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CLINICAL RESEARCH
Arrhythmia/electrophysiology

Left bundle branch block causes relative but not absolute septal underperfusion during exercise

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Aims Left bundle branch block (LBBB) often causes septal perfusion defects in radionuclide myocardial perfusion imaging using exercise (Ex) but rarely using vasodilator stress. We studied whether this is due to an underlying structural disease inherent to spontaneous LBBB or whether it is also found in temporary LBBB induced by right ventricular pacing (PM) indicating a functional rather than a structural alteration.

Methods and results Regional myocardial blood flow (MBF) at rest and at Ex was measured with ^{15}O-H_2O and PET in 10 age-matched healthy volunteers (controls), 10 LBBB patients and 10 PM patients with right ventricular pacing off and on (PM off and PM on). Although at Ex septal MBF tended to be higher in LBBB than in controls (3.04 ± 1.18 vs. 2.27 ± 0.72 mL/min/g; $P =$ ns), the ratio septal/lateral MBF was 19% lower in LBBB than in controls ($P < 0.05$). Similarly, switching PM on at Ex decreased the ratio septal/lateral MBF by 17% ($P < 0.005$).

Conclusion The apparent septal perfusion defect in LBBB is mainly due to a relative lateral hyperperfusion rather than to an absolute septal flow decrease. This pattern seems to be reversibly inducible by right ventricular pacing, suggesting a functional rather than a structural alteration.

Keywords Left bundle branch block • Pacing • Positron emission tomography • Myocardial perfusion • Exercise

Introduction

Spontaneous left bundle branch block (LBBB) is associated with increased cardiovascular and overall mortality.[1–3] Left bundle branch block is characterized by a delay in electrical and accordingly mechanical activation of the left ventricle resulting in intra- and interventricular asynchrony eventually leading to systolic and diastolic dysfunction.[4,5] Right ventricular pacing (PM) mimics electrical and mechanical findings of spontaneous LBBB and may also lead to left ventricular dysfunction.[6]

Both spontaneous as well as PM-induced LBBB are associated with false positive perfusion defects particularly in the septal area during exercise (Ex) radionuclide myocardial perfusion imaging (MPI)[7–12] resulting in numerous coronary angiograms revealing normal coronary arteries. This phenomenon is far less frequent using pharmacological vasodilator stimuli instead of bicycle Ex.[13–15] As potential explanation for the apparently false positive perfusion defects, several mechanisms have been proposed, namely decreased septal perfusion due to asynchronous contraction of the septum,[9] shortened duration of the diastole,[16] diminished septal oxygen demand due to impaired septal wall thickening,[17] and septal small vessel disease or fibrodegenerative changes.[14]

The aim of the present study was to investigate the quantitative regional myocardial perfusion [myocardial blood flow (MBF)] pattern in spontaneous LBBB at rest as well as during (vasodilator and) bicycle stress. Furthermore, we also studied the acute impact of reversible LBBB induced by short-term right ventricular pacing on regional MBF in non-PM dependent subjects in order to discriminate between underlying fixed structural pathology vs. functional (and therefore inducible) alteration.

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Methods

The study protocol was approved by the local ethics committee. All subjects gave informed and written consent before the study.

Study population

Ten age-matched healthy volunteers (controls; mean age 57.5 ± 9.1 years, 6 females and 4 males, QRS length 88 ± 10 ms) served as controls and were compared with 10 patients with permanent spontaneous LBBB (mean age 57.3 ± 11.0 years, 4 females and 6 males, QRS length 145 ± 13 ms). The PM group ($n = 10$, mean age 50.9 ± 12.4, 2 females and 8 males) included seven patients with implanted dual chamber cardioverter–defibrillator due to arrhythmogenic right ventricular cardiomyopathy (ARVC) ($n = 5$), Brugada syndrome ($n = 1$) or acute ventricular fibrillation of unknown origin ($n = 1$), and three patients with an implanted dual chamber pacemaker due to history of vagal syncope ($n = 1$), transient post-operative AV-Block III ($n = 1$) or intermittent Sick Sinus Syndrome ($n = 1$). None of these patients was PM-dependent. All the subjects had no history of and low clinical probability for coronary artery disease (CAD)[18] and no ischaemic symptoms during supine bicycle Ex testing. In the PM group, significant coronary or valvular disease, left ventricular hypertrophy, and other significant left ventricular disease had additionally been excluded by echocardiography and coronary angiography in all patients except in one with ARVC. All participants refrained from ingesting caffeinated beverages or food for 24 h before the study.

Study protocol

In controls, MBF was measured at rest. Supine bicycle Ex (model 380 B, Siemens-Elema AG, Switzerland) was then performed, starting at 25–50 Watts (W) with increase in workload at intervals of 1 min until fatigue occurred. Myocardial blood flow measurement was performed immediately after the end of the Ex, as previously documented.[19–21] In LBBB patients, MBF was measured at rest, during standard adenosine (Ado) infusion (0.14 mg/kg/min),[22,23] and immediately after supine bicycle Ex.

In the PM group, resting MBF was acquired with PM off as well as with PM on. This was followed by two measurements of MBF (PM off and on) during Ado. Supine bicycle Ex was then performed according to the protocol in controls and LBBB patients with PM off and repeated after a 45 min break for recovery with PM on. For PM 'on' settings, the PM was programmed to DDD mode (atrial sensing and ventricular pacing). To ascertain permanent ventricular pacing, a sensed atrioventricular (AV) delay of 30 ms below the intrinsic AV delay was programmed and ventricular capture monitored throughout the scan. Shortening the intrinsic AV delay by 30 ms showed consistent right ventricular pacing with stable paced QRS morphology. In all participants, a CT-transmission scan (80 mA, 140 keV, rotation time 0.5 s) for the purpose of attenuation correction of all emission scans was acquired during the study.[24]

Blood pressure and heart rate were continuously measured by a Finapres™ BP Monitor (BOC Inc., Englewood, CO, USA) and recorded at baseline and at 1 min interval during Ado and Ex. The ECG was monitored continuously throughout the procedure and a 12-lead ECG was recorded at baseline and every minute during Ado and Ex as well as during recovery.

Image acquisition

Scanning was performed at the PET Center of the University Hospital Zurich in Zurich, Switzerland on a Discovery LS PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA), an integration of an Advance NXi PET scanner with a LightSpeed Plus 4-row helical CT scanner. 500–700 MBq ^{15}O-labelled H_2O was injected as an intravenous bolus over 20 s at an infusion rate of 24 mL/min to assess MBF. The line was then flushed for another 2 min. The dynamic two-dimensional image sequences were: 14 × 5 s, 3 × 10 s, 3 × 20 s, and 4 × 30 s.

Image processing

The obtained sinograms were corrected for attenuation and reconstructed on a SUN workstation (Sun Microsystems, Mountain View, CA, USA) using standard reconstruction algorithms. Images were then analysed with the Pmod software package (PCARD, PMOD Technologies Ltd, Adliswil, Switzerland) designed and validated at our institution[20] as previously reported.[20,22,23,25]

Myocardial blood flow and ratio septal/lateral myocardial blood flow

Global and regional MBF is given in mL/min/g. The ratio of septal/lateral MBF was calculated as an indicator for relative differences in regional MBF as the principle of MPI relies on such hyperaemia-induced flow heterogeneities.[26]

Statistical analysis

Data are reported as mean values ± standard deviation (SD). Haemodynamic and PET data at rest and during stress were compared using two-tailed paired or unpaired Student's *t*-test where appropriate. *P*-values less than 0.05 were considered as indicators of statistical significance. Statistical analysis was performed using the SPSS software package (SPSS 12.0.1 for Windows, SPSS Corp.).

Results

All procedures were well tolerated apart from the common side effects caused by Ado. None of the subjects experienced any relevant ECG changes during the procedure.

Haemodynamics and workload

Resting rate pressure product (RPP) (heart rate × systolic blood pressure) and RPP for the immediate post-Ex period (averaged over 4 min) of controls was comparable to RPP in LBBB. Similarly, in the PM group, RPP did not differ significantly from controls neither at rest nor during the post-Ex period (*Table 1*).

Achieved percentage of predicted workload was slightly higher in controls compared with LBBB patients (89 ± 13 vs. 71 ± 15%, $P < 0.05$). In the PM group, no difference in workload was observed during PM off vs. PM on (71 ± 9 vs. 70 ± 12%, P = ns).

Global and regional myocardial blood flow and coronary flow reserve

Global as well as regional MBF was higher in LBBB patients compared with controls both at rest and during Ex. Absolute MBF values were comparable in PM off vs. PM on at rest and during Ex (*Table 2*). Ado-induced MBF in LBBB patients and in the PM group are indicated in *Table 3*. Ex-induced coronary flow reserve (CFR) did not differ between LBBB patients and controls, and was comparable for PM off vs. PM on (except for septal CFR). *Table 4* gives ex- and Ado-induced global and regional CFR values.

Table 1 Haemodynamics

	Controls	LBBB	*P*-value	PM off	PM on	*P*-value
Rest						
SBP	131 ± 15	132 ± 25	ns	125 ± 13	123 ± 13	ns
DBP	79 ± 14	65 ± 22	ns	70 ± 12	71 ± 13	ns
MAP	97 ± 13	88 ± 23	ns	89 ± 11	88 ± 12	ns
HR	67 ± 11	69 ± 6	ns	65 ± 13	72 ± 13	ns
RPP	8735 ± 1275	9163 ± 2081	ns	8123 ± 1846	8845 ± 2130	ns
Exercise						
SBP	155 ± 21	146 ± 24	ns	143 ± 9	131 ± 14	<0.05
DBP	80 ± 16	79 ± 15	ns	79 ± 9	78 ± 8	ns
MAP	105 ± 16	101 ± 17	ns	100 ± 9	96 ± 9	ns
HR	96 ± 15	104 ± 11	ns	86 ± 13	103 ± 10	<0.01
RPP	14654 ± 2068	15000 ± 3155	ns	12186 ± 1765	13353 ± 2075	ns

SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); MAP, mean arterial pressure (mmHg); HR, heart rate (b.p.m.); RPP, rate pressure product (SBP × HR).

Table 2 Global and regional myocardial blood flow (MBF)

MBF	Controls	LBBB	*P*-value	PM off	PM on	*P*-value
Rest						
Global	1.15 ± 0.23	1.82 ± 0.39	<0.001	0.94 ± 0.16	1.10 ± 0.31	ns
Septal	1.11 ± 0.22	1.88 ± 0.59	<0.005	0.84 ± 0.16	1.01 ± 0.35	ns
Anterior	1.15 ± 0.26	1.77 ± 0.64	<0.05	0.93 ± 0.15	1.18 ± 0.39	ns
Lateral	1.17 ± 0.27	1.66 ± 0.48	<0.05	1.04 ± 0.23	1.10 ± 0.31	ns
Inferior	1.16 ± 0.28	2.03 ± 0.57	<0.001	0.93 ± 0.32	1.13 ± 0.32	ns
Exercise						
Global	2.21 ± 0.65	3.90 ± 1.36	<0.005	1.68 ± 0.52	1.55 ± 0.40	ns
Septal	2.27 ± 0.72	3.04 ± 1.18	ns	1.82 ± 0.70	1.52 ± 0.47	ns
Anterior	2.03 ± 0.75	3.89 ± 2.29	<0.05	1.47 ± 0.53	1.39 ± 0.46	ns
Lateral	2.21 ± 0.68	3.71 ± 1.53	<0.05	1.51 ± 0.48	1.50 ± 0.33	ns
Inferior	2.38 ± 0.64	4.46 ± 1.40	<0.001	1.95 ± 0.55	1.82 ± 0.60	ns

All values of MBF are given as mL/min/g.

Ratio of septal/lateral myocardial blood flow

Figures 1 and *2* show septal/lateral MBF ratios for controls vs. LBBB patients, and for PM off vs. PM on patients, respectively. At rest, no significant difference was found in controls compared with LBBB (0.95 ± 0.13 vs. 1.17 ± 0.32, *P*=ns) and in PM off compared with PM on (0.84 ± 0.16 vs. 0.92 ± 0.13, *P*=ns). In contrast, at Ex, the ratio of septal/lateral MBF was 19% lower in LBBB (0.84 ± 0.17) compared with controls (1.03 ± 0.15, $P < 0.05$). Similarly, in the PM group, the ratio of septal/lateral MBF at Ex was 17% lower when PM was switched 'on' compared to 'off' (1.01 ± 0.19 vs. 1.21 ± 0.24, $P < 0.005$; *Figure 3*).

Percent of maximal adenosine-induced myocardial blood flow during exercise in left bundle branch block

In LBBB patients, Ex-induced MBF response in the free wall reached 88 ± 7% of Ado-induced MBF values, whereas this was significantly reduced to 67 ± 5% in the septum ($P < 0.05$).

Discussion

On one hand, our results indicate that LBBB causes a significant shift of septal-to-lateral MBF ratio towards the lateral free wall during Ex. Similarly, inducing a reversible LBBB by right ventricular

pacing leads to an almost identical but reversible shift. On the other hand, absolute flow values document that this shift during Ex is not due to a true septal underperfusion but rather due to an exaggerated hyperperfusion of the lateral free wall. This may explain the apparent septal perfusion defect during Ex in patients with LBBB despite normal coronary arteries, contributing to the numerous false positive results in MPI in LBBB patients using bicycle Ex protocols.[8–11] The fact that this finding can be reproduced by a PM-induced LBBB supports a functional mechanism severely challenging the hypothesis of underlying structural septal microvascular coronary disease in LBBB suggested by other authors.

Ado-induced hyperaemic flow response is thought to reflect the maximal vasodilator capacity.[26] The fact that during ado-induced hyperaemia, no regional shift of the septal-to-lateral MBF and CFR was observed—neither in permanent nor in PM-induced LBBB—excludes both microcirculatory dysfunction and epicardial coronary stenoses, further supporting a functional mechanism for the MBF shift during Ex.

The asynchrony of left ventricular motion with the delayed contraction of the free wall may cause a reduction in workload for the interventricular septum resulting in a diminished oxygen demand in this region. Due to this reduced septal contribution to left ventricular work, there might be an increase in oxygen demand in the lateral wall according to its disproportionate workload explaining our finding of shift in regional MBF balance during Ex.

Thus, the lateral absolute hyperperfusion—mainly found during physical Ex—is most probably caused by this imbalance in workload whereby the relative contribution of the lateral wall to LV contraction increases compared with the septum. As a consequence, the Ex-induced hyperaemic response is more pronounced in the lateral region than in the septum to match its higher increase in workload and oxygen consumption. Notably, the global MBF values in LBBB patients were higher than in controls in all study conditions, reflecting that MBF matches an increased oxygen demand resulting from permanent mechanical dyssynchrony

Table 3 Adenosine induced myocardial blood flow (MBF) response

Adenosine			
MBF	**LBBB**	**PM off**	**PM on**
Global	4.70 ± 1.15	3.40 ± 1.22	3.23 ± 0.82
Septal	4.45 ± 1.12	3.38 ± 1.59	3.07 ± 0.80
Anterior	5.42 ± 2.28	3.54 ± 1.27	3.24 ± 0.83
Lateral	4.60 ± 1.07	3.37 ± 1.24	3.37 ± 0.99
Inferior	4.34 ± 1.21	3.31 ± 1.04	3.33 ± 1.04

All values of MBF are given as mL/min/g.

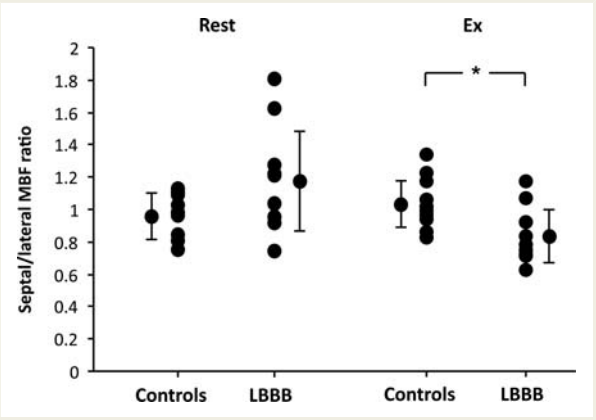

Figure 1 Septal/lateral myocardial blood flow ratios in controls compared with left bundle branch block patients at rest and during supine bicycle exercise. *$P < 0.05$.

Table 4 Global and regional coronary flow reserve (CFR)

CFR	Controls	LBBB	PM off	PM on
Exercise				
Global	2.01 ± 0.72	2.17 ± 0.67	1.80 ± 0.50	1.48 ± 0.42
Septal	2.12 ± 0.74	1.51 ± 0.75	2.11 ± 0.51	1.62 ± 0.55*
Anterior	1.89 ± 0.91	2.39 ± 1.27	1.60 ± 0.56	1.28 ± 0.59
Lateral	1.97 ± 0.72	2.39 ± 1.00	1.53 ± 0.68	1.44 ± 0.37
Inferior	2.22 ± 0.94	2.25 ± 0.85	2.25 ± 0.80	1.74 ± 0.77
Adenosine				
Global		2.63 ± 0.55	3.75 ± 1.36	3.24 ± 1.32
Septal		2.49 ± 0.65	4.16 ± 1.98	3.40 ± 1.38
Anterior		3.10 ± 0.76	3.98 ± 1.59	3.11 ± 1.35
Lateral		2.99 ± 1.01	3.41 ± 1.38	3.43 ± 1.59
Inferior		2.24 ± 0.66	4.02 ± 1.97	3.29 ± 1.65

*$P < 0.05$ vs. PM off.

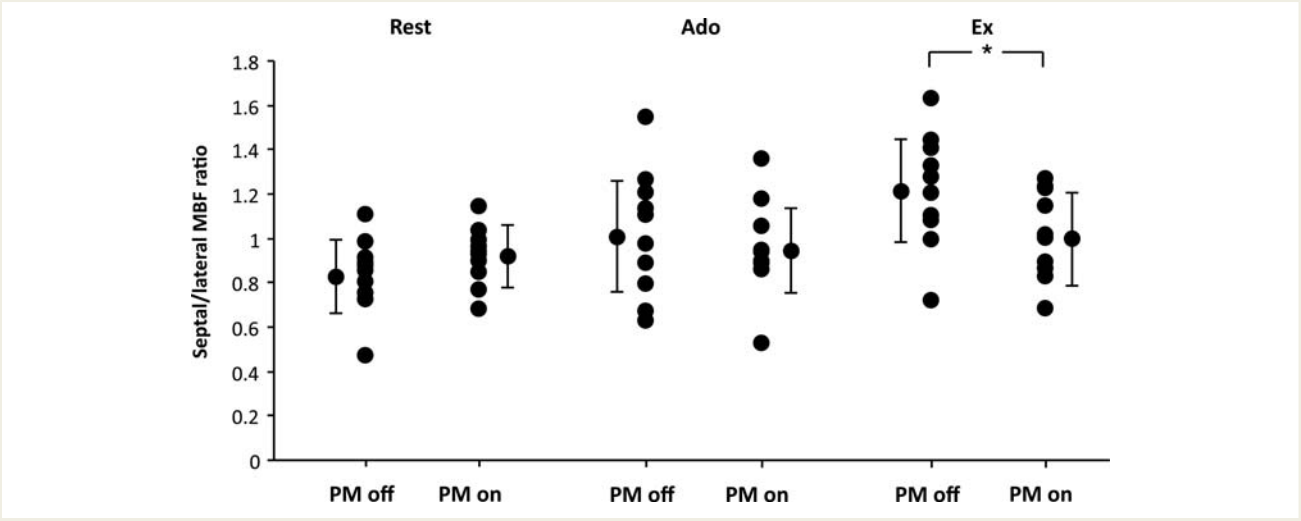

Figure 2 Septal/lateral myocardial blood flow ratios in PM patients with right ventricular pacing 'switched on' compared to 'off' at rest, during adenosine stress, and during supine bicycle exercise. *$P < 0.005$.

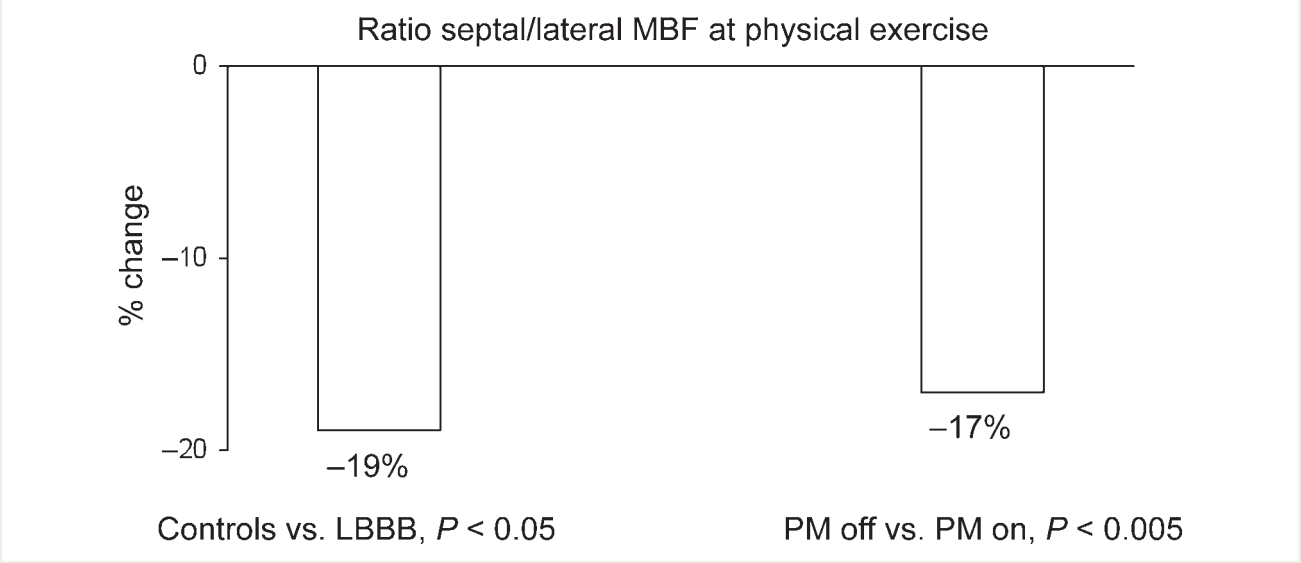

Figure 3 The ratio of septal to lateral myocardial blood flow is an indicator of regional flow distribution pattern. At exercise, this ratio is 19% lower in patients with spontaneous left bundle branch block (LBBB) than in controls indicating a shift of the perfusion balance from the septum towards the lateral free wall. Interestingly, a similar shift (−17%) is observed during temporary LBBB induced by right ventricular pacing (PM on) compared to PM off.

regardless of workload condition. This is further supported by the comparable CFRs in LBBB patients and controls.

Nowak *et al.*[27] have documented a diminution of septal metabolism in patients with LBBB which was attributed to a reduction in septal workload due to the asynchronous activation of the LV contraction. The latter is based on evidence from experimental animal data[28] where rapid RV pacing reduced mechanical work at the site of earliest activation (comparable to the septum in LBBB) by 50%, but increased mechanical work at the opposite site by 50%. The fact that this cannot only be seen in spontaneous LBBB but also be induced by temporary RV pacing suggests a predominantly functional rather than a structural underlying alteration. This might be explained by the profound changes in left-ventricular activation sequence induced by either form of LBBB leading via reversed right-to-left activation of the interventricular septum to a delayed activation of the left ventricular free wall.[29] This causes a markedly retarded contraction of the left ventricle with prolonged left ventricular isovolumetric contraction time and/or delayed mitral valve closure.[30] The amount of this delay has been found to be more pronounced in patients with spontaneous LBBB compared with

patients with PM-induced LBBB[31] in part explaining the more pronounced heterogeneity in Ex-induced regional MBF we found in spontaneous LBBB. Further explanations for this finding in our study are that in the PM group, the individuals served as their own controls, whereas LBBB patients were compared with age-matched controls. In addition, the PM patients were significantly younger and they were not PM-dependent so that LV remodelling due to chronic RV-pacing appears unlikely. Furthermore, the mechanical consequences of the PM-induced LBBB may induce similar but not identical dyssynchrony patterns compared with spontaneous LBBB, which may explain the subtle differences between LBBB and PM on.

Metabolic studies in patients with LBBB have shown that relative septal FDG uptake compared to uptake of radioactive tracer for MBF is markedly reduced during resting condition.[32] Whether this is due to myocardial scaring or rather a result of a reduced septal glucose metabolism due to the low resting septal workload with consequently diminished oxygen demand has not been clarified yet, tough the latter explanation appears most probable in view of our results. This may have implications for treatment of heart failure by resynchronization therapy, as the latter seems to achieve its beneficial mechanical effect primarily by enhanced timing rather than by intrinsic muscle contraction and, therefore, without increasing perfusion demand, underlining the unique characteristics of this treatment.

Study limitations

Only approximately two-thirds of predicted value for upright bicycle Ex was achieved. This, however, corresponds to 100% of predicted Ex capacity using upright bicycle Ex testing as previously reported.[33–35] Although, in PM patients, left ventricular pathology was excluded by echocardiography and coronary angiography, the underlying disease may potentially independently have an influence on myocardial perfusion pattern. Our findings are nevertheless valid as each patient served as his or her own control thereby eliminating such potentially confounding effects. In LBBB patients, no coronary angiogram was obtained and therefore CAD cannot be excluded completely. Nonetheless, in these patients, coronary angiography was not considered justifiable as CAD was excluded clinically and by normal MBF and CFR values by PET.

Finally, in PM 'on' patients, AV synchrony might have been affected by the shortened AV delay, thereby contributing to the reduced global MBF during Ex. Nonetheless, the changes in AV delay are unlikely to explain heterogeneities in regional MBF, as they do not have any effect on intraventricular mechanical synchrony. This was further supported by the similar septal to lateral MBF ratios in our LBBB and PM patients.

Conclusions

We conclude that the apparent relative septal underperfusion during Ex in LBBB patients with normal coronary arteries is due to a lateral hyperperfusion rather than due to a manifest septal flow decrease. The fact that this phenomenon is inducible and reversible by short-term right ventricular pacing suggests a mainly functional (but not structural) alteration as the underlying mechanism of this finding. Quantification of MBF with PET may help avoid misinterpretation of septal perfusion defects in patients with LBBB.

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Conflict of interest: none declared.

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