Multimodality imaging to guide cardiac interventional procedures

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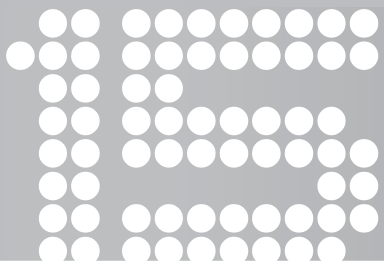

The effect of right ventricular pacing on myocardial oxidative metabolism and efficiency: relation with left ventricular dyssynchrony

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ABSTRACT

Purpose: Right ventricular (RV) apical pacing induces dyssynchrony by left bundle branch block type electrical activation sequence in the heart, and may impair left ventricular (LV) function. Whether these functional changes are accompanied with changes in myocardial perfusion, oxidative metabolism and efficiency, and the relation with the induction of LV dyssynchrony are unknown. Our study was designed to study the acute effects of RV pacing on these parameters.

Methods: Ten patients with normal LV ejection fraction and VVI/DDD pacemaker were studied during AAI-pacing/sinus rhythm without RV pacing (pacing-OFF) and with RV pacing (pacing-ON) at the same heart rate. Dynamic [^{15}O]water and [^{11}C]acetate positron emission tomography was used to measure perfusion and oxidative metabolism (k_{mono}) of the LV. An echocardiographic examination was used to assess LV stroke volume (SV) and LV dyssynchrony. Myocardial efficiency of forward work was calculated as systolic blood pressure x cardiac output/LV mass/k_{mono}.

Results: RV pacing decreased SV in all subjects (mean decrease 13%, from 76 ± 7 to 66 ± 7 ml, p=0.004) but global perfusion and k_{mono} were unchanged. The efficiency tended to be lower with pacing-ON (70 ± 20 vs. 81 ± 21 mmHg·L/g, p=0.066). In patients with dyssynchrony during pacing (n=6) efficiency decreased by 23% (from 78 ± 25 to 60 ± 14 mmHg·L/g, p=0.02) but in patients without dyssynchrony no change in efficiency was detected. Accordingly, heterogeneity in myocardial perfusion and oxidative metabolism was detected during pacing in patients with dyssynchrony but not in those without dyssynchrony.

Conclusions: RV pacing resulted in a significant decrease in SV. However, deleterious effects on LV oxidative metabolism and efficiency were observed only in patients with dyssynchrony during RV pacing.

INTRODUCTION

Right ventricular (RV) apical pacing induces a left bundle branch block (LBBB) type electrical activation sequence in the heart (1). This abnormal activation pattern of the ventricles may have detrimental effects on cardiac structure and function. Several clinical trials have demonstrated an association between RV pacing and an increased risk of heart failure and death (2,3). In addition, RV pacing has been shown to impair left ventricular (LV) function both in normal and failing hearts (4-6). Importantly, it has been demonstrated that this deterioration in LV function is related to the presence of LV dyssynchrony during RV pacing (7).

The exact effects of RV pacing on myocardial perfusion, oxidative metabolism and cardiac efficiency have not been fully elucidated. In experimental LBBB, significant changes in regional myocardial perfusion and glucose metabolism have been observed (8). Similarly, RV pacing may result in regional alterations in glucose metabolism (9). Importantly, the relation between the presence of LV dyssynchrony during RV pacing and changes in myocardial perfusion, oxidative metabolism and cardiac efficiency has not been studied.

Therefore, the objective of the present study was to evaluate the effect of RV pacing on both global and regional oxidative metabolism and perfusion, and myocardial efficiency. In addition, the effect of RV pacing-induced LV dyssynchrony on myocardial oxidative metabolism and efficiency was studied.

METHODS

Study population and study protocol

Ten patients (5 men, mean age 62 ± 17 years) with previously implanted RV or dual-chamber pacemaker and normal LV function were included in the study. None of the patients had ventricular conduction abnormality during atrial rhythm. All the vasoactive medications were withheld 24 hours prior the study. Patient characteristics are summarized in Table 1. [^{11}C]acetate PET imaging was used to measure oxidative metabolism, [^{15}O]H_2O to measure myocardial perfusion and an echocardiographic examination to measure LV volumes, stroke work and dyssynchrony. Patients were studied both during AAI pacing or sinus rhythm without RV pacing (pacing-OFF) and during RV pacing (pacing-ON) at the same heart rate. During pacing-ON, AV delay was kept shorter (mean 129 ± 30 ms) than natural AV delay (mean 262 ± 79 ms) to ensure successful RV pacing (Table 1).

The sequence was pacing-OFF – pacing-ON in seven patients and pacing-ON – pacing-OFF in three patients. The device was programmed to the desired setting at least 1 hour prior to the PET and echocardiographic studies. The PET and echocardiographic examinations were performed during the same day approximately 2 hours apart (Figure 1). A standard 12-lead ECG was recorded every 10 minutes during PET imaging to ensure the appropriate pacing

Table 1. Patient characteristics

Patient	Gender	Age (years)	RV lead location	Dyssynchrony with RV pacing	AV delay pacing-OFF (ms)	AV delay pacing-ON (ms)	QRS duration pacing-OFF (ms)	QRS duration pacing-ON (ms)
1	F	87	septal	yes	170	90	100	140
2	F	47	inferobasal	no	350	120	100	170
3	M	54	septal	no	190	160	110	100
4	M	66	basal	no	270	150	100	160
5	F	62	septum	yes	240	100	100	170
6	M	77	apical	yes	380	180	90	170
7	M	62	septal	no	270	140	110	180
8	M	68	basal	yes	350	120	110	180
9	F	28	apical	yes	250	140	80	180
10	F	73	apical	yes	150	90	80	150
Mean ± SD		62 ± 17			262 ± 79	129 ±30*	98 ± 11	160 ± 25*

* p<0.001 vs. pacing-OFF; AV = atrioventricular; RV = right ventricular.

mode during the study. Maximal time interval between the initiation of atrial and ventricular activations (AV delay) and maximal QRS duration were measured both during pacing-ON and pacing-OFF. The protocol was approved by the institutional ethic review board of Turku University Hospital and was carried out in accordance with institutional guidelines.

Echocardiography

Images were recorded with patients in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parasternal

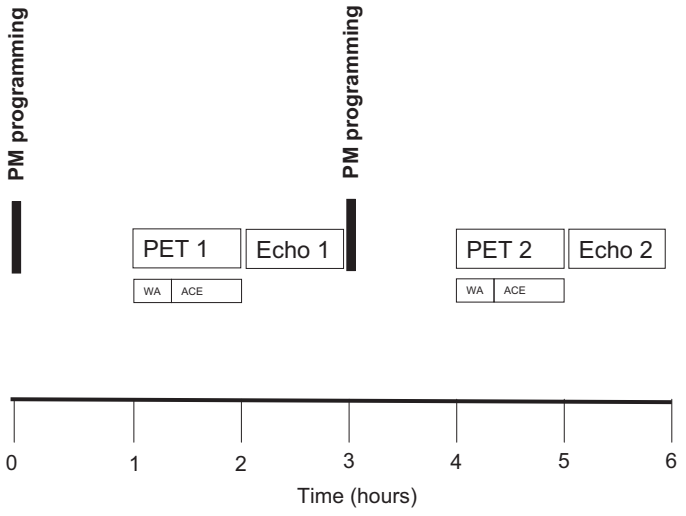

Figure 1. Study flow chart. The sequence was pacing-OFF – pacing-ON in 7 patients and pacing-ON – pacing-OFF in 3 patients. PM = pacemaker; WA = $[^{15}O]H_2O$ PET; ACE = $[^{11}C]$ acetate; PET 1 = first PET study; PET 2 = second PET study; Echo 1 = first echocardiography study; Echo 2 = second echocardiography study.

(long- and short-axis) and apical (2- and 4-chamber) views. Standard two-dimensional images and color Doppler data triggered to the QRS complex were digitally stored in cine-loop format.

Cardiac output and LV work power Cardiac output (CO) was derived from pulsed-wave Doppler analysis. The LV outflow tract velocity-time integral was obtained from the LV long-axis apical view with the sample volume positioned approximately 5 mm proximal to the aortic valve. By measuring the diameter of the LV outflow tract and the heart rate, CO was derived (10). External, or forward, LV work power was calculated (LV work power = systolic blood pressure (SBP) x CO); and subsequently forward LV work power per gram of tissue was calculated as: forward LV work power / LV mass (11).

Left ventricular dyssynchrony Left ventricular dyssynchrony was assessed with the use of speckle-tracking analysis and color-coded tissue Doppler imaging (TDI). Off-line analysis of LV dyssynchrony was performed on digitally stored images (EchoPac version 6.1, General Electric-Vingmed) by an independent observer blinded to all other results; the echocardiographic studies during pacing-OFF and pacing-ON were evaluated in random order.

The assessment of LV dyssynchrony with speckle-tracking analysis has been described in more detail previously (12,13). In brief, speckle-tracking analysis is a technique that tracks frame-to-frame movement of natural acoustic markers on standard gray scale images of the myocardium. With the use of dedicated algorithms, time-strain curves are constructed to assess myocardial strain throughout the cardiac cycle (14,15). Short-axis images of the LV at the level of the papillary muscles were used and automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior, respectively. Time-strain curves for all the 6 segments were then constructed. Subsequently, the time from QRS onset to peak radial strain of each segment was obtained. Left ventricular dyssynchrony was defined as an interval ≥130 ms for the absolute difference in time-to-peak radial strain for the septal or anteroseptal wall versus the posterior or lateral wall (12,13).

In addition, LV dyssynchrony was assessed using color-coded TDI by placing sample volumes in the basal portions of the septum, lateral, anterior and inferior wall (16). The time-to-peak systolic velocity was obtained in these 4 regions and the maximum difference among the 4 regions was used as an indicator of LV dyssynchrony. A delay >65 ms was used as a cut-off value for LV dyssynchrony assessed with TDI, as previously reported (16).

To study the effects of RV pacing and LV dyssynchrony on myocardial oxidative metabolism and efficiency, the PET data were first analyzed based on RV pacing mode only, comparing the two pacing conditions (pacing-ON vs. pacing-OFF). Thereafter, the study population was divided into two groups, according to the presence of LV dyssynchrony during RV pacing.

Positron Emission Tomography

Patients were positioned in a whole body PET scanner (GE Advance Milwaukee, WI, USA) and [^{11}C]acetate and [^{15}O]H_2O PET imaging was performed as previously described (11). The Carimas software package (17) for cardiac image analysis (Carimas, Turku PET Center, Turku, Finland) was used to sample the LV myocardium into polar maps. The resulting polar map represents the tracer uptake in the LV myocardium. Values of regional myocardial blood flow (MBF) expressed in millilitres per gram of tissue per minute and oxidative metabolism (clearance rate constant, k_{mono}, 1/min) were automatically generated on a pixel-by-pixel basis, based on the previously published tracer kinetic models (18-22). Regional values of MBF and oxidative metabolism were then obtained using the conventional 17 segment model. The average values of the septal [2, 3, 8, 9,14] and the lateral [5, 6, 11, 12 and 16] myocardial segments were used to calculate the septal-to-lateral wall ratios. In addition, myocardial efficiency (the relation between the forward work and oxygen consumption) was estimated as: forward LV work power per gram / LV k_{mono} (SBP x CO/LV mass/LV k_{mono}).

Statistical Analysis

All continuous data are expressed as mean ± SD. Comparisons between pacing-OFF and pacing-ON were performed using a two-sided paired t-test; comparisons between dyssynchrony vs. no dyssynchrony were performed using unpaired univariate repeated measurements ANOVA. A p-value < 0.05 was considered statistically significant.

RESULTS

Effects of RV pacing

The patient characteristics, pacing lead positions and the presence of LV dyssynchrony as well as the ECG parameters during pacing-OFF and pacing-ON are presented in Table 1. By definition, AV delay was significantly shorter during pacing-ON than pacing-OFF (129 ± 30 vs. 262 ± 79 ms, $p<0.001$). RV pacing induced clear widening of QRS complex in all except one patient and QRS duration was significantly longer during pacing-ON than pacing-OFF (160 ± 25 vs. 98 ± 11 ms, $p<0.001$).

The hemodynamic, echocardiographic and PET results during pacing-OFF and pacing-ON are summarized in Table 2. There was no significant difference in heart rate and blood pressures during pacing-OFF and pacing-ON (Table 2). In contrast, CO was 13% lower during pacing-ON as compared to pacing-OFF, and LV work power was 13% lower during pacing-ON (Table 2).

For the total study population, the absolute global MBF was comparable during pacing-ON and pacing-OFF, but septal-to-lateral wall MBF ratio was 19% lower during pacing-ON than during pacing-OFF ($p=0.017$) (Table 2). Global myocardial oxidative metabolism (k_{mono}) was comparable during pacing-ON and pacing-OFF. However, the septal-to-lateral wall k_{mono} ratio

Table 2. The effects of RV pacing on hemodynamics, LV function and PET-derived parameters

Measure	Pacing-OFF	Pacing-ON	p-value
Heart rate, bpm	63 ± 8	67 ± 10	0.053
Systolic BP, mmHg	129 ± 25	130 ± 24	0.42
Diastolic BP, mmHg	69 ± 11	72 ± 9	0.27
CO, l/min	4.87 ± 0.69	4.24 ± 0.80	0.0003
LV work power, mmHg·l/min/g	5.17 ± 1.80	4.56 ± 1.78	0.013
MBF, ml/min/g	1.04 ± 0.21	1.05 ± 0.15	0.52
MBF septal/lateral ratio	0.81 ± 0.13	0.66 ± 0.07	0.017
k_{mono}, min^{-1}	0.069 ± 0.016	0.069 ± 0.016	0.94
k_{mono} septal/lateral ratio	1.10 ± 0.19	0.90 ± 0.13	0.009
Efficiency, mmHg·l/g	80.67 ± 20.54	69.93 ± 20.34	0.066

CO = cardiac output; LV = left ventricular; MBF = myocardial blood flow.

was 18% lower during pacing-ON than during pacing-OFF (p=0.009) (Table 2). These changes in LV function and oxidative metabolism resulted in a tendency for lower myocardial efficiency during pacing-ON than during pacing-OFF (p=0.066) (Table 2).

Effects of RV pacing-induced LV dyssynchrony

For the total study population, mean LV dyssynchrony significantly increased during pacing-ON, both assessed with speckle-tracking imaging (pacing-OFF 18 ± 18 ms vs. pacing-ON 121 ± 83 ms, p=0.003) and with TDI (pacing-OFF 12 ± 11 ms vs. pacing-ON 76 ± 39 ms, p=0.001). Using the previously reported cut-off values (12,16), 6 of the 10 patients (60%) developed significant LV dyssynchrony during RV pacing as assessed by echocardiography. The results in patients with dyssynchrony and without dyssynchrony are summarized in Table 3. The blood pressures and heart rates were comparable during pacing-ON and pacing-OFF. In patients with dyssynchrony, CO decreased significantly during pacing-ON as compared with pacing-OFF (from 4.91 ± 0.55 to 4.20 ± 0.69 l/min, p=0.006). In contrast, in the patients without dyssynchrony a moderate decrease in CO was observed during pacing-ON (Table 3). A significant decrease in LV work power was noted only in the patients with LV dyssynchrony during RV pacing (Table 3).

In patients with dyssynchrony, global MBF was not different between the pacing conditions but septal-to-lateral wall MBF ratio was 24% lower during pacing-ON (p=0.016). In patients without dyssynchrony, no difference in global MBF as well as in septal-to-lateral wall MBF ratio was detected between pacing-OFF and pacing-ON (Table 3). Similar to the changes in MBF, in patients with dyssynchrony global k_{mono} was comparable during pacing-ON and pacing-OFF, but the septal-to-lateral wall k_{mono} ratio was 22% lower during pacing-ON than during pacing-OFF (p=0.038). In patients without dyssynchrony, both global k_{mono}, as well as the septal-to-lateral wall k_{mono} ratio were not different between pacing-OFF and pacing-ON (Table 3).

Finally, in patients with dyssynchrony myocardial efficiency was 23% lower during pacing-ON than during pacing-OFF (p=0.023). In contrast, in patients without dyssynchrony myocardial efficiency was comparable during pacing-ON and pacing-OFF (p=0.70)(Figure 2).

Table 3. The effects of RV pacing on hemodynamic, LV function and PET-derived parameters according to the development of dyssynchrony during pacing

	All patients (n=10)	With dyssynchrony (n=6)	Without dyssynchrony (n=4)
MBF, ml/g/min			
Pacing-OFF	1.04 ± 0.21	1.03 ± 0.16	1.07± 0.31
Pacing-ON	1.05 ± 0.15	1.03 ± 0.16	1.07 ± 0.15
p-value*	0.5	0.9	0.5
MBF septal-to-lateral ratio			
Pacing-OFF	0.81 ± 0.13	0.85 ± 0.15	0.75 ± 0.08
Pacing-ON	0.66 ± 0.07	0.65 ± 0.07	0.71 ± 0.04 †
p-value*	0.02	0.02	0.8
k_{mono}, min^{-1}			
Pacing-OFF	0.069 ± 0.017	0.071 ± 0.022	0.068 ± 0.003
Pacing-ON	0.069 ± 0.016	0.074 ± 0.029	0.061 ± 0.006
p-value*	0.9	0.7	0.2
k_{mono} septal-to-lateral ratio			
Pacing-OFF	1.10 ± 0.19	1.11 ± 0.22	1.09 ± 0.17
Pacing-ON	0.90 ± 0.13	0.87 ± 0.05	0.95 ± 0.20
p-value*	0.009	0.04	0.19
CO, l/min			
Pacing-OFF	4.87 ± 0.69	4.91 ± 0.55	4.82 ± 0.95
Pacing-ON	4.24 ± 0.80	4.20 ± 0.68	4.30 ± 1.06
p-value*	<0.001	0.006	0.05
LV work power, mmHg·l/min/g			
Pacing-OFF	5.17 ± 1.80	5.32 ± 2.06	4.95 ± 1.61
Pacing-ON	4.56 ± 1.78	4.52 ± 1.83	4.61 ± 1.97
p-value*	0.013	0.04	0.2
Efficiency, mmHg·l/g			
Pacing-OFF	76.29 ± 23.82	78.11 ± 25.35	73.55 ± 24.78
Pacing-ON	66.37 ± 22.24	60.40 ± 13.93	75.32 ± 31.33 †
p-value*	0.07	0.02	0.7

* Pacing-OFF vs. Pacing-ON; † $p<0.05$ with dyssynchrony vs. without dyssynchrony; CO = cardiac output; MBF = myocardial blood flow; LV = left ventricular

DISCUSSION

RV pacing, myocardial oxidative metabolism and efficiency

To our knowledge, this is the first study to investigate the effect of RV pacing on myocardial oxidative metabolism and efficiency of work. We found that the global LV perfusion and oxidative metabolism remained unchanged despite reduction in LV function during RV pacing. This tended to impair efficiency of cardiac work. Concordantly with the previous study on glucose metabolism, we found an altered distribution of perfusion and oxidative metabolism as septal-to-lateral wall ratios were reduced during RV pacing (9).

In agreement with earlier findings, RV pacing in the present study resulted in a reduction in cardiac output and LV work power and this occurred without changes in hemodynamics and heart rate. Right ventricular pacing causes an activation pattern similar to LBBB, and it reduces the septal-to-lateral wall ratio of mechanical work in the healthy canine heart (23). In a study by Preumont et al. with eight candidates for permanent pacemaker implantation, RV pacing

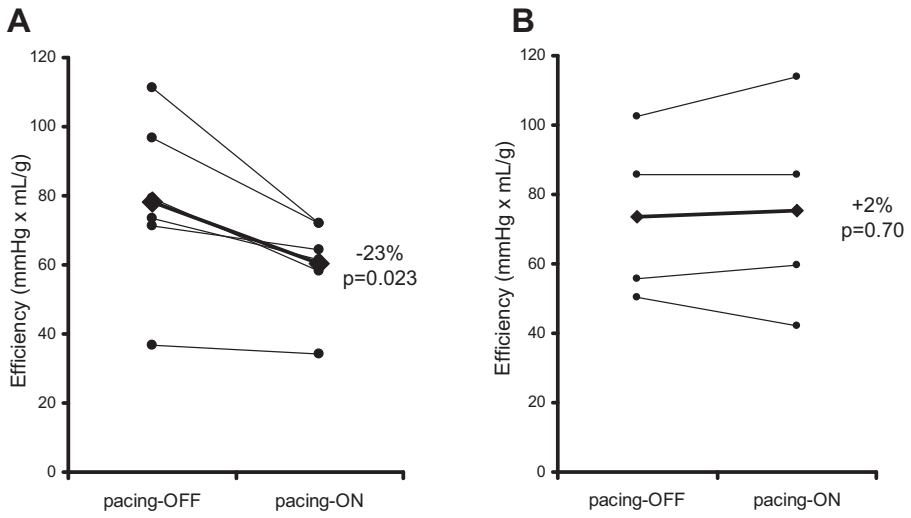

Figure 2. Myocardial efficiency with pacing-OFF and pacing-ON in patients developing dyssynchrony with RV pacing (panel A) and in patients not developing dyssynchrony with RV pacing (panel B). ● = individual values, ♦ = group mean

induced heterogeneity in regional glucose metabolism (9). The defects in glucose uptake were found in the left ventricle near the stimulation site, primarily in the inferior, apical and septal wall. However, the results in the distribution of myocardial perfusion have been more variable either showing no abnormalities (9) or corresponding decrease in septal-to-lateral perfusion (24,25). On the other hand, it was found that regional myocardial perfusion defects may be present in up to 65% of the patients after long-term RV pacing (24,25).

LV dyssynchrony, myocardial oxidative metabolism and efficiency

In the present study, 60% of the patients exhibited significant LV dyssynchrony during RV pacing. Previously, it has been demonstrated that RV pacing may result in significant LV dyssynchrony in a substantial proportion of patients (13). In the present study, speckle-tracking strain analysis was used to assess if patients developed LV dyssynchrony during RV pacing, and cardiac metabolism and efficiency data were analyzed accordingly. Interestingly, during RV pacing QRS duration increased significantly in nine out of ten patients, but significant LV dyssynchrony was noted only in 60% of the patients. This is in agreement with earlier notion that approximately one third of the heart failure patients with prolonged QRS do not demonstrate ventricular dyssynchrony (26).

Importantly, in the patients with LV dyssynchrony during RV pacing, significant changes in septal-to-lateral ratio of MBF and k_{mono} were observed. In contrast, in patients without LV dyssynchrony during RV pacing, no significant changes were noted. These findings emphasize that the perfusion, metabolic and work efficiency abnormalities are paralleling with induced mechanical changes (or LV dyssynchrony). The magnitude of the deterioration of myocardial efficiency in patients who developed dyssynchrony during RV pacing was 23%. Of note, this

large effect was detected in patients with preserved systolic function. In patients with a failing heart, similar degree of effect would likely be clinically significant.

Previous studies in patients with LBBB have demonstrated that LV dyssynchrony is linked with adverse effects on MBF, metabolism and efficiency (27-29). Significant heterogeneity (decreased septal-to-lateral wall ratio) was reported for both MBF (28,29) and oxidative metabolism (11,27,29). Restoration of the normal contraction sequence of the LV by cardiac resynchronization therapy abolishes the heterogeneity and improves myocardial efficiency (11,27). The present study suggests that altered myocardial metabolism and cardiac efficiency may be the underlying mechanism for the deterioration in LV function in patients with LV dyssynchrony during RV pacing.

Study limitations

In the present study a shortened AV delay was used during pacing-ON. This was necessary to enable successful pacing without increasing heart rate. Liebold and coworkers (30) investigated the effect of PR interval during pacing on cardiac function and found that when this interval is shorter LV performance was deteriorated. However, this happened only with very short PR intervals (40 ms) and the optimal interval was 80 ms or higher. In the present study, all PR intervals were 90 ms or higher and, therefore, it is unlikely that a slightly shorter PR interval during RV pacing would contribute to the reduced LV function. In the present study quite a small number of patients was studied. This is especially true for prespecified subgroup analysis. However, each patient was studied twice to allow direct measurement of the effects of RV pacing. Relatively many measurements were performed in a relatively small number of patients. Advanced and very accurate but laborious techniques were applied and we believe that this patients group was large enough to obtain reliable findings.

CONCLUSIONS

RV pacing may result in a significant decrease in LV performance. However, LV oxidative metabolism and efficiency become abnormal only in patients who exhibit LV dyssynchrony during RV pacing. This study emphasizes the importance of synchronous LV contraction also in the non-failing heart. Further studies are needed to assess whether altered myocardial efficiency contributes to the previously suggested unfavorable effects of RV pacing in patients with a failing heart.

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