pacing QRS >200 ms 6MWT <450 m		hospitalization Mortality Patient pacing preference	No difference in QOL
OPSITE [22]	56	Crossover	AVN ablation and PM implantation CRT	QOL 6MWT	Subgroup analysis of • QOL • 6MWT	CRT modestly superior over RV pacing for QOL and 6MWT
PAVE [23]	184	Parallel arms	AVN ablation and PM implantation	6MWT	QOL LVEF	CRT superior over RV pacing for 6MWT and LVEF No differences in QOL
HOBIPACE[24]	30	Crossover	LV systolic dysfunction Permanent ventricular pacing	LVESV LVEF Peak Vo_2	NYHA functional class QOL NT-proBNP Exercise capacity LV dyssynchrony	CRT superior over RV pacing for LVESV, LVEF, peak Vo_2 CRT superior over RV pacing for secondary end points

Trial	n	Design	Inclusion Criteria	Primary End Point	Secondary End Point	Comment
Albertsen *et al*. [25]	50	Parallel arms	High-grade AV block	LVEF	LV dyssynchrony LV diastolic function • LA volumes • LV dimensions • NT-proBNP • 6MWT	No difference in LVEF No differences in secondary end points

AF = atrial fibrillation; AV = atrioventricular; AVN = atrioventricular node; CRT = cardiac resynchronization therapy; HOBIPACE = Homburg Biventricular Pacing Evaluation; LA = left atrial; LVESV = left ventricular end-systolic volume; MUSTIC = Multisite Stimulation in Cardiomyopathies Study; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OPSITE = Optimal Pacing SITE; PAVE = Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation; PM = pacemaker; AVB = atrioventricular block; AVJ = atrioventricular junction; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QOL = quality of life; QRS = QRS complex; SND = sinus node dysfunction; 6MWT = 6-min walk test; Vo_2 = maximal oxygen uptake

In the Homburg Biventricular Pacing Evaluation (HOBIPACE) trial, 30 patients with standard indications for permanent pacing and an LVEF ≤40% were randomized between RV pacing and CRT. After 3 months of pacing, crossover to the other pacing modality was performed. The LV end-systolic volume was 177.3 ± 68.7 ml at baseline and decreased modestly with RV pacing (160.2 ± 73.4 ml, $p < 0.05$). When compared with RV pacing, CRT significantly reduced LV end-systolic volume by 17% (133.1 ± 66.5 ml, $p < 0.001$). [24]

Although some trials have demonstrated a clear long-term benefit of CRT over RV pacing with regard to peak VO_2 or the distance walked during the 6-min walk test, others have demonstrated only modest or no benefit at all. [2,22,24]

In developing countries such as South Africa, RV pacing still remains the most common choice due to resource constraints, cost effectiveness and limited skilled staff.

8. Rationale for this study:

From the large pacing mode selection trials and observational studies, it has become apparent that a considerable amount of RV pacing may be associated with a worse clinical outcome. Unfortunately, it remains unclear if there is an "optimal amount" of RV pacing and which patients are most susceptible to the deleterious effects of RV pacing. The negative effects may be related to the induction of ventricular dyssynchrony by RV apical pacing. Future studies are needed to address these remaining questions.[2] Additional analyses will perhaps identify cohorts of patients for whom biventricular pacing would confer a clear benefit.

All the literature is from studies done abroad and limitations to these studies were the small sample sizes and the absence of sequential echocardiographic monitoring of the LV function in each patient.

RV pacing is an important tool in the South African context, where resources and skilled staff are limited. This study attempted to elucidate the local South African experience by evaluating the effects of RV pacing on LV function by assessing the EF on echocardiography in patients attending the pacemaker clinic at IALCH from 2003 to 2012.

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Part 2: A submission ready manuscript (as per the South African Medical Journal Author Guidelines)

Evaluation of the ejection fraction post right ventricle pacemaker insertion at Inkosi Albert Luthuli Central Hospital (IALCH), Durban, KwaZulu-Natal (KZN)

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Abstract

Background

Pacing of the right ventricle has become a standard, widespread procedure. In recent years, the potential detrimental effects of RV pacing have been studied with one of the complications being the deterioration of the left ventricular ejection fraction (EF) as a direct result of RV pacing.

Objective

To evaluate the effects of RV pacing on LV function by assessing the EF on echocardiography, pre- and post- pacemaker insertion, at Inkosi Albert Luthuli Hospital (IALCH), a government hospital in Durban, KwaZulu-Natal(KZN).

Methods

A retrospective chart review of 465 patients managed at IALCH pacemaker clinic from 2003 up to 2012 was undertaken. Adult patients 18 years and older with a documented EF pre- and post-RV pacemaker insertion were included. Patients were excluded if they had coronary artery disease (CAD), unrepaired valvular heart disease, atrial fibrillation or dual chamber pacemakers. RV pacing was performed through insertion of a lead in the subclavian vein with placement of the sensing and pacing electrode in the RV apex. The EF was measured using 2D echocardiography and calculated using the Simpsons method. LV dysfunction was defined as an EF <50%.

The Intercooled Stata Version 13 Package was used to analyse the data. Descriptive statistics were used to present categorical variables. The mean and standard deviation were used to analyse continuous variables and the percentages of frequencies. Two group comparisons were made using a two sample *t* test. The two sample *t* test was used to calculate the change in the EF between baseline and follow-up. The Kruskal Wallis equality test was used to assess categorical variables when comparing more than two subgroups due to the small study numbers. A *p* value of <0.05 was considered statistically significant.

Results
Of the 465 patients screened, 35 patients satisfied the inclusion criteria with pre- and post-pacemaker insertion ejection fractions. The mean age was 62 years. Complete heart block (57%) and second degree heart block (20%) were the main indications for pacing. The VVI pacing mode was applied to majority (54%) of the patients. The study did not show any significant decline in the LVEF in patients with RV pacing, p= 0.10. Age and gender had no impact on the LVEF. Similarly, hypertension, diabetes mellitus, dyslipidaemia and valve repair had no significant impact on the LVEF. 8 patients had LV dysfunction at baseline, of these 1 had a deterioration in EF from 42% to 36%, 2 remained the same and 5 showed a mean increase in EF of 5.4% between baseline and follow-up, p = 0.03.

Conclusion
This study showed no significant change in EF following pacemaker insertion. This is important as the RV remains the most common site of lead placement, especially in the resource limited environment.

Keywords:
Dyssynchrony, echocardiography, ejection fraction, left ventricular function, right ventricular pacing

Abbreviations:

RV – right ventricle/ ventricular
LV – left ventricle/ ventricular
IALCH – Inkosi Albert Luthuli Hospital
KZN – KwaZulu-Natal
EF – ejection fraction
CRT - cardiac resynchronization therapy
CAD – coronary artery disease
LVEF – left ventricular ejection fraction
AV – atrioventricular

Background

Pacing of the right ventricle has become a standard, widespread procedure because it is convenient, easily accessible, well-tolerated, effective and usually provides appropriate sensing and threshold parameters. [1,2] Despite its widespread use, only a few studies have looked at the effects of single chamber right ventricular(RV) pacing on left ventricular(LV) function in patients with sinus node dysfunction or atrioventricular node dysfunction.[3] In addition, these studies have produced conflicting results with no consensus reached. Furthermore, the limitation to these studies were the small sample sizes and the absence of sequential echocardiographic monitoring of LV function in each patient. In recent years, the potential detrimental effects of RV pacing have been studied and LV dyssynchrony has been shown to be a critical factor in causing LV dysfunction. [4]
To the best of the authors' knowledge, no such studies have been conducted in South Africa.

Clinical and experimental studies examining RV pacing observed that this technique caused a prolonged QRS duration, LV asymmetrical hypertrophy, dilatation, remodeling, mitral valve regurgitation, altered myocyte histology, reduced exercise capacity and coronary perfusion abnormalities. [5] Stimulation of the RV leads to an abnormal electrical and mechanical activation pattern by bypassing the physiological conducting system. [2,6] It alters the electrical activation of the LV and leads to dyssynchrony in LV contraction, resulting in impaired haemodynamic function.[7]

RV pacing has been shown to cause heart failure symptoms with and without previous systolic LV dysfunction.[8] The Mode Selection Trial (MOST) showed an increased risk in hospitalisation in patients with RV pacing.[4,9] Unfortunately, the exact amount of RV apical pacing that negatively affects cardiac function remains unclear from the trials. The negative effects may be more pronounced in certain patient populations. Patients at risk of adverse effects of RV apical pacing include those with underlying conduction disease and patients with ischaemic heart disease. It has been suggested that patients who require pacing for a longer period of time and patients with depressed LV function at baseline are more susceptible to the deleterious effects of RV apical pacing.[4]

All the literature is from studies done abroad and limitations to these studies were the small sample sizes and the absence of sequential echocardiographic monitoring of the LV function in each patient. [4,6,9,11]

RV pacing is an important tool in the South African context, where resources and skilled staff are limited. This study attempted to elucidate the local South African experience by evaluating

the effects of RV pacing on LV function by assessing the EF on echocardiography in patients attending the pacemaker clinic at IALCH from 2003 to 2012.

This study reviewed data collected from Inkosi Albert Luthuli Central Hospital (IALCH), which is a government hospital in Durban, KwaZulu-Natal (KZN), South Africa. The objective of the study was to evaluate the effects of RV pacing on LV function in a setting where the majority of patients requiring a permanent pacemaker receive single chamber RV apical pacing. The focus of this study was to assess the effect of RV pacing on LV function by assessing the ejection fraction (EF), at echocardiography, prior to, and after pacemaker insertion.

Methods

Study Design:

Study Population – patients attending the pacemaker clinic at Inkosi Albert Luthuli Hospital (IALCH) from 2003 up to 2012.

Sample Strategy – retrospective chart review. The medical records of patients attending the pacemaker clinic over this period were reviewed.

Sample size – The sample size was determined by the number of patients who met the inclusion criteria over the study period. Of the 465 patients screened, 35 were eligible for the study.

Inclusion Criteria:
Adult patients 18 years and older with a documented EF pre- and post- pacemaker insertion were included.

Exclusion criteria:
Patients were excluded if they had coronary artery disease (CAD), unrepaired valvular heart disease, atrial fibrillation or dual chamber pacemakers.

Procedure of RV pacing:
RV pacing was performed through insertion of a lead in the subclavian vein with placement of the sensing and pacing electrode in the RV apex.

Measurement of EF:
EF was measured using 2D echocardiography and was calculated using the Simpson's method.[12]
LV dysfunction was defined as a left ventricular ejection fraction (LVEF) < 50%, as per the Heart Failure Society of South Africa and the European Society of Cardiology 2012 guidelines.[13]

Statistical Analysis:

The Intercooled Stata Version 13 Package was used to analyse the data. Descriptive statistics were used to present categorical variables. The mean and standard deviation were used to analyse continuous variables and the percentages of frequencies. Two group comparisons were made using a two sample *t* test. The two sample *t* test was used to calculate the change in the EF between baseline and follow-up. The Kruskal Wallis equality test was used to assess categorical variables when comparing more than two subgroups due to the small study numbers. A *p* value of <0.05 was considered statistically significant.

Results

Baseline patient characteristics

Of 465 patients screened, 35 satisfied the inclusion criteria with pre- and post- pacemaker insertion EF and were eligible for the study. The baseline characteristics and comorbidity profile of the study population has been summarised in Table 1. The mean age was 62 years with a M:F ratio of 7:3. Almost half the subjects had a history of hypertension. The most common indication (57%) for pacing was complete heart block, followed by second degree AV block (20%). Sick sinus syndrome and symptomatic bradycardia accounted for the remaining 22% of the patients. The VVI pacing mode was applied to the majority of patients. The average duration of pacing was 3.41 years.

Gender and age did not have an effect on the EF. Similarly, hypertension, diabetes mellitus, dyslipidaemia and valvular heart disease had no significant impact on the LVEF. Analysis of variance (ANOVA) showed no significant changes in the EF in patients with different pacemakers.

Table 1: Baseline characteristics of study patients and a correlation between patient variables

Variables	All Patients *n* = 35	Mean change in EF(%)	Standard deviation	*p* value
Sex, n (%)				0.55
- **Male**	11 (31%)	-2.09	9.3	
- **Female**	24 (69%)	-4.3	10.9	
Average age (years)	62 ±17.4			0.9
- **≤ 45**	6	-4	8.9	
- **> 45**	29	-3.6	10.8	
Indications for pacing, n (%)				0.35
- **Complete heart block**	20 (57%)	-3.4	10.3	
- **Second degree AV block**	7 (20%)	-2.2	11.8	

- **Symptomatic bradycardia**	4 (11%)	-0.5	13.9	
- **Sick sinus syndrome**	4 (11%)	-2.7	1.5	
Pacing Mode, n (%)				
- **VVI**	19(54%)	-0.1	9.3	
- **VVIR**	13(37%)	-8.3	11.1	
- **VDD**	3(9%)	-6	6	
Average duration of pacing (years)	3.41			
Duration of pacing, n (%)				0.31
- **<1 year**	12(34%)	-0.5	6.8	
- **1-5 years**	13 (37%)	-5	12.2	
- **>5 years**	10 (29%)	-5.7	11.3	
Co-morbidities, n (%)				
- **Hypertension (HPT)**	17(49%)	-1.5	10.3	0.26
- **Diabetes Mellitus (DM)**	7 (20%)	-10.4	12.1	0.05
- **Dyslipidaemia**	5 (14%)	1.6	4.9	0.22
Valvular heart disease (repaired), n (%)	7 (20%)	-1	10.2	0.45
- **Mitral valve replacement(MVR)**	3 (9%)			
- **Aortic valve replacement (AVR)**	3 (9%)			
- **Dual valve replacement (DVR)**	1 (3%)			

VVI - single chamber ventricular pacing; VVIR - single chamber ventricular pacing, rate responsive;
VDD - single chamber ventricular pacing with dual chamber sensing and inhibition

Evaluation of Ejection Fraction

Overall, amongst the 35 subjects, there was no significant change in mean EF from baseline EF (55%) to follow-up EF (52%), with an average change in EF of -3.6%, $p = 0.10$.

Of the 35 study subjects, the study identified 8 patients with LV dysfunction at baseline. (Table 2) None of the 8 subjects were previously diagnosed with CAD and were therefore included in the study. These subjects showed a mean increase in ejection fraction of 5.4% between baseline and follow-up EF, compared to the remaining 27 with normal LV function at baseline who showed a mean decrease of 6.33%. The difference was statistically significant, $p = 0.03$. Of the 8 patients, 2 had no change, and 1 showed a deterioration in EF between baseline and follow-up (Table 3).

Table 2: Clinical profile of subjects with reduced baseline EF

No	Baseline EF	Follow-up EF	Change in EF	Indication for pacing	Duration of pacing (yrs)	Pacing Mode	Co-morbidities
1	43	56	13	SB	4	VVI	HPT
2	42	36	6	CHB	2	VDD	Nil
3	40	49	9	CHB	1	VVI	HPT
4	43	43	-	AVB	4	VDD	Nil

5	42	52	10	AVB	2	VVI	MVR
6	40	40	-	CHB	1	VVI	HPT,DM
7	45	50	5	CHB	7	VVI	AVR
8	46	58	12	SB	1	VVI	HPT/ LIPID

Abbreviations as per Table 1

Of the 35 subjects, 11 had evidence of LV dysfunction at follow-up, of whom 4 subjects had reduced EF at baseline (Table 3). As expected, these patients showed a statistically greater change in EF compared to patients with preserved LV function at follow-up, with $p = 0.006$. Although the cause for this deterioration was not clearly established it was not thought to be due to CAD. The greatest change in EF (26%) between baseline and follow-up occurred in the subject with the longest duration of pacing (9 years).

Table 3: Clinical profile of subjects with reduction in EF at follow-up

No	Baseline EF	Follow-up EF	Change in EF	Indication for pacing	Duration of pacing (yrs)	Pacing Mode	Co-morbidities
1	68	42	26	CHB	9	VVI	DM
2	42	36	6	CHB	2	VDD	Nil
3	59	37	22	AVB	2	VVIR	Nil
4	54	38	16	CHB	2	VVIR	MVR
5	54	35	19	CHB	1	VVIR	Nil
6	43	43	-	AVB	4	VDD	Nil
7	40	40	-	CHB	1	VVI	DM, HPT
8	54	48	6	CHB	6	VVIR	HPT/ AVR
9	55	45	10	CHB	8	VVI	LIPID
10	65	45	20	SB	3	VVIR	HPT/ DM
11	40	49	9	CHB	1	VVIR	HPT

Abbreviations as per Table 1

Discussion

RV pacing and the effect on LV function

The main finding in this study was that RV pacing was accomplished without a significant change in EF in the majority of subjects. Age and gender had no impact on the change in EF. Hypertension, diabetes mellitus, dyslipidaemia, and valvular heart disease had no statistically significant change in EF.

An important finding in our study is that there was worsening of the EF in almost a quarter of the subjects. Although subjects included had no history of CAD, coronary angiograms were not performed in these subjects so it is not clear whether underlying CAD was present and could have accounted in part for deterioration in LV function. In the absence of overt coronary disease it appears that conventional RV pacing itself could be the mechanism since it has been shown that RV pacing produces a variable amount of ventricular dyssynchrony in most patients. Some studies have suggested that patients who require pacing for a longer period of time and patients with depressed LV function at baseline are more susceptible to the deleterious effects of RV pacing.[2,3]

From the large pacing mode selection trials and observational studies, it has become apparent that ~~R~~RV pacing may be associated with a worse clinical outcome. The Danish Multicenter Randomized Trial on Single Atrial Lead Pacing versus Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE) study showed no correlation between heart failure and RV pacing.[10] The Preventing Ventricular Dysfunction in Pacemaker Patients without Advanced Heart Failure (PREVENT – HF) study and The Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization (BIOPACE) study did not demonstrate statistically significant differences between biventricular and RV pacing.[9,11] The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) trial showed an improvement in cardiac function in patients with biventricular pacing.[10]

Unfortunately, it remains unclear if there is an "optimal amount" of RV pacing and which patients are most susceptible to the deleterious effects of RV pacing. The negative effects may be related to the induction of ventricular dyssynchrony by RV apical pacing. Future studies are needed to address these remaining questions.[6] Additional analyses will perhaps identify cohorts of patients for whom biventricular pacing would confer a clear benefit.

Limitations of the study

The study was clearly limited by the low number of eligible patients out of 465 subjects who underwent pacemaker insertion. Because of the retrospective nature of the study there was a lack of complete datasets. Most patients who require a pacemaker do not routinely have a baseline echocardiographic assessment done prior to insertion of the pacemaker. The greatest limitation of the study was that EF was the only modality of LV functioning that was assessed. Evaluation of the EF on echocardiography is subjective and user dependent. This study also lacked control variables.

Optimal pacing lead location

The optimal pacing lead location for patients with a standard indication for ventricular pacing remains controversial.[4] From the larger pacing mode selection trials and the observational studies, there is a clear association between conventional RV pacing and the risk of adverse events. However, in daily clinical practice not all patients who receive RV pacing will experience

adverse events.[2] Moreover, the RV pacing site is not standardised and this poses a limitation in establishing the optimal lead location for pacing.

Pacing from the RV outflow tract, septal pacing and direct His bundle pacing have been suggested as alternative pacing sites as they are in closer proximity to the normal conduction system and may result in less electrical activation delay and less mechanical dyssynchrony.[4] The potential benefit of pacing from non-right ventricle apical sites that can theoretically closely simulate the normal cardiac electrical activation sequence needs to be further explored. [12]

This study has highlighted that we have no local or international guidelines to aid clinicians in monitoring patients after pacemaker insertion. This issue needs to be addressed as the indications for pacing are expanding. Furthermore, the lead location in the RV is not standardised or documented in patients clinical records. Since the lead location may play a role in the development of LV dysfunction, this needs to be monitored in an attempt to establish the optimal pacing site. Also, since the duration of pacing may play a role in the development of LV dysfunction. This issue needs to be explored in future studies.

Conclusion

This study showed no significant change in EF in the majority of subjects undergoing pacemaker insertion. While current literature shows that RV pacing is a safe, simple, and effective, we have shown that almost a quarter of the subjects had deterioration in the EF for which there was no clear explanation and therefore possibly due to RV pacing associated LV dysfunction.

In the absence of clear monitoring guidelines, the authors recommend a standardised approach to all patients in whom RV pacing is considered appropriate, since RV pacing remains the most common site of lead placement, especially in the resource limited environment. Routine echocardiography to assess EF and more sensitive parameters of LV function such as tissue Doppler and strain imaging should be undertaken prior to insertion of the pacemaker or immediately thereafter. Regular monitoring at standardised time intervals with repeated echocardiography to monitor LV function using sensitive techniques to detect early changes in LV segmental contractility. Clear documentation of indications for pacing, pacing lead location, pacing mode and co-morbidities should be included. The finding of deterioration in LV contractility should be accompanied by a careful search for a course including coronary disease and myocarditis as well as an reappraisal of the pacing mode in such cases.

Conflicts of interest: None

Acknowledgements: None

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Appendices

Appendix 1: The final Study Protocol

TITLE OF THE STUDY:

The effects of right ventricular pacing on left ventricular function

AIM OF THE STUDY:

To determine the effect of right ventricular pacing on left ventricular function

SPECIFIC OBJECTIVES:

1. To determine if right ventricular pacing causes left ventricular dysfunction
2. To determine if there is a correlation between left ventricular function at the time of pacemaker insertion and subsequent deterioration of left ventricle function

BACKGROUND AND LITERATURE REVIEW:

THE EFFECTS OF RIGHT VENTRICULAR PACING ON LEFT VENTRICULAR FUNCTION

For more than 2 centuries, abnormalities of cardiac impulse formation and propagation have been recognized as potentially lethal causes of cardiovascular illness. The only effective treatment for symptomatic bradycardia caused sinus node dysfunction and atrioventricular block is cardiac pacing. [(1)]

Cardiac pacing has been in existence for more than 50 years and during that time both clinical practice and an impressive body of research have proved its effectiveness objectively in terms of patient's quality of life, morbidity and mortality. [(2)]

Pacing of the right ventricle has become a standard, widespread procedure because it is convenient, easily accessible, well-tolerated, effective and usually provides appropriate sensing and threshold parameters. [(1,3)] With the appearance of new indications for cardiac pacing which includes patients with heart failure and left bundle branch block and the benefits of cardiac resynchronization therapy, the use of right ventricular pacing has come into the spotlight. In recent years, the potential detrimental effects of right ventricular pacing has been studied and left ventricular dyssynchrony has been shown to be a critical factor in causing left ventricular dysfunction. [(4)]

Clinical and experimental studies examining right ventricle pacing observed that this technique caused prolonged QRS duration, left ventricle asymmetrical hypertrophy, dilatation, remodeling, mitral valve regurgitation, altered myocyte histology, reduced exercise capacity and coronary perfusion abnormalities.[(5)] Stimulation of the right ventricle leads to an abnormal electrical and mechanical activation pattern by bypassing the physiological conducting system. [(3)] It alters the electrical activation of the left ventricle and leads to dyssynchrony in left ventricular contraction, resulting in impaired haemodynamic function.[(6)] Dyssynchronous left ventricle activation during right ventricle pacing was described in small studies almost 30 years ago in mongrel dogs and in humans.[(7)]

Studies have shown that right ventricular pacing does not produce the same amount of dyssynchrony in all patients. Some studies have suggested that patients who require pacing

for a longer period of time and patients with depressed left ventricular function at baseline are more susceptible to deleterious effects of right ventricular pacing.[1,4] Other studies have shown that right ventricular pacing causes heart failure symptoms in patients with and without previous systolic left ventricular dysfunction, but the mechanical consequences are of greater importance in individuals with severely impaired left ventricle function. [7]

The optimal pacing lead location for patients with a standard indication for ventricular pacing remains controversial.[5] From the larger pacing mode selection trials and the observational studies, there is a clear association between conventional right ventricular pacing and the risk of adverse events. However in daily clinical practice not all patients who receive right ventricular pacing will experience adverse events. [4]

Pacing from the right ventricle outflow tract, septal pacing and direct His bundle pacing have been suggested as alternative pacing sites, they are in closer proximity to the normal conduction system and may result in less electrical activation delay and less mechanical dyssynchrony. [4] The potential benefit of pacing from non-right ventricle apical sites that can theoretically closely simulate the normal cardiac electrical activation sequence needs to be further explored. [8]

Noting that right ventricular pacing causes a broad QRS complex and produces dyssynchrony, the question arises whether patients who do not meet the criteria for cardiac resynchronization therapy would benefit from biventricular pacing rather than right ventricular pacing only. Biventricular pacing has been primarily introduced to correct pre-existing interventricular and intraventricular conduction delays, thereby improving ventricular function. Biventricular pacing has shown good results in patients with systolic heart failure. [1] Few clinical investigations have compared ventricular pacing sites in patients who do not meet the clinical requirements for cardiac resynchronization therapy. [5]

Since the implantation of the first artificial pacemaker in 1958, these devices have become the treatment of choice in bradycardias. Despite its widespread use, only a few studies have looked at the long term effects of only right ventricular pacing on left ventricular function in patients with sinus node dysfunction or atrioventricular node dysfunction. [9] Furthermore, the limitation to these studies were the small sample sizes and the absence of sequential echocardiographic variables of left ventricle function in each patient. To the best of our knowledge, no such studies have been done in South Africa. Thus there is a need for larger and longer term clinical trials to assess the effect of right ventricular pacing on left ventricular function and to address the effect of alternative pacing sites.

Pacemaker technology has evolved over the years from right ventricular pacing to dual chamber and now cardiac resynchronization therapy. Various therapeutic options have been suggested in patients requiring a conventional pacemaker. The upgrade to cardiac resynchronization therapy may partially reverse the deleterious effects of right ventricular pacing. New pacing strategies and alternative right ventricular pacing sites may prevent the induction of left ventricle dyssynchrony and the deterioration of left ventricular function. [4]

This study will review data collected from Inkhosi Albert Luthuli Central Hospital (IALCH), which a government hospital in Kwa-Zulu Natal. It will evaluate the effects of right ventricular pacing on left ventricle function in a setting where majority of the patients requiring a permanent pacemaker receive single chamber right ventricular pacing. It will assess whether there is a correlation between left ventricular function at the time of pacemaker insertion and subsequent development of left ventricular dysfunction.

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STUDY DESIGN:

Study Population – Patients attending Albert Luthuli Central Hospital (IALCH) Pacemaker Clinic from 2003 upto 2012

Sample Strategy – Since this is a retrospective study, no sampling methods will be used.

Statistical planning (variables/confounders) – left ventricular function, pre pacemaker insertion, post pacemaker insertion

Sample size – Depends on the number of patients that meet the inclusion criteria after screening

Inclusion criteria:

1. Age above 18 years

2. Patients with documented ejection fractions (EF) pre and post pacemaker insertion

Exclusion Criteria:

1. Coronary Artery Disease

2. Valvular Heart Disease - unrepaired

3. Atrial Fibrillation

4. Patients with dual chamber pacemakers

Data Collection methods and tools – this is a retrospective study and will use data that has already been collected

Data analysis techniques and statistical analysis:

The Statistical Package for Social Sciences (SPSS) version 21 will be used to analyze the data.

Descriptive statistics, which include frequency and percentage distribution tables, charts and graphs will be used to present categorical variables. Measures of central tendency (mean, median and mode) and dispersion (variance, range and standard deviation) will be calculated for continuous variables. The paired samples t test will be used in determining the link between right ventricular pacing and left ventricular dysfunction by comparing the ejection fraction before and after pacemaker insertion. If the data are not normal distributed an equivalent non parametric test will be performed.

STUDY LOCATION:

Inkhosi Albert Luthuli Central Hospital (IALCH) – Kwa-Zulu Natal

STUDY PERIOD:

Patients attending the Pacemaker Clinic at IALCH from 2003 – upto 2012

LIMITATIONS TO THE STUDY:

1. This is a retrospective chart review and obtaining data maybe be difficult
2. Most patients who require cardiac pacing do not routinely have a baseline echocardiograph prior to pacemaker insertion
3. Study does not have controls
4. Only one modality is being assessed – ejection fraction by echocardiography and this is subjective and user dependant

ETHICAL CONSIDERATIONS:

Patient confidentiality will be maintained at all times. Data will be collected on a password protected computer and I will be the only person with access to it. Patients will be identified by numbers.

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Appendix 2: Authorship Guidelines as per the South African Medical Journal (SAMJ).

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields.*References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and*Conclusion.*

Scientific letters will be considered for publication as shorter ***Research articles***.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minumum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets**(parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources.*Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.*Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name

of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

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As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).

8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Appendix 3: Ethical approvals

BREC approval:

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

24 October 2013

Dr. S Kasipersad
Department of Internal School of Medicine
Nelson R Mandela School of Medicine
University of KwaZulu-Natal
shelina@telkomsa.net

PROTOCOL: The long-term effects of right ventricular pacing on left ventricular function.
REF:BE068/13.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 13 March 2013.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 14 October 2013 to queries raised on 08 July 2013 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 24 October 2013.

This approval is valid for one year from **24 October 2013.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **12 November 2013.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor D.R Wassenaar
Chair: Biomedical Research Ethics Committee

Professor D Wassenaar (Chair)
Biomedical Research Ethics Committee
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban, 4000, South Africa
Telephone: +27 (0)31 260 2384 **Facsimile:** +27 (0)31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx
ounding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

Hospital approval:

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For **King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH)** studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Declaration of all funding applications / grants, please supply substantiating documentation.
5. Complete the attached KEH Form - *"Research Details"*

Once the document has been signed it should be returned to **Mrs Patricia Ngwenya:** Biomedical Research Ethics Administrator, Room N40, Govan Mbeki Building, Westville Campus, University of KwaZulu-Natal.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:
INKOSI ALBERT LUTHULI
HOSPITAL, 800 BELAIR ROAD;
CATO MANOR, DURBAN

Investigator/s:
Principal: DR SHERLINA KASIPERSAD
Co-investigator: DR KONNUSAMY
Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager: P.D. Reddy
Date: 10/10/2013

Site 2 address:
_____
_____
_____

Investigator/s
Principal: _____
Co-investigator: _____
Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:
_____
Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

Provincial approval:

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
10 – 103 Natalia Building, 330 Langalibalele Street
Private Bag x9051
Pietermaritzburg
3200
Tel.: 033 – 3953189
Fax.: 033 – 394 3782
Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 291/13
Enquiries : Mr X Xaba
Tel : 033 – 395 2805

Dear Dr S. Kasipersad

Subject: Approval of a Research Proposal

1. The research proposal titled **'The long-term effects of right ventricular pacing on left ventricular function'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 21/10/2013

Appendix 4: Data collection template

CASE NO	STUDY NO	SEX	AGE	AGE ≤45	AGE >45	INDICATION FOR PACING	PACING MODE	DURATION OF PACING	DURATION < 1YR	DURATION 1-5 YRS	DURATION 5-10YRS	BASELINE EF (BE)	BE < 50	BE ≥50	F/U EF (FE)	FE < 50	FE≥ 50	CHANGE IN EF	HPT	DM	LIPID	VALVE REPAIR	VALVE
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Appendix 5: Raw data

Legend for Data:
STUDY NO
- Represents unique number for each patient, to ensure patient confidentiality
SEX
1 = Male
2 = Female
AGE: ≤ 45 yrs or > 45 yrs
1 = Yes
2 = No
INDICATION FOR PACING
CHB – complete heart block
AVB - 2nd degree atrioventricular block
SSS – sick sinus syndrome
SB – sinus bradycardia
Pacing Mode
VVI - single chamber ventricular pacing
VVIR - single chamber ventricular pacing, rate responsive
VDD - single chamber ventricular pacing with dual chamber sensing and inhibition
Duration of pacing
1 = Yes
2 = No
Baseline ejection fraction (BE)/ Follow-up ejection fraction (FE) - subgroups <50 or ≥50
1 = Yes
2 = No
HPT – hypertension
DM – diabetes mellitus
LIPID – dyslipidaemia
VALVE REPAIR - valvular heart disease, repaired
HPT/ DM/ LIPID/ VALVE REPAIR
1 = Yes
2 = No
VALVE
0 = no valves
1 = mitral only
2 = aortic only
3 = mitral and aortic