

Effects of Selective Site Pacing On the Haemodynamics and Functional Recovery in Patients Requiring Permanent Right Ventricular Pacing

Albouaini K, Alkarmi A, Matata B, Modi S, Barker D, Patwala A, Pyatt J, Rao A, Gammage M, Wright D J

Conflict of Interest: None to declare

The right ventricular apex (RVA) has been the elective site for placing endocardial pacing leads since 1959 when Furman described the use of the transvenous route for pacemaker implantation(1).

This site was used because it was readily identified, easily accessible, and associated with a stable position with reliable chronic pacing parameters.....

(1) Furman S, Schwedel JB. An intracardiac pacemaker for Stokes-Adams seizures. N Engl J Med 1959 Nov 5;261:943-8.

It was recognised however, that pacing from the RVA did not reproduce normal ventricular conduction or contraction(2;3). Subsequent studies have confirmed a causal relationship between right ventricular apical pacing and heart failure, atrial fibrillation (AF), thromboembolic events and premature death (4-6).

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(6) Steinberg JS, Fischer A, Wang P, Schuger C, Daubert J, McNitt S, et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. *J Cardiovasc Electrophysiol* 2005 Apr;16(4):359-65.

Efforts to reduce right ventricular pacing have been suggested using prolonged atrioventricular (AV) delays and minimal right ventricular pacing algorithms.

However, this is not possible in patients with AV conduction abnormalities or following AV node ablation. Therefore, alternative right ventricular (RV) sites have been evaluated.

Such sites have provided similar long term safety and lead performance (7;8).

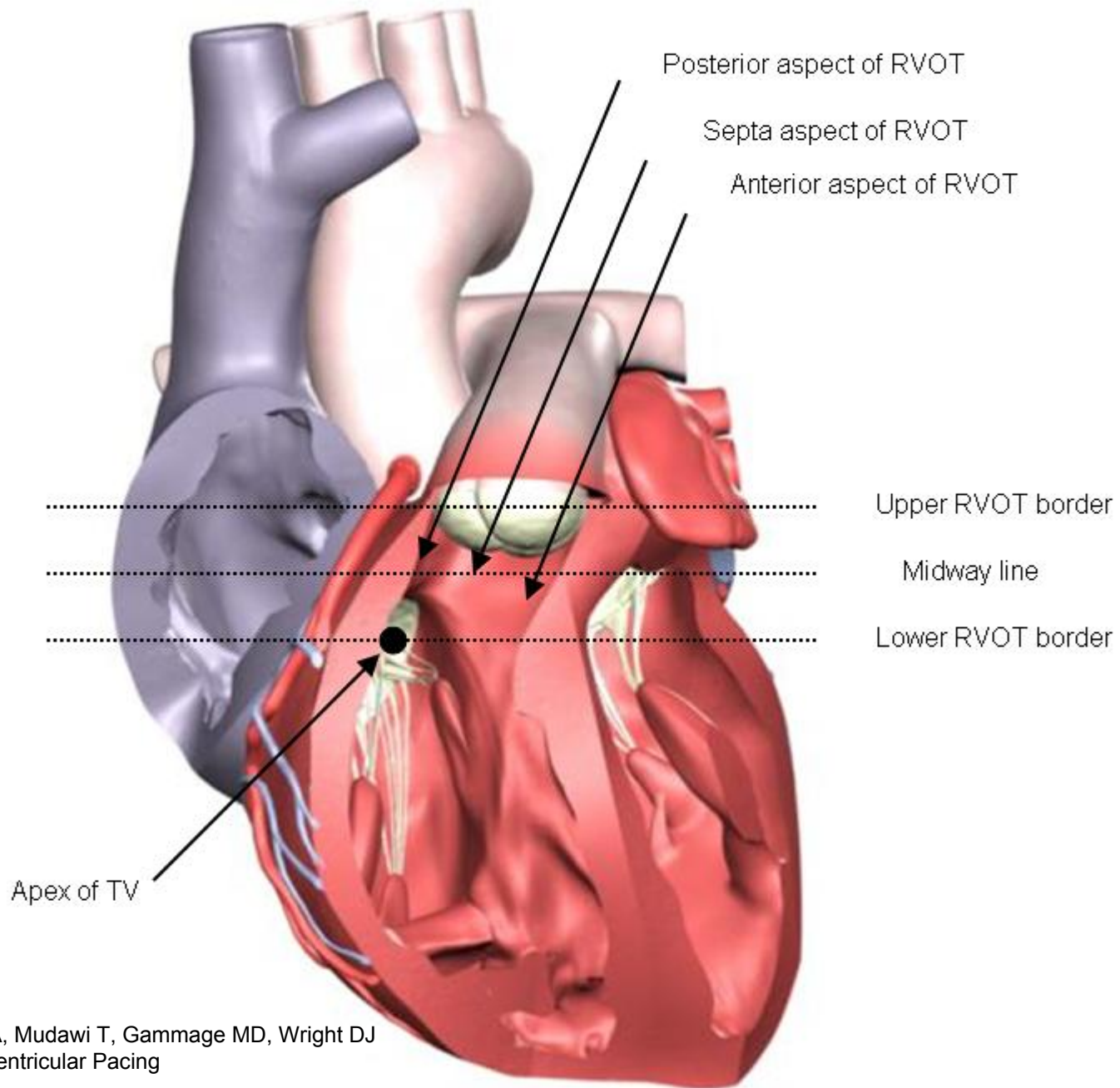
However, trials assessing acute and medium-term haemodynamic changes with selective site pacing (SSP) have provided conflicting results. (9-16). These trials were of **variable designs** and utilised **different endpoints**. Selective site pacing trials have also faced other challenges such as inclusion of **heterogeneous patient groups** and absence of **long term follow-up** data (17-22).

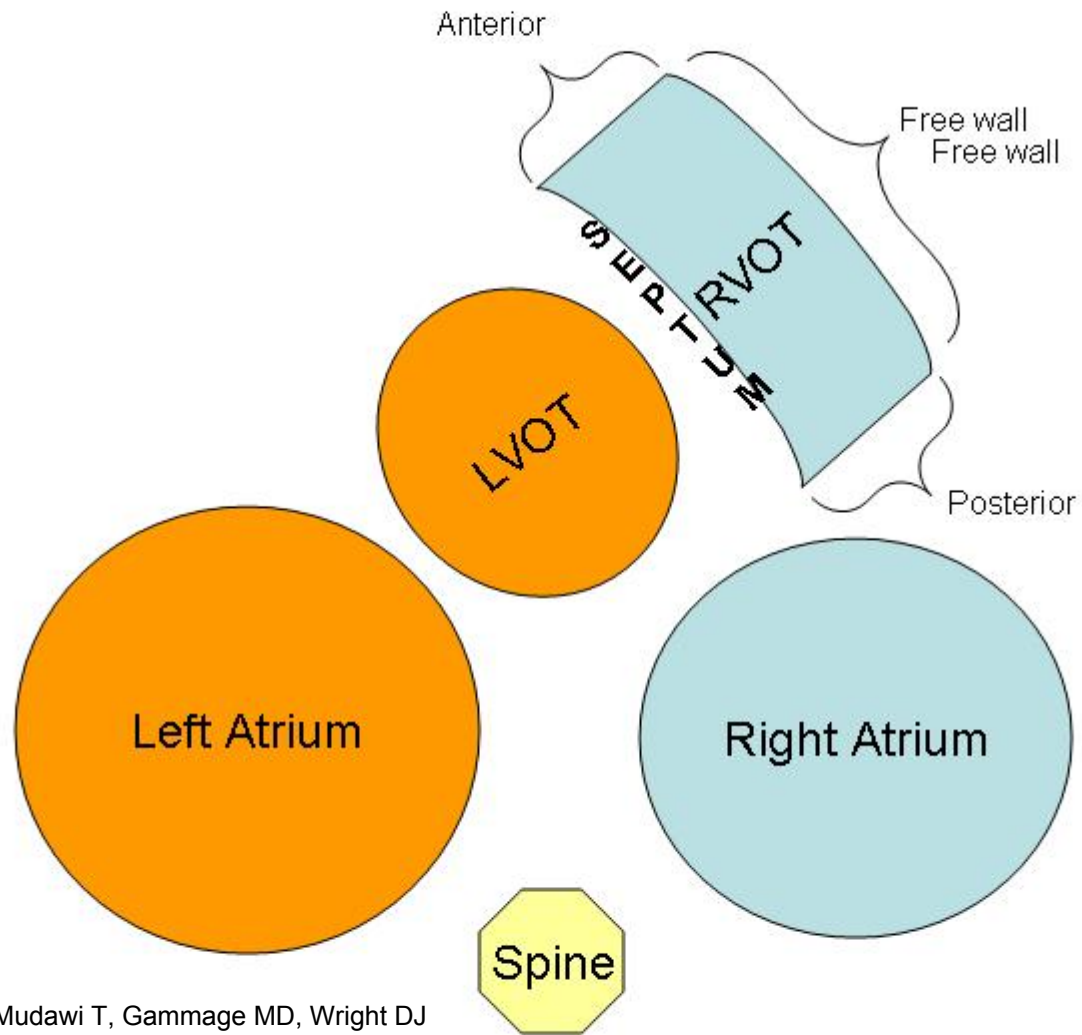
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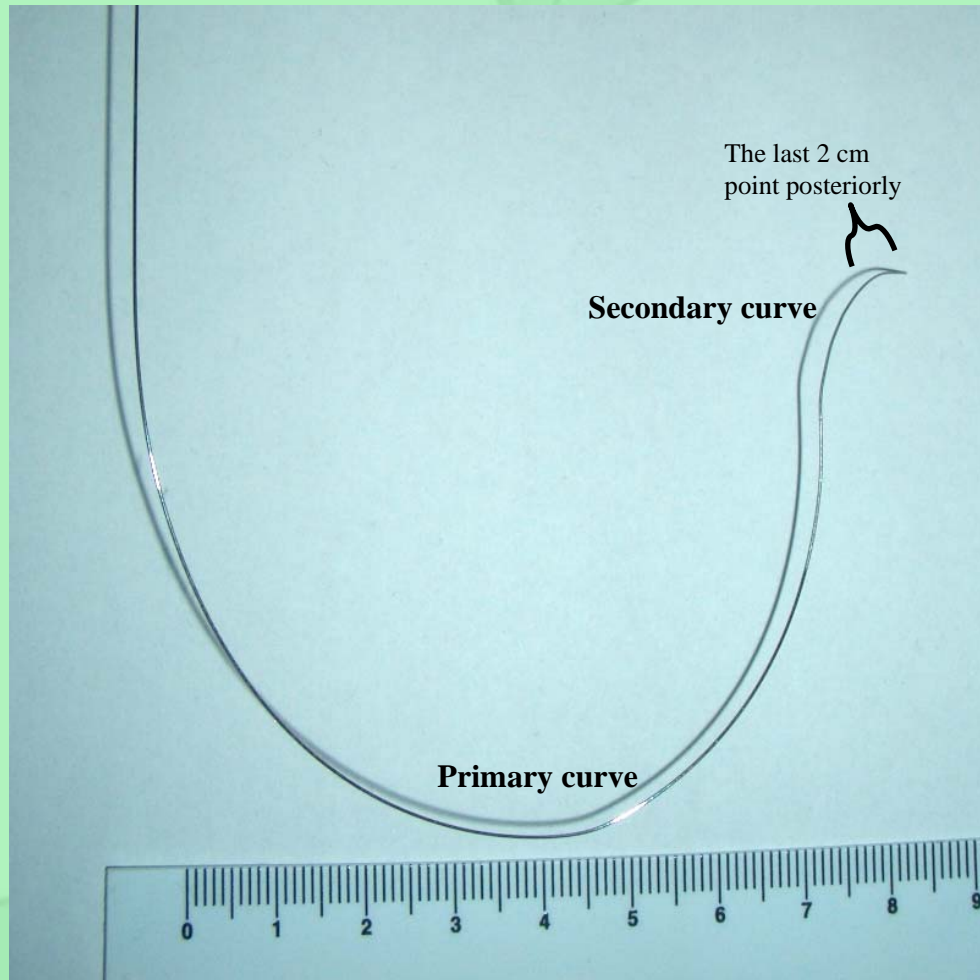
RVOT

Anatomy & Fluoroscopy









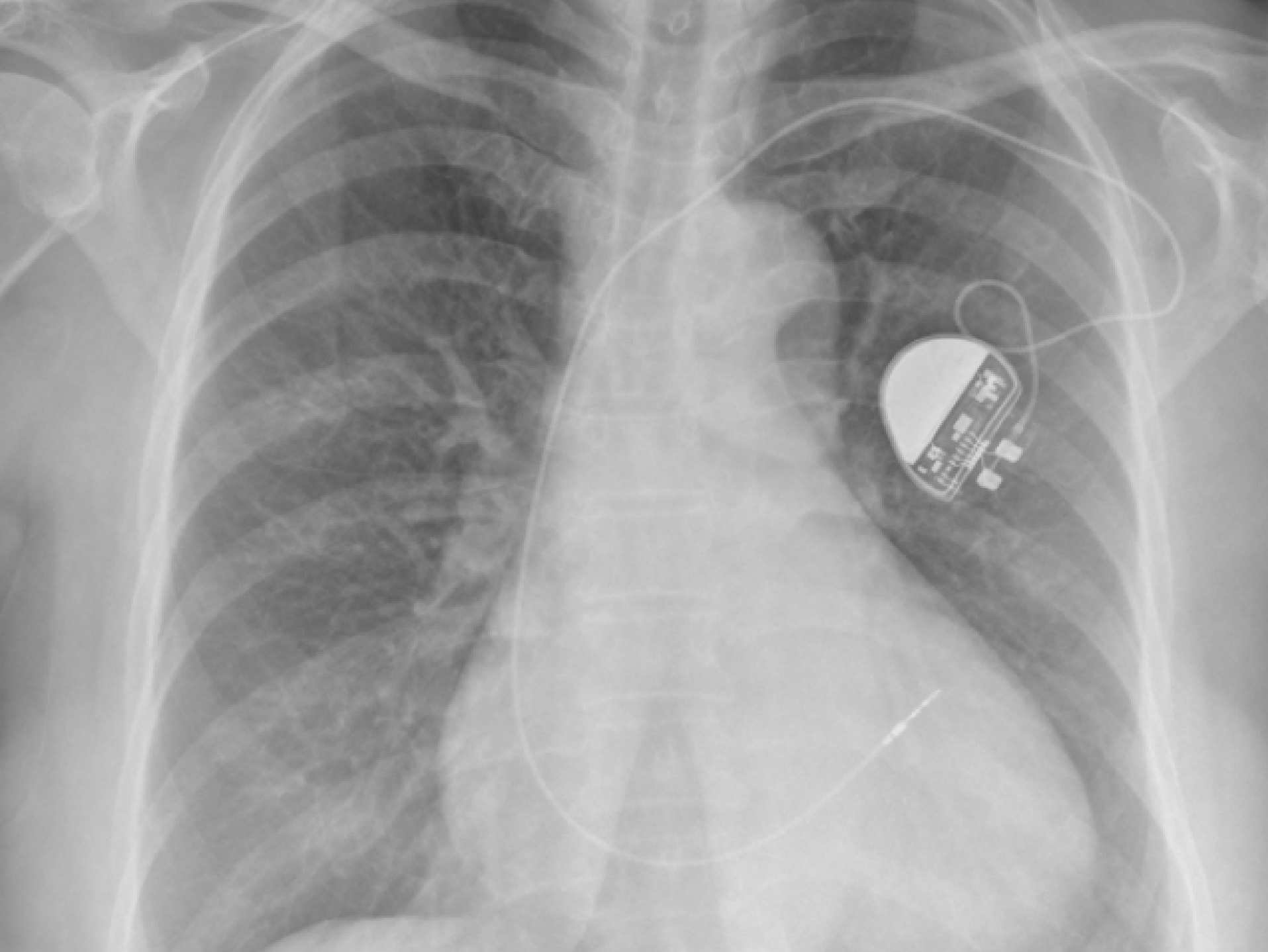
Albouaini K, Alkarmi A, Mudawi T, Gammage MD, Wright DJ
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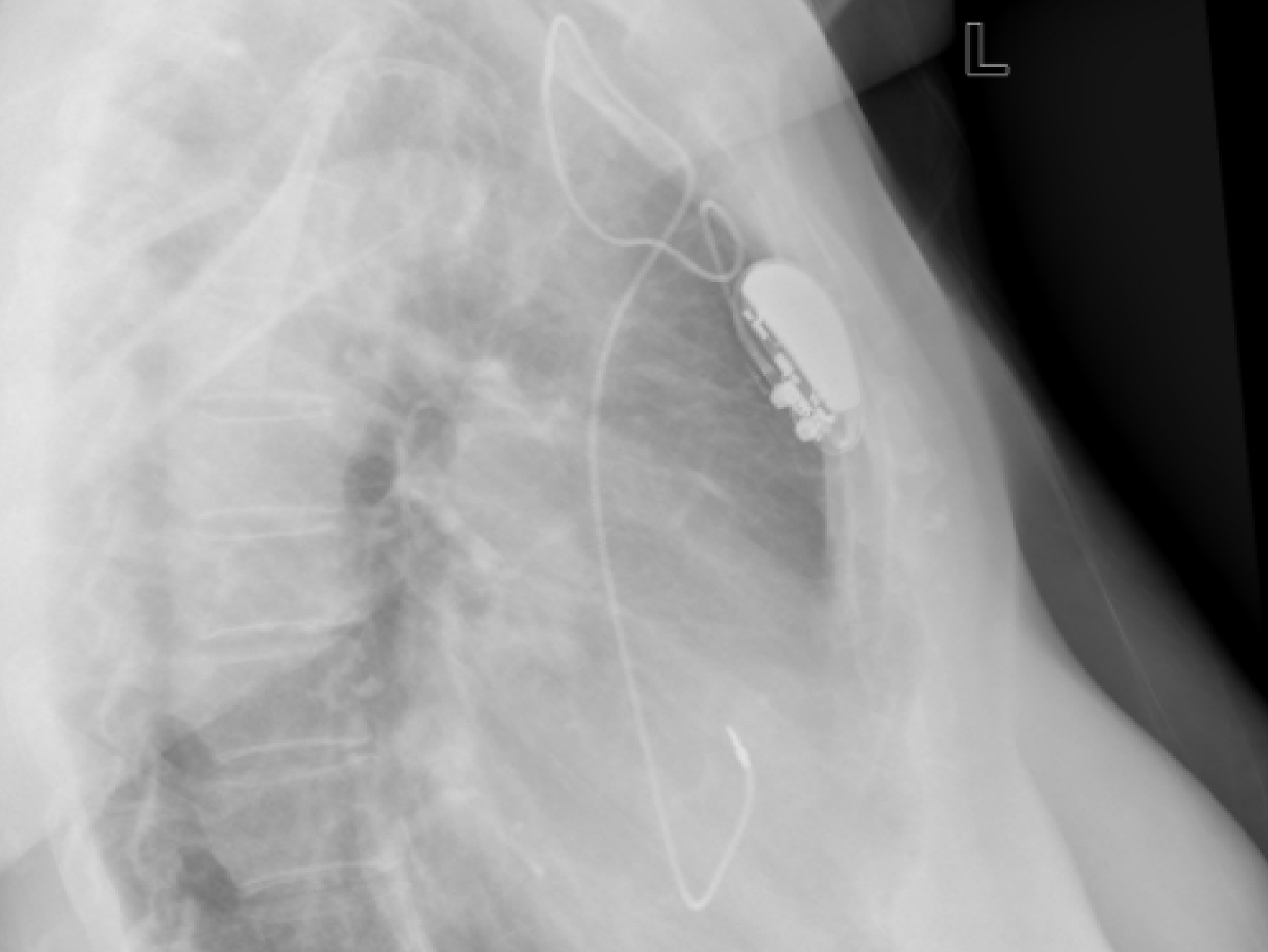
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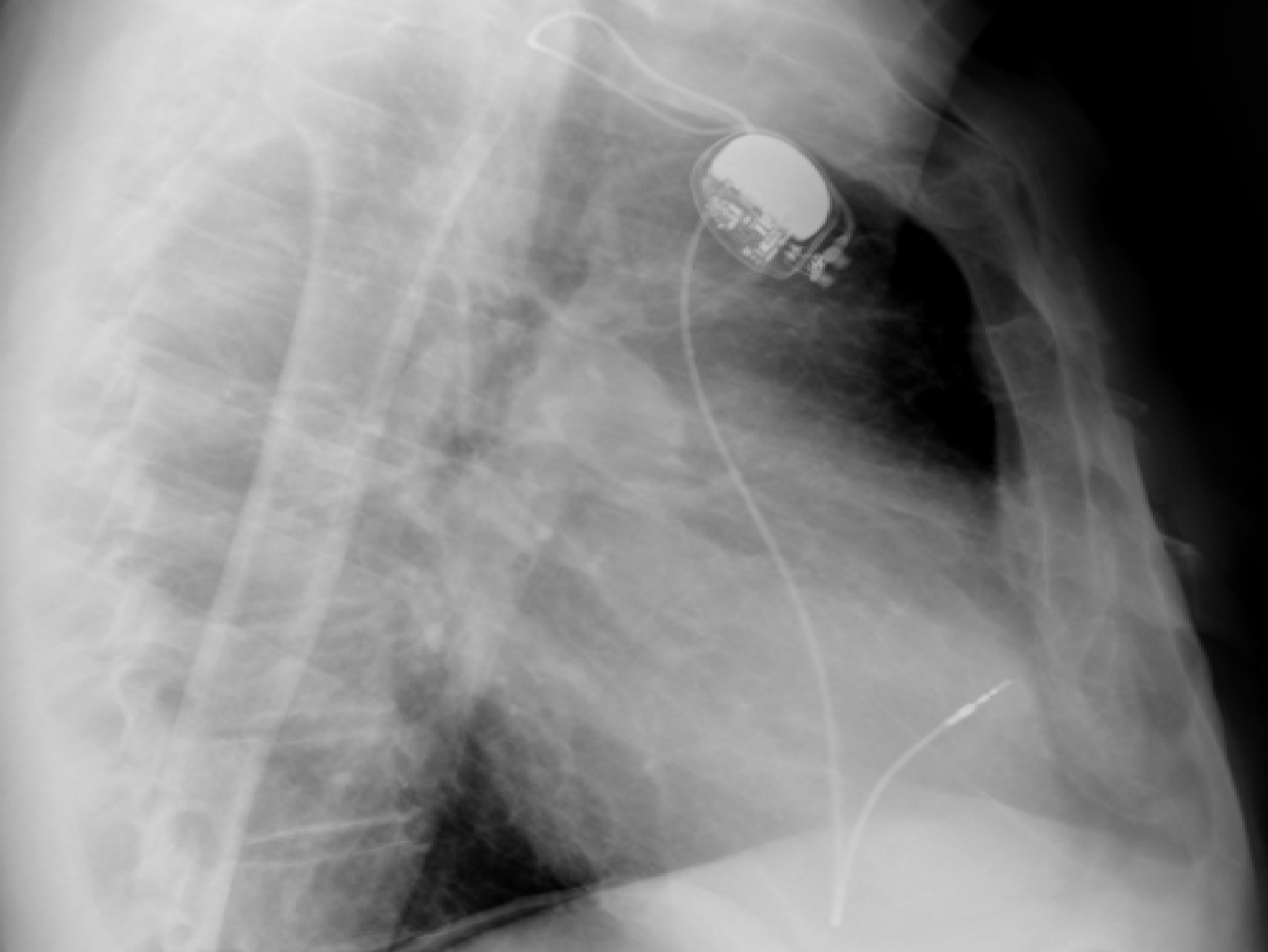
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Methods



Study Population

All patients were recruited from a single centre, at the Liverpool Heart and Chest Hospital between 2006 and 2008.

Inclusion criteria

Patients were considered eligible for the study if they were able to provide informed consent and had persistent atrial fibrillation / flutter requiring **atrioventricular node (AVN) ablation**, or **high grade AVN block**.

Exclusion criteria

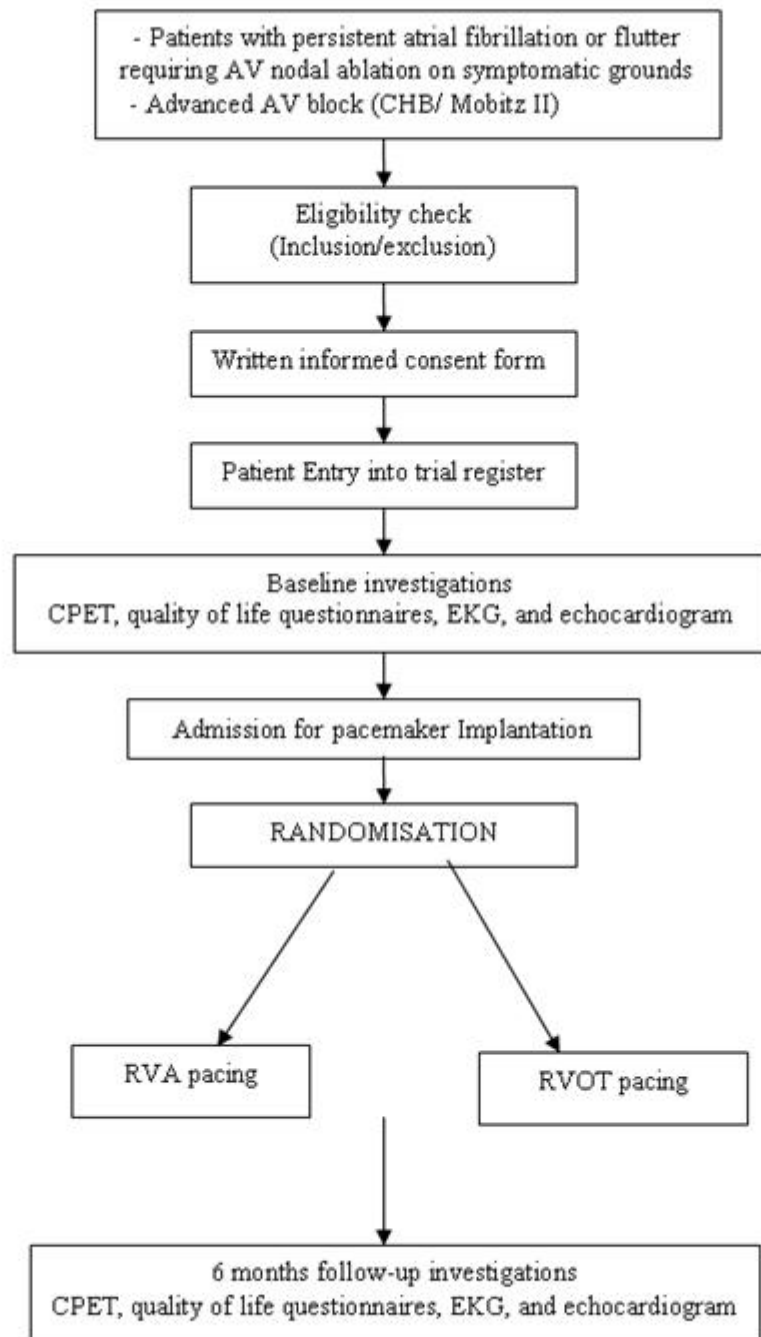
Indication for ICD or CRT

Exercise limitation due to pathological process such as respiratory, neurological or rheumatological disease

Significant valvular heart disease

Percutaneous or surgical revascularisation within the last 3 months

Life expectancy of < 2 years



Primary outcome measure:

1- Peak oxygen consumption, PVO₂ (ml/kg/min)

Secondary outcome measures:

2- NYHA class

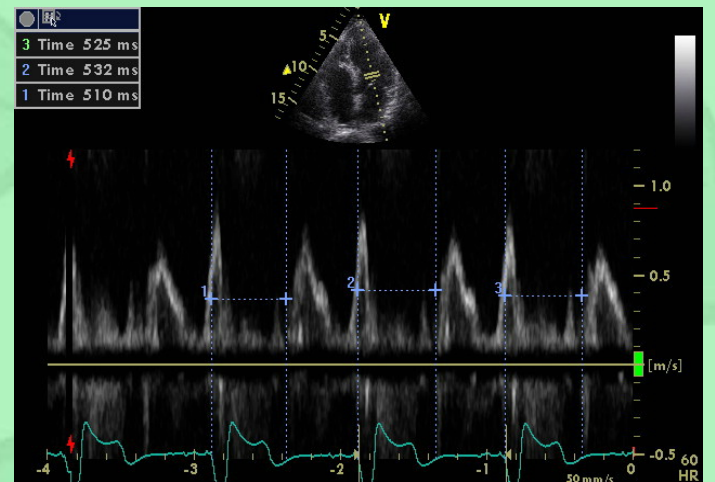
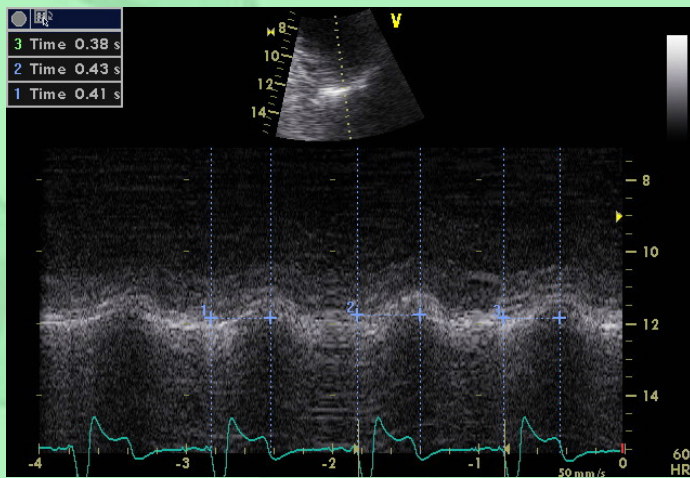
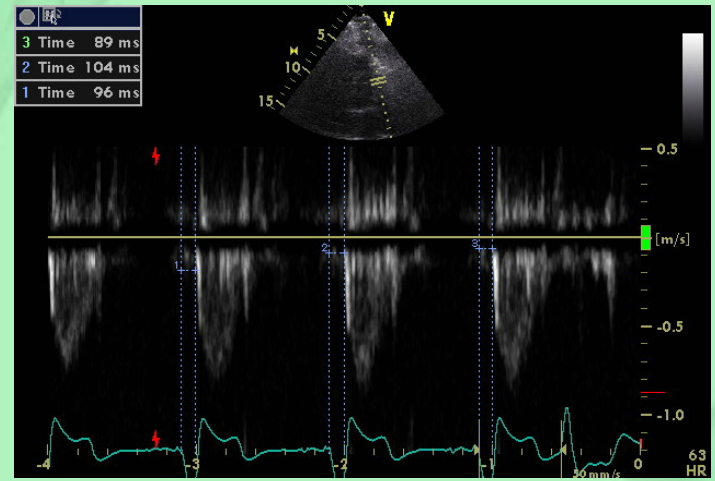
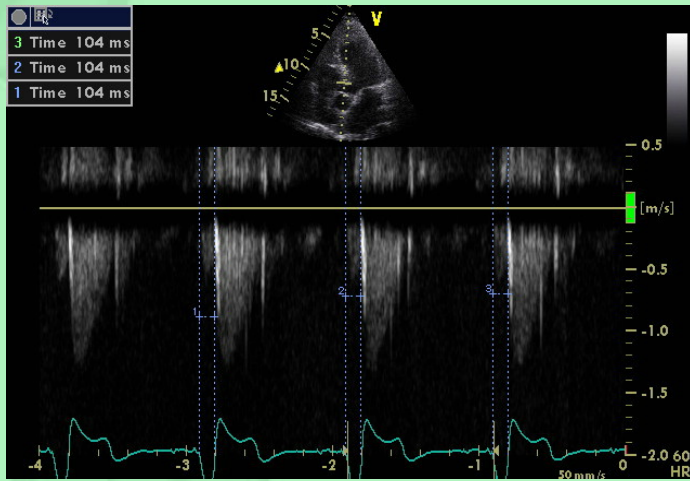
3- Health-related quality of life (QOL) as measured by the Minnesota Living with Heart Failure (MLWHF) and Short Form-36 health survey (SF-36) scores

4- QRS duration by standard 12-lead electrocardiogram (ECG)

5- Left ventricular end-diastolic diameter (LVEDD)

Left ventricular ejection fraction (LVEF) and the left ventricular outflow tract velocity time integral (VTI)

Left ventricular dyssynchrony as assessed in the Cardiac Resynchronisation in Heart Failure trial (CARE-HF) trial(23)



Statistical Analysis

The primary analyses were as ***per intention to treat*** while secondary analyses were as ***per protocol basis***. Data were expressed as percentages and mean values \pm standard deviation. P-values of 0.05 or less were considered significant. All analyses were performed using **SPSS** for Windows Version 11.0.0 (Sep. 2001) and **StatsDirect** Version 2.7.2 (Sep. 2008). Categorical and dichotomous variables were compared by using the χ^2 and Fisher's exact tests. Continuous variables were compared using Student's t-test when data was normally distributed or Wilcoxon rank sum test when variables were non-normally distributed. **Mann-Whitney Test** was then used to compare variables differences between RVA and RVOT groups.

Results & Discussion



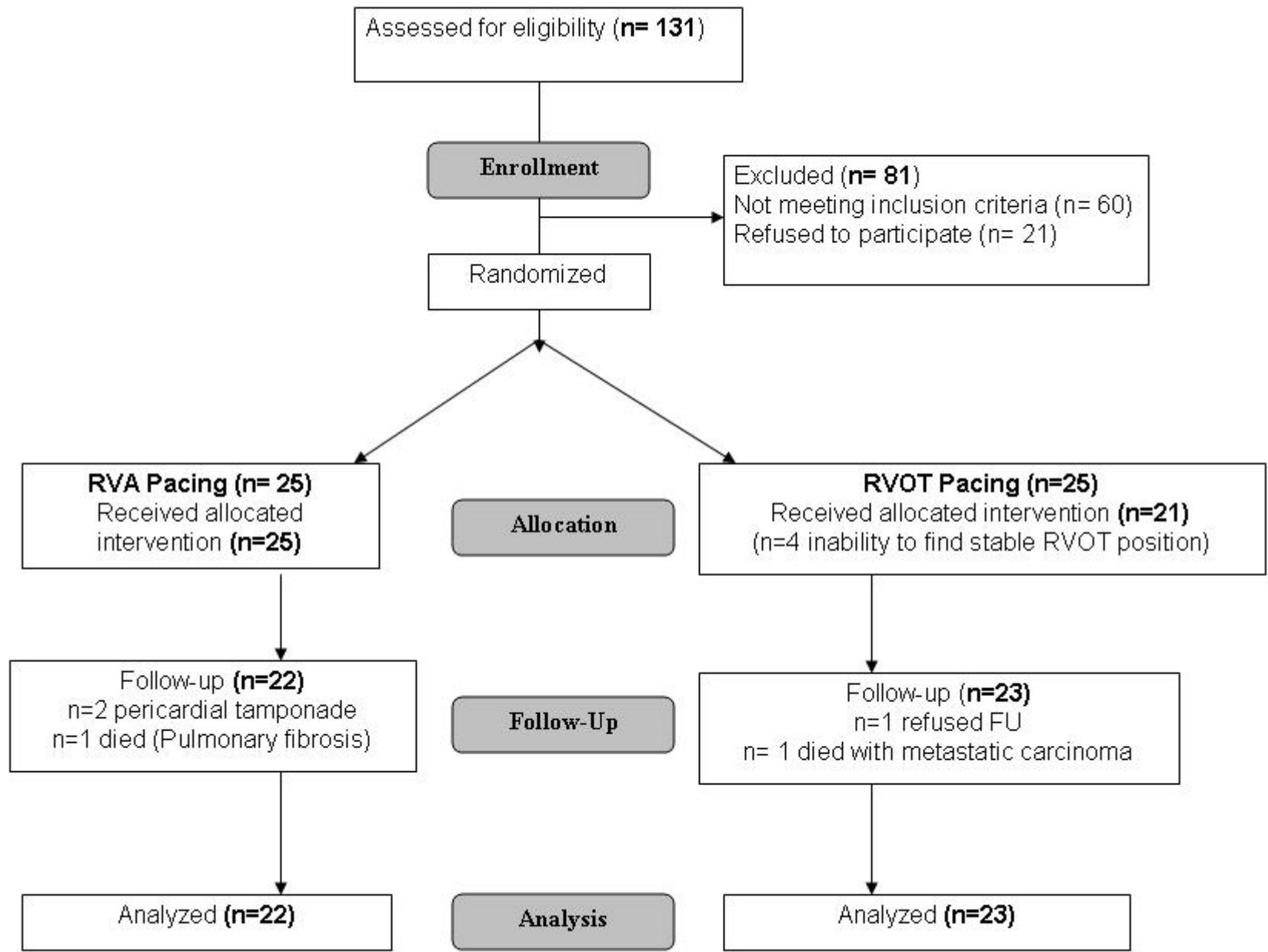


Table 1: Baseline characteristics		
	RVA Group Mean \pm SD	RVOT Group Mean \pm SD
Age (years)	74 \pm 8	72 \pm 8
Males	17 (68%)	15 (60%)
Females	8 (32%)	10 (40%)
Height (cm)	171.4 \pm 7.8	170 \pm 8.7
Weight (kg)	79 \pm 23	82 \pm 19
Atrioventricular block	56%	56%
AV node ablation	44%	44%
NYHA class I / II / III	8 / 64 / 28 %	12 / 56 / 32 %
Hypertension	30%	26%
Hyperlipidaemia	20%	16%
Diabetes	12%	12%
Smoker/ ex-smoker	20%	18%
Previous MI	10%	2%
Previous HF	6%	2%
PVD	2%	2%
Beta blocker	10%	10%
Calcium antagonist	22%	18%
ACE-I	20%	14%
ARB	10%	6%
Aspirin	20%	20%
Digoxin	6%	8%
Variables are presented as mean \pm SD when appropriate		

Four patients (16%) allocated to have RVOT had RVA lead due to an inability to find a stable RVOT lead position with satisfactory parameters. These patients remained in the RVOT group for **intention to treat analysis**. However, if included in the RVA group, analysis was conducted on **per protocol basis**.

On reviewing the chest X-ray (both postero-anterior and lateral) in the RVOT group, the right ventricular lead was positioned in the :

- free RVOT wall in 10 cases
- anterior RVOT in 9 cases
- RVOT septum in 2 cases

Table 2: Baseline and 6 month follow-up data				
		Baseline (M ± SD)	FU (M ± SD)	P Value
PVO2	RVA	16.8 ± 5.1	16.5 ± 4.6	NS
	RVOT	16 ± 3.4	14.7 ± 3.7	NS
Exercise Time	RVA	366 ± 180	423 ± 222	NS
	RVOT	378 ± 131	407 ± 190	NS
NYHA class	RVA	2.2 ± 0.5	1.8 ± 0.8	**
	RVOT	2.2 ± 0.6	1.4 ± 0.6	**
MLWHF	RVA	45 ± 20	26 ± 25	**
	RVOT	49 ± 19	18 ± 22	**
QRSd	RVA	106 ± 20	165 ± 21	**
	RVOT	115 ± 25	174 ± 19	**
LVEDD	RVA	47 ± 6	47 ± 5	NS
	RVOT	49 ± 6	49 ± 8	NS
EF	RVA	57 ± 7	50 ± 10	**
	RVOT	60 ± 8	50 ± 7	**
(**) = P < 0.005; (*) = P < 0.05; (NS) = P > 0.05				

1- Cardiopulmonary Exercise Test

This was performed on 21 patients at baseline (12 RVA and 9 RVOT) and on 34 patients at follow-up (17 in each group). This was due to the fact that

high grade AV block is a relative contraindication for CPET

significant proportion of the study population were unable to exceed the anaerobic threshold due to the underlying indication for pacing.

We therefore were unable to include these outcomes.

We were unable to detect any significant changes in exercise time or PVO₂ in either group or any inter-group differences

2- NYHA class

All patients showed a significant improvement in NYHA heart failure classes (Table 2, mean NYHA class of 2.22 ± 0.6 at baseline versus 1.6 ± 0.7 at 6 months; $P < 0.0001$).

Comparison of between group changes showed no superiority for RVOT in **intention to treat** analysis. NYHA class dropped by a mean of 0.36 ± 0.78 in the RVA group and by 0.78 ± 0.67 in the RVOT group, $P=0.08$.

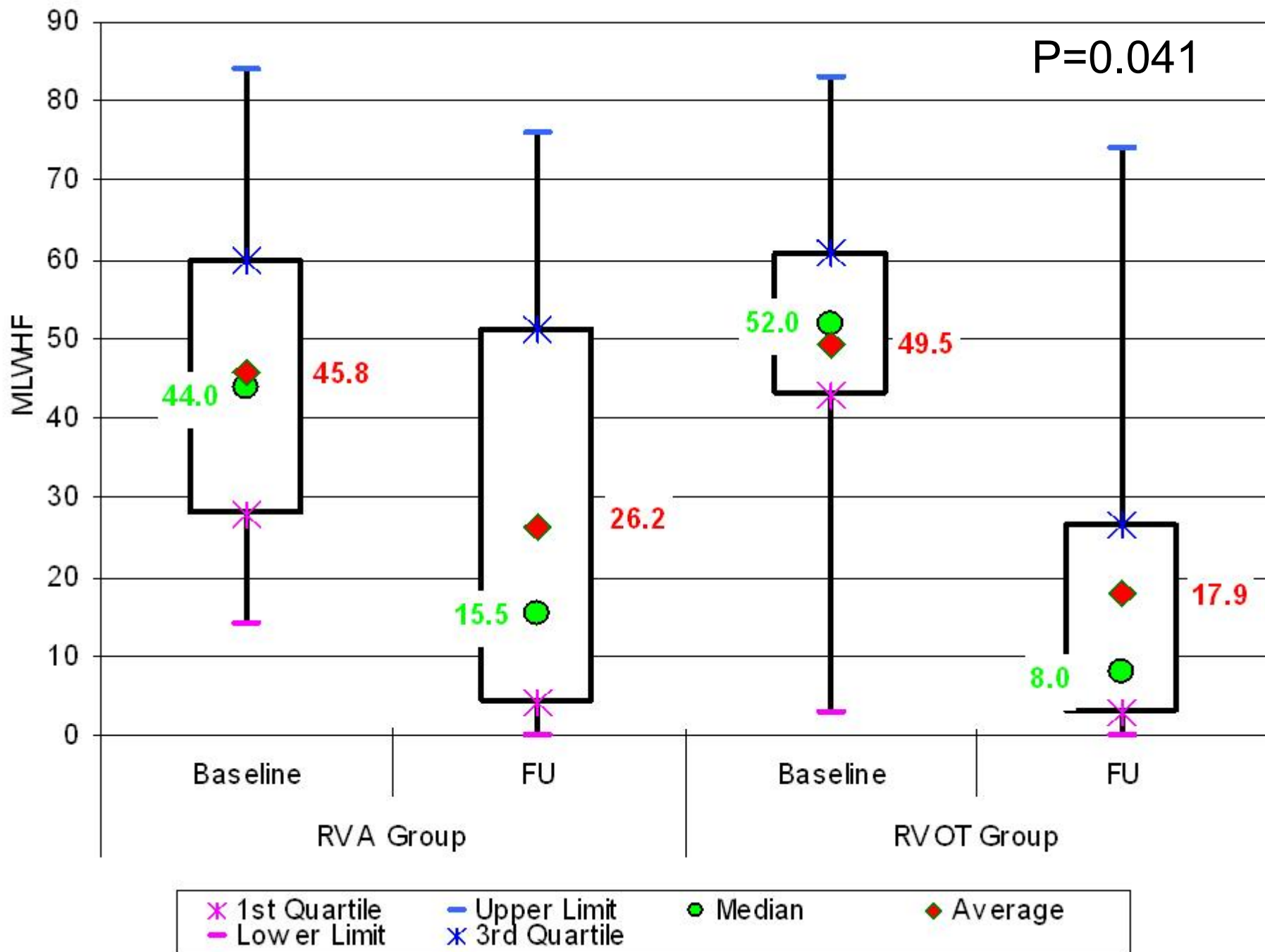
In contrast, **as per protocol** analysis showed that RVOT patients had significantly greater improvement; NYHA class dropped by a mean of 0.38 ± 0.80 in the RVA group and by 0.84 ± 0.60 in the RVOT group, $P=0.04$.

3- Minnesota LWHF questionnaire

Scores improved significantly on follow-up in the whole study population and in each study group (Figure 3 and Table 2).

Comparison of between group changes showed superiority for RVOT. **Intention to treat analysis** revealed that the MLWHF score dropped by 21 ± 22 in the RVA group as compared with 32 ± 19 in the RVOT group, $P=0.041$.

Did your heart failure prevent you from living as you wanted during the last month by:		No		Very Little		Very Much	
1.	Causing swelling in your ankles, legs, etc.?	0	1	2	3	4	5
2.	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
3.	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4.	Making your working around the house or yard difficult?	0	1	2	3	4	5
5.	Making your going places away from home difficult?	0	1	2	3	4	5
6.	Making your sleeping well at night difficult?	0	1	2	3	4	5
7.	Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8.	Making your working to earn a living difficult?	0	1	2	3	4	5
9.	Making your recreational past times, sports or hobbies difficult?	0	1	2	3	4	5
10.	Making your sexual activities difficult?	0	1	2	3	4	5
11.	Making you eat less of the foods you like?	0	1	2	3	4	5
12.	Making you short of breath?	0	1	2	3	4	5
13.	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14.	Making you stay in a hospital?	0	1	2	3	4	5
15.	Costing you money for medical care?	0	1	2	3	4	5
16.	Giving you side effects from medication?	0	1	2	3	4	5
17.	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18.	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
19.	Making you worry?	0	1	2	3	4	5
20.	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21.	Making you feel depressed?	0	1	2	3	4	5
Sub totals :							
TOTAL SCORE :							



4- SF-36 health survey

Scores significantly improved at follow-up with the exception of 2 indices (Table 3): Bodily Pain and General Mental Health.

Intention to treat analysis revealed a significant improvement in favour of RVOT pacing (Figure 4) in terms of the following:

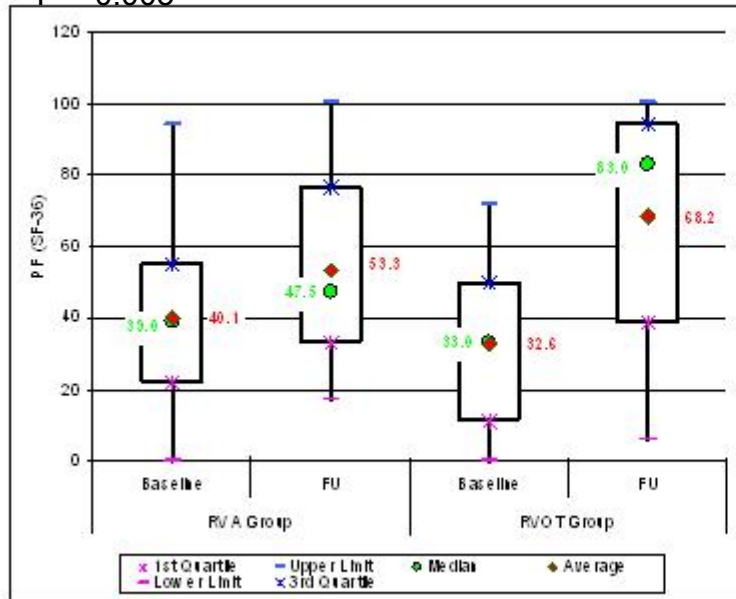
- 1) **Physical Function**: where the average increase in the score was 11 ± 26 in the RVA group and 36 ± 28 in the RVOT group, $P = 0.005$.
- 2) **Role Limitation due to Emotional Problem**: where the average increase in the score was 4 ± 54 in the RVA group and 43 ± 46 in the RVOT group, $P = 0.016$.
- 3) **Vitality Energy Fatigue**: where the average increase in VEF score was 7 ± 24 in the RVA group and 26 ± 27 in the RVOT group, $P = 0.024$.

Table 3: SF-36 Health Survey mean scores

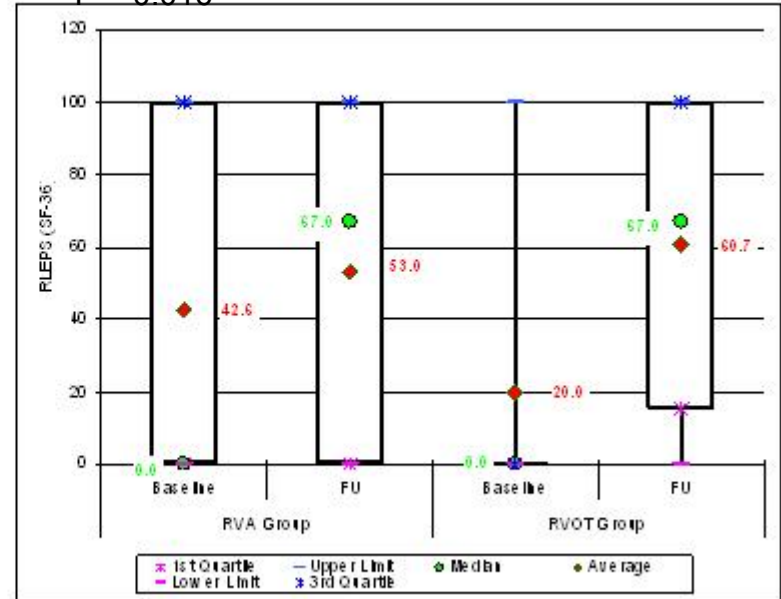
		Baseline score (M ± SD)	FU score (M ± SD)	P Value
PF	RVA	40 ± 26	53 ± 27	*
	RVOT	33 ± 21	68 ± 32	**
RL	RVA	25 ± 38	53 ± 44	**
	RVOT	14 ± 31	67 ± 41	**
BP	RVA	69 ± 20	68 ± 25	NS
	RVOT	68 ± 31	70 ± 31	NS
SF	RVA	47 ± 32	64 ± 33	**
	RVOT	54 ± 26	73 ± 26	**
GMH	RVA	61 ± 21	61 ± 23	NS
	RVOT	58 ± 23	72 ± 18	*
RLEP	RVA	42 ± 49	53 ± 43	NS
	RVOT	20 ± 38	60 ± 43	**
VEF	RVA	38 ± 21	47 ± 22	*
	RVOT	35 ± 20	61 ± 22	**
GHP	RVA	51 ± 23	55 ± 24	NS
	RVOT	45 ± 18	58 ± 25	*
HCTLY	RVA	26 ± 20	70 ± 32	**
	RVOT	25 ± 26	85 ± 26	**

(**) = P < 0.005; (*) = P < 0.05; (NS) = P > 0.05

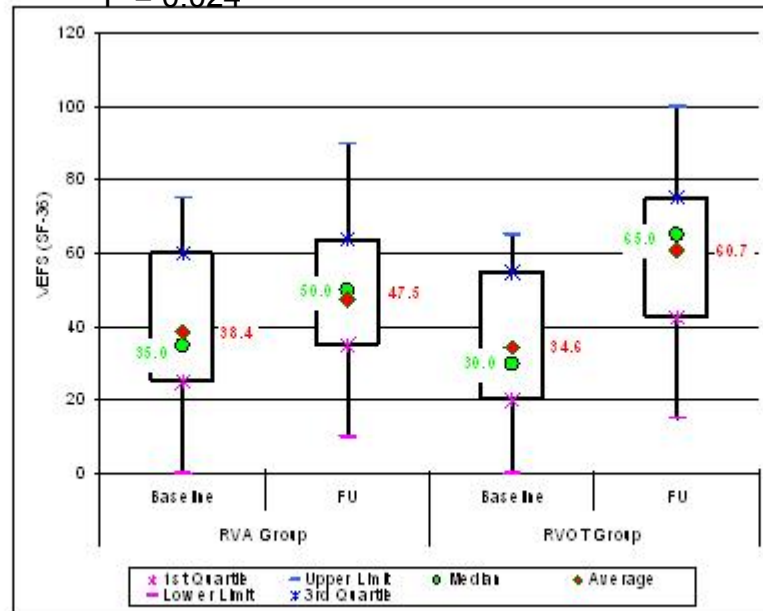
P = 0.005



P = 0.016



P = 0.024



5- Electrocardiogram

On analysing the whole study population, QRS duration increased significantly from a mean of 110 ± 22 ms at baseline to 170 ± 20 ms on 6-months follow-up, $P < 0.0001$.

Analysis showed no significant differences between the two groups at 6 months follow-up!!!!

6- Echocardiogram

Analysis of the data from the whole group showed that LVEF dropped by 6.1%, from 59.1 ± 7.8 to 53 ± 8.8 , $P < 0.0001$. We were unable to detect any significant change in LVEDD.

No significant difference was detected in between group analysis in any echocardiographic parameter including the CARE-HF echo dyssynchrony criteria (Table 2).

Study Limitations

It is possible that the study missed a real difference between the study groups in terms of PVO2 and echocardiographic data because of the relatively **small study sample** or the relatively **short follow-up** that was not long enough to show the LV remodelling effects. Furthermore, **CPET was not performed in patients with AV block.**(24)

The RVOT in our study was only defined **fluoroscopically**, not electrocardiographically. When the post-implant ECGs in the RVOT group were analysed, negative or isoelectric QRS vector in lead I was seen in 43% of the RVOT implants. This ECG finding has a 90% positive predictive value for RVOT septal placement(25).

Moreover, the **heterogeneity in lead position** might account for heterogeneity in patients' clinical response.

(24) Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. Heart 2007 Oct;93(10):1285-92.

(25) McGavigan AD, Roberts-Thomson KC, Hillock RJ, Stevenson IH, Mond HG. Right ventricular outflow tract pacing: radiographic and electrocardiographic correlates of lead position. Pacing Clin Electrophysiol 2006 Oct;29(10):1063-8.

CONCLUSION

RVOT pacing, at 6 months, was not superior to RVA in terms of PVO₂.

In contrast, RVOT pacing offered a more significant improvement in health-related quality of life scores.

Both RVA and RVOT pacing comparably worsened echocardiogram parameters.

Effects of Selective Site Pacing On the Haemodynamics and Functional Recovery in Patients Requiring Permanent Right Ventricular Pacing

Albouaini K, Alkarmi A, Matata B, Modi S, Barker D, Patwala A, Pyatt J, Rao A, Gammage M, Wright D J

International Standard RCT Registration Number: ISRCTN67629267

Objectives: To assess whether right ventricular outflow tract (RVOT) pacing is superior to right ventricular apex (RVA) pacing in terms of haemodynamic and functional capacity.

Background: Right ventricular apical pacing, although providing an easily accessible and stable position, results in dyssynchronous left ventricular contraction. Therefore, alternative sites have been proposed. Studies to date have failed to identify the optimal right ventricular pacing site.

Methods: We randomised 50 patients requiring permanent right ventricular pacing to RVA (n=25) or RVOT (n=25) pacing. Baseline and 6 month follow-up investigations included: electrocardiogram, New York Heart Association (NYHA) class, Minnesota Living with Heart Failure score (MLWHF), Short Form-36 health survey (SF-36), echocardiogram, and cardiopulmonary exercise test. The primary outcome was the peak oxygen consumption (PVO₂). Investigators were blinded, on follow-up, to the lead position.

Results: There were no significant differences in PVO₂ between the study groups. The MLWHF scores improved significantly in the RVOT group (32 ± 19) compared to the RVA group (21 ± 22, P=0.041). SF-36 indicated significantly better scores in RVOT patients in the areas of Physical Function, Role Limitation due to Emotional Problems, and Vitality Energy Fatigue. Interestingly, there were no differences in the echocardiographic parameters or paced QRS duration between groups.

Conclusion: In patients requiring permanent right ventricular pacing, RVOT lead position provided superior improvements in quality of life scores compared to RVA position.