Resynchronization therapy

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IDENTIFICATION OF PATIENTS WHO WILL BENEFIT FROM RESYNCHRONIZATION THERAPY

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In patients with severe heart failure and left bundle branch block, cardiac resynchronization therapy is associated with an improvement in symptoms. However, not all patients benefit from this device. The rationale of implanting a biventricular pacing is represented by the possibility of synchronizing areas of the left ventricle that are asynchronous at baseline. If this is the case, reverse remodeling associated with cardiac resynchronization therapy (CRT) should be more evident when baseline left ventricular asynchrony is present. We investigated the value of echocardiographic left ventricular asynchrony in predicting long-term reverse remodeling 1 year after CRT in 25 patients with advanced heart failure and left bundle branch block (QRS ≥ 140 ms). The baseline QRS duration and septal-to-posterior wall motion delay (a left intraventricular asynchrony parameter) were both significant predictors, but the predictive accuracy of septal-to-posterior wall motion delay was significantly higher. In patients with advanced heart failure, the use of this simple and reliable parameter could contribute towards identifying the patients most likely to benefit from CRT.

The benefit offered by cardiac resynchronization therapy (CRT) in patients with severe heart failure and left bundle branch block who remain symptomatic despite receiving "optimal" medical treatment[1-3] depends upon the possibility of correcting the deleterious effect of asynchrony generated by left ventricular conduction delay. By doing so, CRT could counteract progressive ventricular enlargement and remodeling, and thus slow heart failure progression. Therefore, the identification of baseline mechanical ventricular asynchrony could be useful in selecting patients who most benefit from CRT. We have recently suggested that the presence of a prolonged septal-to-posterior wall motion delay (SPWMD), a measure of intraventricular asynchrony, may be a useful parameter for selecting patients who most benefit in terms of reverse remodeling 1 month after CRT[4]. SPWMD is evaluated by calculating the shortest interval between the maximum posterior displacement of the septum and the maximum displacement of the left posterior wall using a mono-dimensional short-axis view at the papillary muscle level[4].

To evaluate the long-term predictive value predictive value of SPWMD, we studied 25 patients with severe heart failure, left bundle branch block, left ventricular dysfunction, in optimal medical therapy, who underwent biventricular pacing implantation.

As a whole, the patients showed an improvement in left ventricular end-diastolic and end-systolic volume index after 1 month (from 139 ± 52 to 114 ± 38 and from 107 ± 43 to 83 ± 32 ml/m^2, respectively, $p < 0.001$) and a further improvement after 1 year (91 ± 39 and 63 ± 35 ml/m^2, respectively, $p < 0.001$ vs baseline and vs 1 month evaluation). After 1 year, 17 patients who showed a reduction in left ventricular end-systolic volume index > 15% were considered responders. The percentage of non-responders was higher among the ischemic than the non-ischemic patients (68 vs 33%, $p < 0.05$). The ROC curves for 1 year post-CRT reverse remodeling showed that the AUC of SPWMD (0.96, confidence interval 0.80-0.99) was significantly greater than that of the duration of QRS (0.74, confidence interval 0.53-0.89) but not significantly different from that of the PQ interval

(0.84, confidence interval 0.63-0.95). All of the 1 year responders had a baseline SPWMD of ≥ 100 ms, a PQ interval of ≥ 180 ms and a QRS duration of ≥ 145 ms. Using these cut-off values, the specificity of SPWMD was 75% with a positive predictive value of 89% and an accuracy of 92%; the specificity of the PQ interval was 25% with a positive predictive value of 74% and an accuracy of 76%, and the specificity of the QRS duration was 13% with a positive predictive value of 71% and an accuracy of 72%.

After 1 year the patients with left ventricular asynchrony (SPWMD ≥ 100 ms) showed a significant and progressive improvement not only in terms of left ventricular end-diastolic volume index (76 ± 23 vs 141 ± 37 ml/m^2, $p < 0.01$) and left ventricular end-systolic volume index (49 ± 22 vs 108 ± 31 ml/m^2, $p < 0.01$), but also in terms of left ventricular ejection fraction (38 ± 10 vs 24 ± 5%, $p < 0.01$), E-wave deceleration time (260 ± 71 vs 208 ± 56 ms, $p < 0.05$), and a smaller area (3.7 ± 1.9 vs 5.8 ± 2.9 cm^2, $p < 0.01$) and a shorter duration of mitral regurgitation (405 ± 89 vs 500 ± 112 ms, $p < 0.01$).

The results of the present study show that SPWMD distinguishes patients who will experience post-CRT reverse remodeling from those who will not, therefore the presence of SPWMD at baseline also identifies the patients most likely to benefit from CRT in the short as well as in the long term.

Other echocardiographic measures of asynchrony have been suggested to predict functional improvement after CRT; most of them require sophisticated and not widely available techniques[5-7], whereas SPWMD is a reliable measure of left intraventricular asynchrony that can be easily obtained using mono-dimensional echocardiography, and can therefore be proposed as a simple parameter for patient selection.

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ABLATE AND PACE THERAPY FOR ATRIAL FIBRILLATION: LEFT VENTRICULAR PACING FOR EVERYBODY OR ONLY IN PATIENTS WITH CONGESTIVE HEART FAILURE?

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An acute echocardiographic intrapatient comparison between left ventricular over right ventricular pacing was performed within 24 hours after atrioventricular junction ablation in 44 patients affected by permanent atrial fibrillation. Rhythm regularization achieved with atrioventricular junction ablation improved ejection fraction with both right ventricular and left ventricular pacing; left ventricular pacing provided a modest additional favorable hemodynamic effect reflected by a further increase in ejection fraction and a reduction of mitral regurgitation. The effect seemed to be equal in patients with both depressed and preserved systolic functions and in those with and without native left bundle branch block.

Is the effect of resynchronization therapy the same for atrial fibrillation and for sinus rhythm patients?

A major difference between resynchronization therapy in atrial fibrillation and in sinus rhythm is that in the former situation the resynchronization pacing must be preceded by ablation of the atrioventricular (AV) junction. The perfect control of heart rate achieved by ablation and pacing therapy should potentially be associated with an improvement of cardiac performance; this has been confirmed in a few clinical not controlled studies[1-4]. One

recent randomized controlled study[5] showed that the long-term clinical effects of ablation and pacing therapy were superior to those obtained with drug therapy. Thus, the combination of two therapies, namely AV junction ablation and left ventricular (LV) (or biventricular) pacing seems to have a potential additive beneficial effect in patients with atrial fibrillation and heart failure.

There is increasing evidence for the favorable effect of cardiac resynchronization pacing in patients with heart failure and intraventricular conduction delay who are in sinus rhythm either during acute hemodynamic or clinical follow-up studies. Much less is known with regard to patients with permanent atrial fibrillation. An acute hemodynamic study[6] showed similar hemodynamic benefits of LV based pacing either in sinus rhythm or in atrial fibrillation. Capillary wedge pressure decreased from 24 ± 4 mmHg at baseline to 19 ± 5 and 21 ± 6 mmHg during LV or biventricular pacing respectively; aortic systolic blood pressure increased from 116 ± 19 mmHg at baseline to 123 ± 18 and 121 ± 18 mmHg during LV or biventricular pacing. In another small acute controlled study[7], LV pacing, compared with right ventricular (RV) pacing, caused an improvement of ejection fraction from 34 ± 14 to 37 ± 12% and aortic flow integral from 19 ± 14 to 21 ± 14 cm. The magnitude of the acute improvement is, however, modest. How much these hemodynamic effects correlate with the clinical outcome is uncertain. The results of the first randomized clinical study have recently been reported[8]. The intention-to-treat analysis did not show any statistically significant difference in either primary or secondary endpoints between biventricular and RV pacing; however, in the on-treatment analysis, the mean walked distance increased significantly by 9.3% and peak oxygen uptake increased by 13% during biventricular pacing. The average magnitude of the effect was modest, although very helpful, in terms of clinical improvement. This is not surprising if we consider that, in atrial fibrillation patients, an improvement is achieved by AV junction ablation *per se*, which reduces the amount of the potential additional benefits obtainable through LV pacing.

On the other hand, it is apparent from the literature that upgrading to biventricular pacing is greatly effective in patients with congestive heart failure with low ejection fraction who have had the prior intervention of AV junction ablation and RV pacing[9].

Unanswered questions in patients with atrial fibrillation

Question 1. Should resynchronization therapy be offered to all patients at the time of AV junction ablation or should be the stimulation system upgraded to LV pacing later only in those patients who develop heart failure?

Question 2. Should resynchronization pacing be the mode of choice for all patients undergoing "conventional" AV junction ablation because of uncontrolled high ventricular rate or should it be reserved only to those patients with baseline bundle branch block and heart failure (conventional indication to resynchronization therapy)?

The OPSITE study

The results of the Optimal Pacing Site (OPSITE) study will hopefully help to answer these questions. The OPSITE study is a prospective randomized, single blind cross-over comparison between RV and LV pacing for patients with permanent atrial fibrillation undergoing ablation and pacing therapy. The study consists of an acute and a chronic evaluation. The protocol has been published previously[10].

The following patients were eligible for enrolment in the OPSITE study:

- patients with permanent atrial fibrillation in whom a clinical decision was made to undertake complete AV junction ablation and ventricular pacing because of drug-refractory, severely symptomatic, uncontrolled high ventricular rate;
- patients with permanent atrial fibrillation, drug-refractory heart failure, depressed LV function and/or left bundle branch block (LBBB) in whom a clinical decision was made to undertake LV synchronization pacing.

Patient exclusion criteria were as follows: heart failure NYHA class IV; severe concomitant non-cardiac diseases; need for surgical intervention; myocardial infarction within 3 months; sustained ventricular tachycardia or ventricular fibrillation; previously implanted pacemaker.

Two different subgroups were predefined for analysis: patients with an ejection fraction > 40% and absence of LBBB pattern (group A), and patients with heart failure, i.e. those with an ejection fraction ≤ 40% and/or LBBB pattern (group B).

Chronic phase results are expected by the end of 2004. In this report we describe the results of the acute comparison of RV and LV pacing[11] in a model of atrial fibrillation and AV junction ablation which allows the net effect of LV over RV pacing to be studied without the confounding effect of two other variables which can influence cardiac performance, namely the effect of atrial contribution (including the effect of the PR interval) and the irregularity of the ventricular rhythm. Single-site LV pacing was compared with single-site RV pacing in order to eliminate the potential confounding effect of simultaneous biventricular stimulation. Moreover, the acute evaluation was performed shortly after ablation allowing a minimum time for cardiac adaptation which is another confounding factor.

The acute non-invasive study was performed within 24 hours after AV junction ablation, consisted of echocardiographic evaluation and the measurements of QRS duration. The pacemaker was alternately pro-

grammed to pace in LV or RV only in randomized order, at a rate of 70 b/min. The RV and LV pacing studies were performed during the same session; the operator who performed the test and analyzed the records was not informed of the mode of pacing.

The baseline characteristics of the 44 enrolled patients are listed in the table I.

Compared with RV pacing, LV pacing caused a +5.7% increase of ejection fraction and a 16.7% decrease of mitral regurgitation score; QRS width was 4.8% shorter with LV pacing (Table II). Similar results were observed in patients with or without systolic dysfunction and/or native LBBB, except for a greater improvement in mitral regurgitation in the latter group (Tables III and IV). Compared with pre-ablation measures (Table II), ejection fraction increased by 11.2 and 17.6% with RV and LV pacing respectively, mitral regurgitation score decreased by 0 and 16.7% and diastolic filling time increased by 12.7 and 15.6%.

The main findings of this study are that rhythm regularization achieved with AV junction ablation improves ejection fraction with both RV and LV pacing; however, LV pacing gives an additive modest favorable hemodynamic effect as judged by a further increase of ejection fraction and a reduction of the magnitude of mitral regurgitation. This effect seems to be equal in patients with and without depressed systolic function and in patients with and without LBBB. As a consequence of the protocol used, the effect of LV pacing could be evaluated without several potentially confounding factors, i.e. the effect of atrial contribution (including the effect of the PR interval), irregularity of the ventricular rhythm, simultaneous biventricular stimulation and cardiac adaptation to chronic stimulation.

Table I. Patients' characteristics at enrolment.

No. patients	44
Age (years)	72 ± 8
Males	24 (54%)
Duration of atrial fibrillation (years)	5.9 ± 4.2
No. hospitalizations per patient	3.3 ± 2.6
NYHA class	2.4 ± 0.5
Minnesota Living with Heart failure Questionnaire score	49 ± 17
6-min walking test (m)	292 ± 103
Standard electrocardiogram	
Heart rate (b/min)	101 ± 25
Left bundle branch block	22 (50%)
Other intraventricular conduction disturbances	10 (23%)
Holter monitoring	
Minimum heart rate (b/min)	65 ± 32
Mean heart rate (b/min)	91 ± 18
Maximum heart rate (b/min)	143 ± 41
Associated structural heart disease	
Coronary artery disease	15 (34%)
Others	29 (66%)
Concomitant medications	
Digoxin	32 (72%)
Diuretics	35 (80%)
Nitrates	7 (16%)
ACE-inhibitors	33 (75%)
Beta-blockers	22 (50%)
Calcium antagonists	10 (23%)
Apirin	4 (9%)
Warfarin	37 (84%)
Class I antiarrhythmic drugs	3 (7%)
Amiodarone	7 (16%)
Sotalol	1 (2%)

Table II. Results.

	Baseline	RV	LV	RV vs baseline		LV vs baseline		LV vs RV	
				% difference	p*	% difference	p*	% difference	p*
EF (%)	36.6 ± 13.0	40.7 ± 14.9	43.0 ± 14.2	+11.2	0.03	+17.5	0.001	+5.7	0.002
LVEDD (mm)	56.7 ± 10.2	57.4 ± 10.2	57.2 ± 10.5	+1.2	NS	+0.9	NS	-0.4	NS
LVESD (mm)	48.8 ± 10.6	43.4 ± 11.5	42.7 ± 12.1	-11.1	NS	-12.5	NS	-1.6	NS
IRT (ms)	84.7 ± 21.2	79.9 ± 30.2	78.8 ± 28.1	-5.7	NS	-7.0	NS	-1.3	NS
MR (score)	1.8 ± 0.7	1.8 ± 0.9	1.5 ± 0.7	0	NS	-16.7	0.002	-16.7	0.001
FVI Ao (cm)	19.7 ± 8.9	17.6 ± 6.8	18.7 ± 6.8	-10.7	0.02	-5.1	NS	+6.2	NS
E max (cm/s)	106.9 ± 34.6	104.5 ± 31.2	105.2 ± 31.5	-2.2	NS	-1.6	NS	+0.4	NS
FVI Mi (cm)	18.6 ± 11.9	17.9 ± 7.1	18.2 ± 8.3	-3.6	NS	-2.2	NS	+1.7	NS
DT (ms)	198 ± 71.4	205 ± 75	205 ± 80	+3.5	NS	+3.5	NS	0	NS
DFT (ms)	313 ± 98	353 ± 71	362 ± 88	+12.7	0.02	+15.6	0.004	+2.5	NS
QRS (ms)	134 ± 37	187 ± 39	178 ± 36	+37.5	0.001	+30.9	0.001	-4.8	0.04

DFT = diastolic filling time; DT = deceleration time; EF = ejection fraction; E max = maximum protodiastolic mitral flow; FVI Ao = aortic flow-velocity integral; FVI Mi = mitral flow-velocity integral; IRT = isovolumetric relaxation time; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; RV = right ventricle. * paired Student's t-test.

Table III. Comparison between group A and group B patients.

	Group A (n=14)				Group B (n=30)				p** (group A vs B)
	RV	LV	% difference	p*	RV	LV	% difference	p*	
EF (%)	53.8 ± 12.9	55.6 ± 11.1	+3.5	NS	34.7 ± 11.5	37.1 ± 11.4	+6.9	0.004	NS
LVEDD (mm)	50.4 ± 6.1	50.0 ± 6.6	-0.8	NS	60.6 ± 10.2	60.6 ± 10.4	0	NS	NS
LVESD (mm)	34.6 ± 5.7	33.0 ± 6.3	-3.7	0.03	47.6 ± 11.3	47.3 ± 11.4	-0.6	NS	NS
IRT (ms)	67.9 ± 25.7	70.2 ± 24.1	3.4	NS	85.3 ± 30.8	82.6 ± 29.3	-3.2	NS	NS
MR (score)	2.2 ± 1.0	1.5 ± 0.7	-31.8	0.005	1.6 ± 0.7	1.5 ± 0.7	-6.3	0.02	0.01
FVI Ao (cm)	18.2 ± 6.1	18.9 ± 6.8	+3.8	NS	17.3 ± 7.2	18.6 ± 6.9	+7.5	NS	NS
E max (cm/s)	107 ± 39	109 ± 38	+1.8	NS	103.5 ± 27.4	103.6 ± 28.5	0	NS	NS
FVI Mi (cm)	18.8 ± 7.8	19.4 ± 10.4	+3.2	NS	17.5 ± 6.8	17.6 ± 7.3	+0.6	NS	NS
DT (ms)	210 ± 51	207 ± 58	-1.4	NS	202.6 ± 84.0	204.4 ± 88.9	+0.8	NS	NS
DFT (ms)	347 ± 48	372 ± 74	-0.5	NS	356.1 ± 79.0	358.2 ± 94.4	+0.6	NS	NS
QRS (ms)	179 ± 33	168 ± 27	-6.1	NS	191 ± 39	186 ± 34	-3.0	NS	NS

DFT = diastolic filling time; DT = deceleration time; EF = ejection fraction; E max = maximum protodiastolic mitral flow; FVI Ao = aortic flow-velocity integral; FVI Mi = mitral flow-velocity integral; IRT = isovolumetric relaxation time; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; RV = right ventricle. * paired Student's t-test; ** unpaired Student's t-test.

Table IV. Comparison between patients with and without left bundle branch block (LBBB).

	No LBBB (n=22)				LBBB (n=22)				p** (LBBB vs no LBBB)
	RV	LV	% difference	p*	RV	LV	% difference	p*	
EF (%)	48.2 ± 15.5	50.5 ± 13.7	+4.7	NS	33.3 ± 9.7	35.5 ± 10.4	+6.6	0.01	NS
LVEDD (mm)	53.0 ± 7.1	52.5 ± 7.1	-0.5	NS	61.8 ± 11.1	62.0 ± 11.4	+0.3	NS	NS
LVESD (mm)	34.6 ± 5.7	33.0 ± 6.3	-3.7	0.03	47.6 ± 11.3	47.3 ± 11.4	-0.6	NS	NS
IRT (ms)	72.5 ± 28.6	75.7 ± 25.7	+4.4	NS	87.3 ± 30.5	81.9 ± 30.6	-6.2	NS	NS
MR (score)	1.9 ± 0.9	1.4 ± 0.6	-26.4	0.001	1.7 ± 0.8	1.5 ± 0.8	-11.8	NS	0.03
FVI Ao (cm)	17.2 ± 7.3	18.4 ± 6.2	+6.9	NS	17.9 ± 6.4	18.9 ± 7.5	+5.5	NS	NS
E max (cm/s)	108.3 ± 36.8	109.9 ± 35.4	+1.4	NS	100.8 ± 24.6	100.4 ± 27.0	-0.1	NS	NS
FVI Mi (cm)	19.2 ± 8.5	19.8 ± 10.0	+3.1	NS	16.5 ± 4.8	16.3 ± 5.6	-1.3	NS	NS
DT (ms)	214 ± 61	209 ± 68	-2.3	NS	196 ± 87	202 ± 92	+3.0	NS	NS
DFT (ms)	341 ± 64	361 ± 81	+5.8	NS	367 ± 78	363 ± 99	-0.3	NS	NS
QRS (ms)	178 ± 38	169 ± 27	-5.1	NS	196 ± 36	190 ± 35	-3.1	NS	NS

DFT = diastolic filling time; DT = deceleration time; EF = ejection fraction; E max = maximum protodiastolic mitral flow; FVI Ao = aortic flow-velocity integral; FVI Mi = mitral flow-velocity integral; IRT = isovolumetric relaxation time; LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; RV = right ventricle. * paired Student's t-test; ** unpaired Student's t-test.

An increase in ejection fraction over baseline was already present as a result of RV pacing. Since a direct improvement of cardiac function by RV pacing is unlikely, this improvement seems likely to be due to the effects of rhythm regularization and reduction of ventricular rate following AV junction ablation resulting in improvements in ventricular filling, the Frank-Starling mechanism and the interval-force relation[12,13]. In addition, RV pacing showed a neutral effect on mitral regurgitation and indeed a worsening of aortic and mitral flow, probably reflecting the asynchronous contraction caused by non-physiological pacing from the apex of the right ventricle. Thus the cardiac performance of AV junction ablation and RV pacing is the net result of two opposite effects.

LV pacing, compared to RV pacing, reduced substantially the magnitude of mitral regurgitation and did not worsen aortic and mitral flow. The observed modifications were generally modest and, in some way, contrasting. Anyway, in general, it seems that LV pacing is able to counteract some of the adverse effects of RV pacing.

Conclusions

Rhythm regularization achieved with AV junction ablation improved ejection fraction with both RV and LV pacing; LV pacing provides a modest additional favorable hemodynamic effect reflected by a further increase in ejection fraction and reduction of mitral regurgitation.

The effect seems to be equal in patients with both depressed and preserved systolic functions and in those with and without native LBBB. How much these hemodynamic effects correlate with the clinical outcome is uncertain. Our observation potentially extends the indication for LV pacing to all patients who are candidates for ablation and pacing therapy or, owing to the modest acute effect, limit the indication for LV pacing only to the patients who develop overt heart failure late after ablation. The results of the chronic phase of the OPSITE study will hopefully answer this question.

Appendix

The OPSITE study is officially endorsed by the Working Group on Cardiac Pacing of the European Society of Cardiology.

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