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Relationship between mechanical and metabolic dyssynchrony with left bundle branch block: Evaluation by 18-fluorodeoxyglucose positron emission tomography in patients with non-ischemic heart failure

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BACKGROUND: Ventricular dyssynchrony is a common finding in patients with heart failure (HF), especially in the presence of conduction delays. The loss of ventricular synchrony leads to progressive impairment of contractile function, which may be explained in part by segmental abnormalities of myocardial metabolism. However, the association of these metabolic disarrangements with parameters of ventricular dyssynchrony and electrocardiography (ECG) findings has not yet been studied.

METHODS: Our aim was to determine the correlation between the presence of left bundle branch block (LBBB) with left ventricular (LV) mechanical synchrony assessed by multiple-gated acquisition scan (MUGA) and with patterns of 18-fluorodeoxyglucose (^{18}FDG) uptake in patients with non-ischemic heart failure. Twenty-two patients with non-ischemic cardiomyopathy, LV ejection fraction (LVEF) $\leq$45% and New York Heart Association (NYHA) Functional Class II or III symptoms under standard medical therapy were included, along with 10 healthy controls matched for age and gender. A 12-lead ECG was obtained to measure the length of the QRS. Mechanical LV synchrony was assessed by MUGA using phase analysis. All patients and controls underwent positron emission tomography with ^{18}FDG to determine the distribution of myocardial glucose uptake. The standard deviation of peak ^{18}FDG uptake was used as an index of metabolic heterogeneity. Student's *t*-test and Pearson's correlation were used for statistical analysis.

RESULTS: The mean age of the patients with HF was 54 $\pm$ 12 years and 72% were male. The length of the QRS was 129 $\pm$ 31 milliseconds and LBBB was present in 9 patients. Patients with HF had decreased LV ^{18}FDG uptake compared with controls (7.56 $\pm$ 3.36 vs 11.63 $\pm$ 4.55 standard uptake value; $p = 0.03$). The length of the QRS interval correlated significantly with glucose uptake

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heterogeneity ($r = 0.62$; $p = 0.002$) and mechanical dyssynchrony ($r = 0.63$; $p = 0.006$). HF patients with LBBB showed marked glucose uptake heterogeneity compared with HF patients without LBBB (41.4 ± 10 vs 34.7 ± 4.9 ml/100 g/min, respectively; $p = 0.01$).

CONCLUSIONS: Patients with non-ischemic heart failure exhibit a global decrease in myocardial glucose uptake. Within this group, subjects who also have LBBB exhibit a marked heterogeneity in segmental glucose uptake, which directly correlates with QRS duration.

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Congestive heart failure (HF) is a progressive disorder characterized by gradual deterioration of left ventricular function. Despite advances in pathophysiologic knowledge and therapy, its treatment remains challenging, carrying high hospitalization rates and poor quality of life.[1] Even with the best modern therapy, HF is still associated with an annual mortality rate of 10%,[2,3] and >50% within 5 years.

Ventricular dyssynchrony is a common finding in patients with HF, especially in the presence of conduction delays. The loss of ventricular synchrony leads to progressive impairment of contractile function.[3] In addition, an overwhelming amount of evidence from randomized, controlled trials supports the clinical benefits of cardiac resynchronization therapy (CRT), which has been shown to reverse ventricular remodeling and to slow disease progression.[2,4–6] This is especially evident in patients with prolonged QRS and left bundle branch block (LBBB) morphology.[7]

The deleterious consequences of dyssynchrony are due in part to hemodynamic effects, but some evidence suggests that segmental abnormalities in myocardial energy metabolism may play a role in the deterioration of contractile function. It is well known that HF leads to a shift in myocardial metabolism making the heart less oxygen efficient,[8–10] but the role of these metabolic changes in disease progression is still controversial.

Recent evidence suggests that, in patients with HF and ventricular dyssynchrony, the utilization of substrates by the myocardium is not homogeneous.[11–13] This cannot be explained by reductions in regional perfusion[14] and may be related instead to local changes in myocardial metabolic machinery. Metabolic heterogeneity implies differences in local energy availability, which can translate into segmental contractile abnormalities.

Studies of glucose utilization in HF have yielded conflicting results, but many studies have shown that it is increased early stages. In advanced heart failure, insulin resistance develops in the myocardium, and most studies have shown a decline in glucose utilization.[15] However, the association of these metabolic disarrangements with parameters of electrical and mechanical dyssynchrony has not yet been explored.

The aim of our study was to evaluate the correlation between QRS duration and presence of LBBB with left ventricular (LV) mechanical synchrony and patterns of 18-fluorodeoxyglucose (^{18}FDG) uptake in patients with non-ischemic HF.

Methods

Patients

A prospective study was conducted in 22 patients with non-ischemic cardiomyopathy and low ejection fraction, and 10 matched controls. Patients were eligible if they fulfilled the following criteria: (a) LVEF (LV ejection fraction) ≤45% confirmed by MUGA; (b) New York Heart Association (NYHA) Functional Class II or III; (c) optimal medical treatment, including beta-blockers at the maximal tolerated dose, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, spironolactone and diuretics; (d) clinical stability as defined by the absence of changes in therapy or clinical status in the last 4 weeks; and (e) normal coronary angiography.

Exclusion criteria were: (a) hypertrophic or congenital cardiomyopathy; (b) uncontrolled hypertension, defined as systolic pressure of >160 mm Hg or diastolic pressure >90 mm Hg; (c) history of angina or myocardial infarction; (d) history of diabetes mellitus or impaired fasting glucose (defined as fasting plasma glucose >100 mg/dl or concurrent diabetes medication).

Ten healthy controls matched for age and gender were included. All controls were asymptomatic; received no pharmacologic therapy; and had normal physical examination, echocardiogram, ECG and exercise stress test findings.

The study was approved by the ethics committee of our institution and written informed consent was obtained from all participants prior to inclusion.

Evaluation of mechanical synchrony using MUGA

Labeling of autologous red blood cells was performed with 99m-technetium (^{99m}Tc) using an in vitro technique. Images were acquired on a dual-detector SPECT gamma camera (ADAC Forte, Milpitas, CA) with a low-energy, long-bore, general-purpose collimator. After 30 minutes post-injection, ECG-gated images were obtained at a rate of 20 frames per cycle (imaging time 10 minutes, 500 cycles), as stated in the *Guideline of the Society of Nuclear Medicine Procedure for Gated Equilibrium Radionuclide Ventriculography* (2002, version 3). Planar image acquisition was performed in the left anterior oblique projection to optimize separation of the right ventricle (RV) from the LV.[16] A blinded, experienced nuclear medicine physician defined regions of interest with manual correction of LV and RV borders. LVEF, LV end-diastolic volume and phase analysis were calculated using specialized software (Mirage, version 5.4; Segami Corp., Columbia, MD).

Phase analysis was applied to scintigraphic data, studying each image spatial coordinate in the R–R interval time by Fourier transformation. From the first derivate of the transformation, a phase angle was calculated for each coordinate and was encoded in a color scale to form a parametric image called a "phase image." This image represents the relative sequence and pattern of ventric-

ular contraction during the cardiac cycle. Finally, intraventricular mechanical dyssynchrony was evaluated using the standard deviation (SD) of the LV phase distribution. The larger the phase SD, the higher the degree of mechanical dyssynchrony.[17]

Glucose uptake distribution by PET

All patients and controls underwent cardiac positron emission tomography (PET) with ^{18}FDG for evaluation of glucose uptake distribution on a 64-slice PET/computed tomography (CT) scanner (Siemens, Knoxville, TN).

For that purpose, patients received a 75-g oral glucose load. Ninety minutes after glucose loading, 5 mCi of ^{18}FDG was injected and 13 dynamic images of the myocardium were obtained during 60 minutes of uptake.[18,19] Reconstructed PET images formatted in short axis, long axis and vertical long axis were obtained for visual analysis of the myocardial ^{18}FDG distribution using QPS 2008 software with the PET processing option (Cedars Sinai Medical Center, Los Angeles, CA).

LV peak glucose uptake was evaluated using the maximum standardized uptake value (SUV), calculated as: myocardium's maximum radioactivity concentration (kBq/g) ÷ injected dose (kBq) ÷ patient's body weight (g). Polar maps (bullseye) were created using the aforementioned QGS software, to obtain the relative glucose uptake among different segments, and the SD of segmental ^{18}FDG uptake was computed as an index of myocardial metabolic heterogeneity.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables expressed as percentages. The distribution of continuous variables was determined by Kolmogorov–Smirnov test. Comparisons were performed using Student's *t*-test for normally distributed variables and the Mann–Whitney *U*-test for non-normally distributed variables. Correlation between two variables was obtained using Pearson's or Spearman's test as needed. Data analysis was performed using SPSS, version 16.0 (SPSS, Inc., Chicago, IL).

Results

Clinical characteristics

The mean age of patients with HF was 54 ± 12 years and 72% were male. The mean LVEF was 32.1 ± 11.6%. Nineteen patients were in sinus rhythm at the time of evaluation and the other 3 were in atrial fibrillation. QRS length at baseline ECG was 129 ± 31 milliseconds; in 12 cases, the QRS interval was >120 milliseconds, and 9 patients (41%) had an LBBB morphology. Three patients had non-specific intraventricular conduction delay with QRS >120 milliseconds and there were no patients with RBBB. One patient had both atrial fibrillation and LBBB. LVEF was not significantly different between patients with or without LBBB (30.0 ± 9.3 vs 32.5 ± 13.1, respectively; $p = 0.6$). The baseline characteristics of the patients are presented in Table 1.

Table 1 Baseline Characteristics of Patients ($n = 22$)

Characteristic	
Age, years (mean ± SD)	54 ± 12
Male gender, *n* (%)	16 (72%)
LV ejection fraction (mean ± SD)	32.1 ± 11.6%
No LBBB	32.5 ± 11.0%
LBBB	30.0 ± 9.3%
Etiology, *n* (%)	
Idiopathic	17 (77%)
Hypertensive	5 (23%)
Sinus rhythm, *n* (%)	19 (86%)
QRS length, ms (mean ± SD)	129 ± 31
LBBB, *n* (%)	9 (41%)
RBBB, *n* (%)	0 (0%)
Risk factors, *n* (%)	
Hypertension	10 (45%)
Smoking history	5 (23%)
Dyslipidemia	5 (23%)
Diabetes	0 (0%)
Medications, *n* (%)	
ACE inhibitors/ARB	20 (91%)
Beta-blocker	20 (91%)
Digoxin	6 (27%)
Spironolactone	18 (81%)
Furosemide	16 (72%)

Mechanical synchrony

Mechanical LV synchrony was assessed by MUGA using phase analysis, as described previously. Ventricular synchrony, measured as the phase analysis SD, was significantly altered in patients with HF compared with normal controls (77.8 ± 22.4 vs 31.9 ± 1.5 milliseconds; $p = 0.02$).

QRS length was linearly correlated with extent of mechanical dyssynchrony ($r = 0.63$; $p = 0.006$). LVEF showed a significant correlation with LV dyssynchrony ($r = -0.53$; $p = 0.02$). Among patients with HF, those with LBBB displayed more accentuated dyssynchrony evaluated with the same technique (95.1 ± 18.8 vs 66.2 ± 16.9 ms; $p = 0.01$).

^{18}FDG uptake

^{18}FDG myocardial uptake was significantly lower in subjects with HF compared with normal controls (7.56 ± 3.36 vs 11.63 ± 4.55 SUV; $p = 0.03$), as shown in Figure 1. This finding was not associated with a significant increase in global heterogeneity in ^{18}FDG uptake, expressed as standard deviation of ^{18}FDG uptake (37.6 ± 7.9 vs 32.6 ± 2.3 in patients with HF and controls, respectively; $p = 0.1$). Figure 2 shows a representative PET image in an HF patient and a healthy subject.

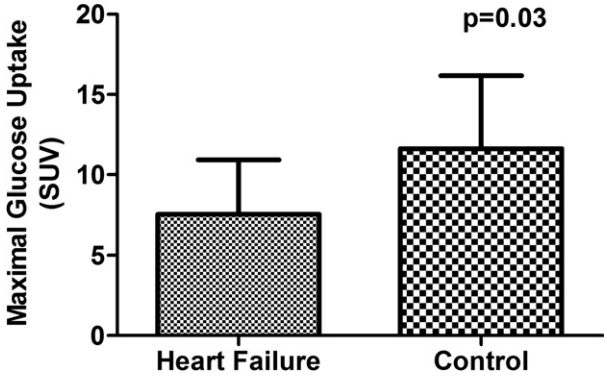

Figure 1 Global ^{18}FDG uptake in heart failure patients and healthy volunteers.

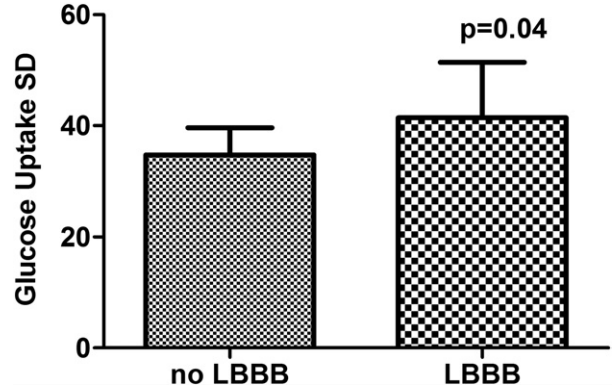

Figure 3 Correlation between QRS interval length and metabolic heterogeneity, evaluated by ^{18}FDG uptake standard deviation.

Intense myocardial glucose metabolism was seen in all normal subjects, with homogeneous ^{18}FDG uptake throughout the myocardium in all of them. Among the HF patients, 4 had completely normal and homogeneous myocardial glucose uptake, 3 had a severe diffuse decrease of glucose metabolism, and 3 had a markedly heterogeneous ^{18}FDG distribution in at least one LV wall. All patients with LBBB had some degree of diffuse septal decrease of glucose metabolism, which was severe in 2 of 9 patients and mild in 5. In 13 patients without LBBB, absent septal uptake was seen in 2, severe decrease in another 2 and mild decrease in 2.

Although patients with HF and LBBB showed similar levels of ^{18}FDG uptake compared with HF subjects without LBBB (8.37 $\pm$ 3.06 vs 6.97 $\pm$ 3.58 SUV, respectively; $p = 0.3$), this conduction abnormality was associated with marked glucose uptake heterogeneity (41.4 $\pm$ 10 vs 34.7 $\pm$ 4.9 for HF patients with and without LBBB, respectively; $p = 0.01$), as shown in Figure 3.

Global heterogeneity in ^{18}FDG uptake correlated highly with QRS length ($r = 0.62$; $p = 0.002$), as shown in Figure 4. On the contrary, no correlation was found between ^{18}FDG uptake SD and LVEF ($r = 0.12$; $p = 0.57$).

Discussion

The main finding in our study is that in patients with HF there is a decrease in total glucose uptake, as demonstrated by ^{18}FDG PET, but only LBBB patients showed marked heterogeneity in this substrate uptake.

Evidence suggests that HF progression is mediated, in part, by alterations in myocardial metabolism induced by neurohumoral activation.[9] HF leads to compensatory activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system, which in turn increases circulating free fatty acids (FFAs), inhibiting the uptake of glucose by the heart and skeletal muscle.[10] Increased plasma glucose, together with pancreatic damage mediated by FFAs and cytokines, further promotes insulin resistance. On the other hand, FFAs are transported into the mitochondria, resulting in uncoupling of cellular respiration and decreased adenosine triphosphate (ATP) production.

Our study had provided new evidence about the relationship between ventricular synchrony and cardiac metabolism, showing that only patients with LBBB present either mechanical dyssynchrony assessed by MUGA and glucose

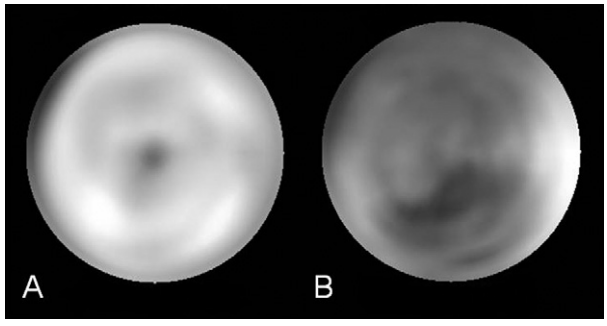

Figure 2 Bullseye of ^{18}FDG uptake using PET. Images show the difference in glucose uptake between a healthy volunteer with intense and homogeneous uptake of marked glucose (A) and a patient with heart failure, with heterogeneous uptake of the tracer (B).

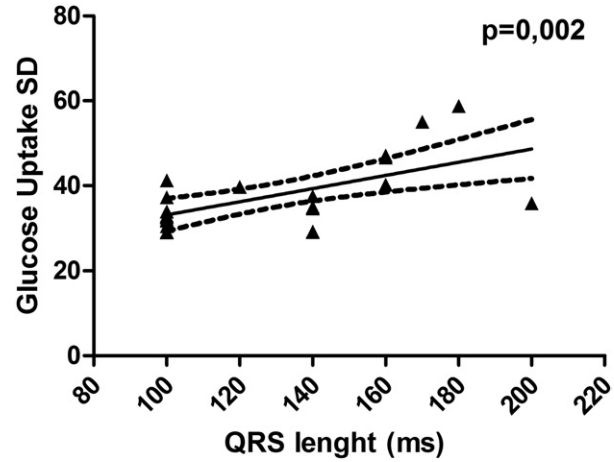

Figure 4 Correlation between LV mechanical dyssynchrony (SPECT phase analysis) and metabolic heterogeneity, evaluated by ^{18}FDG uptake standard deviation.

uptake heterogeneity. This uptake heterogeneity has been described by other investigators.[14,20] However, to our knowledge, this is the first study showing "metabolic dyssynchrony" associated with mechanical dyssynchrony in patients with HF, LBBB and normal coronary arteries.

The underlying pathophysiology of "metabolic dyssynchrony" in patients with LBBB is not clear. A reduction of septal perfusion due to an increase in intramyocardial pressure in the septum during diastole has been postulated, but studies have failed to prove this hypothesis.[14,21] Moreover, this decrease in septal glucose uptake exceeded what is expected based on concomitant perfusion imaging, suggesting that metabolic changes are—at least to a certain extent—independent of local changes of perfusion in the failing heart.[22]

To explain these findings, some investigators have proposed a perfusion-independent alteration of transmembrane glucose transport or the subsequent phosphorylation kinetics,[10] likely due to an interference in cellular membrane pumps through a modification in electric potentials. This is underscored by evidence of preserved septal uptake and beta-oxidation of FFAs, which do not need pumps to enter myocardial cells.[23,24] On the other hand, dyssynchrony is associated with regional differences in gene expression.[25,26] Recently, several small studies in human subjects have demonstrated downregulation of metabolic pathways when the lateral wall was compared with the anterior wall.[27] The temporal disparity in stretch and loading between the septal (early-activated) and lateral (late-activated) regions results in heterogeneous gene expression of many proteins involved in metabolic pathways. Evidence from experimental models suggests that the reduced septal workload and subsequently reduced ATP requirements repress expression of the glucose transporter GLUT-4, resulting in regional insulin resistance with reduction of insulin-dependent myocardial glucose oxidation.[28] Nowak et al demonstrated that cardiac resynchronization therapy restores homogeneous glucose metabolism with minimal influence on myocardial perfusion.[22]

We found a significant correlation between QRS width and glucose uptake heterogeneity. Because most of the subjects with prolonged QRS had LBBB, it is not possible to determine whether this correlation is explained by QRS prolongation itself or by the presence of LBBB. The mechanism of metabolic heterogeneity may be a consequence of focal myocardial fibrosis, endothelial dysfunction or inhomogeneous distribution of wall stress.[11,29] It would be of interest to know whether this process is susceptible to pharmacologic modulation, even in patients with normal QRS width.

A major limitation of our study is the lack of rubidium or ammonia perfusion imaging to compare with ^{18}FDG imaging, which could clarify whether changes in septal glucose uptake depend on changes in local perfusion. Also, ^{18}FDG uptake should be interpreted carefully, because ^{18}FDG is not a direct marker of glucose metabolism. ^{18}FDG is transported into heart muscle cells and phosphorylated by hexokinase to ^{18}FDG-6-phosphate, but it is not metabolized further in the glycolytic pathway, remaining trapped in the myocardium. The rate of glucose metabolism could be directly assessed with the tracer ^{11}C-glucose, but the technique is complex and requires blood sampling with metabolite analysis.[30] Another limitation is that the use of >20 frames per cycle could result in a better evaluation of cardiac synchrony using MUGA, although there is clinical evidence of successful description of dyssynchrony with as few as 16 frames per cycle.[16,31]

In conclusion, among patients with HF, QRS duration is associated with mechanical dyssynchrony. Only patients with LBBB exhibit both mechanical dyssynchrony and evidence of glucose uptake heterogeneity. Although it is not currently possible to establish a causal relationship between the mechanical and metabolic abnormalities seen in these patients, it could be expected that interventions of mechanical dyssynchrony with resynchronization devices associated with metabolic modulation therapies could improve heart function in patients with non-ischemic heart failure and left bundle branch block.

Disclosure statement

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