Myocardial contrast echocardiography in the evaluation of myocardial perfusion in patients with left bundle branch block and coronary artery disease

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Left bundle branch block; Myocardial contrast echocardiography; Myocardial perfusion scintigraphy.

Background. **In patients with left bundle branch block (LBBB), conventional tests such as electrocardiography and myocardial scintigraphy poorly evaluate coronary artery disease. It has been reported that myocardial contrast echocardiography (MCE) is capable of identifying patients with a postinfarction contractile reserve and myocardial functional recovery, also allowing the early identification of late left ventricular remodeling. The purpose of this study was to evaluate, retrospectively, myocardial perfusion in selected patients with LBBB.**

Methods. **Thirty patients (mean age 56 ± 8 years) with LBBB, 15 with normal coronary arteries at angiography and 15 with a previous myocardial infarction and a critical one-vessel residual stenosis at angiography, underwent MCE from June 2000 to May 2001. MCE results were compared with rest thallium-201 myocardial scintigraphy.**

Results. **Among 15 LBBB patients with normal coronary arteries, MCE demonstrated normal perfusion in 14 patients, whereas 1 subject showed an impairment of septal perfusion. In the same group, rest thallium-201 myocardial scintigraphy showed an impaired septal perfusion in 14 patients, whereas 1 subject had a normal perfusion (MCE specificity 93% vs myocardial scintigraphy specificity 7%). Among 15 LBBB patients with coronary artery disease, MCE correctly identified a contrast defect in 14/15 patients, whereas rest thallium-201 myocardial scintigraphy demonstrated a perfusion defect in 15/15 patients (MCE sensitivity 93% vs scintigraphy sensitivity 100%). The two techniques showed a good agreement as for myocardial perfusion in the anterior wall (86.6% anterobasal; 86.6% mid-anterior; 80% distal anterior), the inferior wall (86.6%), the distal segment of the posterior lateral wall (83.3%), but a low concordance was found as for the basal septum (16.6%) and mid-distal septum (33.3%).**

Conclusions. **MCE allows a diagnostic benefit in the detection of microvascular damage in patients with LBBB and unknown coronary artery disease, also in the presence of discordance with rest thallium-201 myocardial scintigraphy.**

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Introduction

Left bundle branch block (LBBB) is a quite common disorder. It is often associated with organic heart disease. Although the Framingham study showed that the association of coronary artery disease with LBBB increases the mortality for cardiovascular disease[1], patients with no clinical evidence of heart disease have an excellent 2-year prognosis[2]. It has also been demonstrated that the presence of LBBB could be considered as an independent predictor for several causes of mortality. Thereby, it is important to determine whether patients with LBBB also have coronary artery disease or other organic heart disease.

The noninvasive diagnostic investigation in LBBB patients has always been quite difficult. At present, only coronary angiography permits to rule out accurately the presence of coronary artery disease in LBBB patients. Thus, many patients undergo coronary angiography to achieve a definite diagnosis, which cannot be obtained with other diagnostic techniques. In fact, exercise-induced ECG ST-segment changes are non-specific in presence of LBBB[3]. Other techniques such as exercise myocardial perfusion scintigraphy, while being more sensitive than ECG, have several limitations and thus poorly discriminate myocardial perfusion. The principal limit is represented by false-positive perfusion defects in septal perfusion, which frequently occur in patients with abnormal conduction[4-6]. Likewise, radionuclide ventriculography is hampered by the asynchronous contraction at rest, which worsens during exercise[7]. However, although pharmacological coronary vasodilation with intravenous dipyridamole[8-11] or adenosine[12,13] and pharmacological stress with dobutamine[13] appear to be associated with higher specificity than that of exercise, there are still false-positive results. Although dobutamine echocardiography satisfactorily discriminates with high specificity, sensitivity ad accuracy, patients with LBBB and previous myocardial infarction, its accuracy turns out to be reduced in the evaluation of interventricular septal ischemia, because of the septal dyskinesia at rest, secondary to LBBB. Previous studies[14,15] reported that myocardial contrast echocardiography (MCE), in patients with a recent myocardial infarction submitted to primary coronary angiography, predicts the contractile reserve, the functional recovery and early identifies the patients prone to late left ventricular dilation, by the assessment of the microvascular integrity within the risk area.

The purpose of this study was to assess, retrospectively, myocardial perfusion in patients with LBBB with normal coronary arteries or associated with coronary artery disease (left anterior descending coronary artery [LAD] disease in previous myocardial infarction) by MCE and to compare MCE with rest myocardial scintigraphy results.

Methods

Patients. The study included 30 patients (14 men, 16 women, mean age 56 ± 8 years), with complete and permanent LBBB, without diabetes, hyperlipidemia and other dysmetabolic disease, who underwent coronary angiography and stress/rest thallium-201 myocardial scintigraphy from June 2000 to May 2001. LBBB was defined according to standard ECG criteria (QRS ≥ 0.12 s, no evidence of R' wave in V_1; no evidence of Q septal wave in V_5-V_6, and I, aVL).

Of the 30 patients enrolled, 15 (group 1) with chest pain syndrome had normal coronary arteries at angiography, whereas the other 15 (group 2) suffering from a previous Q wave anterior wall myocardial infarction had a critical LAD residual stenosis. A previous Q wave myocardial infarction was considered if chest pain occurred > 6 months previously and there was a Q wave on precordial leads. All patients undergoing MCE were informed on the purpose and the nature of the study and provided their informed consent.

Exclusion criteria were galactosemia, age < 18 years, acute life-threatening diseases, diabetes mellitus, dysmetabolic disorders, significant valvular disease, left ventricular ejection fraction < 50%, bad echocardiographic quality in obese patients and women with large breasts. All patients continued their cardioactive therapy.

The study targets were the following: 1) assessment of septal perfusion using MCE in patients with LBBB and normal coronary arteries or previous myocardial infarction due to LAD disease; 2) comparison of MCE results with those of rest scintigraphy.

Myocardial contrast echocardiography. Microvascular perfusion was assessed using MCE (HP Sonos 5500) by intravenous injection 6.5 g of microbubbles (Levovist). Standard echocardiography views were obtained by one sonographer in order to evaluate myocardial contrast perfusion. Each view was divided into 6 segments based on the standard American Society of Echocardiography criteria[16]. Only images and segments that were technically adequate were analyzed. Myocardial contrast enhancement was graded by two experienced observers, with a scale of 0 to 2 (0, no enhancement; 1, partial enhancement; 2, full enhancement). In order to avoid inter- and intraobserver variability in interpreting MCE, all left ventricular myocardial segments were independently reviewed by two observers and once again 2 weeks later by one of them.

Triggering modality definition. To define the best triggering modality to perform MCE in LBBB patients, we studied microvascular perfusion in 10 patients with normal coronary arteries, 5 of them with LBBB and the remaining 5 without LBBB. Microvascular perfusion was qualitatively assessed at the end-diastolic and end-systolic frames of the post-injection cycle showing the best delineation between contrast-enhanced and non-contrast-enhanced myocardium. Among these 10 patients with or without LBBB we triggered at 2, 3, 4 heart beats, verifying time and intensity of myocardial perfusion. An increase in the interval between ECG triggers (pulse interval) to every three cardiac cycles, allowed a complete microbubble replenishment. Moreover, in the 5 patients with LBBB, we set the triggering delay in two different time points: one when end-systole or end-diastole was observed for posterior wall movement in M-mode and the other one when these points were observed for septal movement. It has been noted that triggering at the end-systolic frame of the septum could reveal myocardial perfusion better than at the end-diastolic frame since adjustment of end-systolic ECG gating setting with the interventricular septal motion minimizes the clutter (flash) artifact due to cardiac motion. Thus, the best opacification was qualitatively visualized by triggering one frame every three cardiac cycles, in end systole, and when the acquisition delay of the end-systolic frame was set with the interventricular septal motion.

Myocardial contrast echocardiography in the entire study group. We evaluated perfusion in group 1 and 2 of patients with LBBB, comparing MCE and scintigraphy results with the presence or absence of diseased LAD. Clearly, in this setting, we investigated particularly the interventricular septum and anterior wall, which were both considered divided into three segments (basal, mid, distal). Likewise, the inferior wall and the distal segment of the posterior and lateral wall (apex) were similarly investigated. Because of the worst echocardiographic resolution in mid and basal segments of the posterolateral wall, which conversely are better evaluated by myocardial scintigraphy, we did not investigate these segments. The assessment of myocardial perfusion by MCE has been compared to myocardial scintigraphy, evaluating the accuracy of both methods in the discrimination of perfusion into the interventricular septum, anterior wall and distal segment of the inferior and lateral wall vs coronary angiography.

Stress/rest thallium-201 single photon emission computed tomography. Thirty consecutive patients with LBBB were selected among patients studied for suspected coronary artery disease with stress/rest thallium-201 single photon emission computed tomography (SPECT) as part of the institutional protocol. Only the rest scintigraphy results were compared to basal MCE perfusion results. We used a dual-head SPECT gamma camera (Optima NX, General Electric, Milwaukee, WI, USA), with a step-and-shoot approach every 6° over 180° clockwise circular orbit beginning at a 45° right anterior oblique projection and ending at 45° left posterior. Filtered back-projection was performed using a Butterworth filter with a frequency of 0.4 cycles/pixel to reconstruct transverse tomograms of the left ventricle. Attenuation correction was also performed. The images were further processed to obtain the short-axis and long-axis sections perpendicular to the cardiac axes. The tomograms were divided into 13 segments for qualitative interpretation. Three short-axis slices (apex, mid-ventricular, base) were divided into four regions. The apex was interpreted from the vertical long-axis view at the mid-ventricular level. Perfusion was scored qualitatively by consensus of two experienced observers who were unaware of the patients' data (0 = severe perfusion defect, 1 = moderate perfusion defect, 2 = mild or equivocal perfusion defect, 3 = normal perfusion). Patterns of perfusion defects were separately determined in each segment for rest and stress studies. Briefly, the reversibility of radiotracer uptake was defined according to the changes in segmental score between the stress and rest studies. A reversible defect was considered to be present if a completely reversible or partially reversible uptake defect in at least two adjacent segments was present in the territory of ischemia-related vessel and this was considered a sign of stenosis. A nonreversible uptake defect was scored if uptake was worse in the rest compared to the stress image. Defects in short-axis slices were confirmed in the other two planes. Myocardial segments were assigned to individual coronary arteries: the anterior and septal segments at the apical level, the anterior and anteroseptal segments at the mid and basal ventricular level were assigned to LAD; the inferior segment at the apical level, the inferior and inferoseptal segments at the mid and basal ventricular level to the right coronary artery; the lateral segment at the apical level, the anterolateral and inferolateral segments at the mid and basal ventricular level to the left circumflex artery. For quantitative assessment polar mapping was performed as previously described[17]. To assess the severity of the defect, a region of interest was drawn on the abnormal segments. Counts in the septal region were quantified and normalized to the highest count region. The delayed images were similarly analyzed. The concordance between MCE and rest myocardial scintigraphy has been calculated as percentage of perfusion defect and normal perfusion estimated in both groups of patients by MCE and scintigraphy.

Coronary angiography. All patients enrolled into the study underwent coronary angiography performed via the femoral artery, using the Judkins technique to define coronary anatomy. The left coronary artery was imaged in multiple standard views including frontal, 30° right anterior oblique, 45° left anterior oblique with a 30° cranial angulation, 30° right anterior oblique with a 15° caudal angulation. The right coronary artery was imaged in right anterior oblique and left anterior oblique views. Significant disease was defined by ≥ 50% luminal coronary stenosis in ≥ 1 native coronary artery and/or their major branches. Critical disease was identified by ≥ 75% diameter in a major epicardial coronary artery. Furthermore, the evaluation of left ventricular wall motion has been performed in sagittal-plane angled views.

Statistical analysis. All variables were expressed as mean ± SD. The specificity has been calculated in the usual manner (rate of true negative). The results were expressed as rate of concordance of overall segments compared.

Results

Stress/rest thallium-201 single photon emission computed tomography. In 14 patients with normal coronary arteries and LBBB, qualitative interpretation showed perfusion defects in the LAD area both basal and exercise-induced, while 1 patient showed normal perfusion. The septal region was involved in all cases. The extension of the defects to the anterior region was observed in 5 patients and to the apex in 9 patients.

In the 15 patients with LBBB and previous myocardial infarction qualitative interpretation showed irreversible perfusion defects in the LAD area. Among these 15 patients, 8 patients also showed the extension of the defects to the inferior region (apical segment).

By quantitative analysis the polar map confirmed the qualitative classification in all patients.

Coronary angiography. Among the 30 patients with LBBB, coronary angiography showed in 15 patients no significant stenosis and in the remaining 15 a critical one-vessel residual stenosis (> 75%) of the LAD. These patients also showed no significant stenosis of the right coronary artery and of the circumflex artery.

Myocardial contrast echocardiography. Among the 15 patients with LBBB and normal coronary arteries (group 1) myocardial scintigraphy at rest demonstrated an impaired septal perfusion in 14 patients, while only 1 patient had normal myocardial perfusion. On the other hand, MCE showed a normal perfusion in 14 patients whereas there was an impaired septal perfusion in 1 patient only. This patient, who was the first to be evaluated, had hypertrophic disease localized in the mid-ventricular septum, which caused an evident perfusion defect at MCE located in the mid septum.

In the 30 patients with LBBB, the sensitivity and specificity of MCE for detecting perfusion defects in patients with coronary artery disease in the LAD was 93% (14/15) and 93% (14/15), respectively (Fig. 1); conversely, myocardial scintigraphy showed a great sensitivity (15/15, 100%), but a low specificity (1/15, 7%) (Table I).

Among the 15 patients with LBBB and LAD residual stenosis related to myocardial infarction (group 2), the rate of concordance between MCE and myocardial scintigraphy in the assessment of perfusion for each myocardial segment is shown in figure 2. In evaluating perfusion for each ventricular segment, the two methods showed a good concordance in the basal, mid and distal segments of the anterior wall (rate of concordance of 80, 86.6 and 80%, respectively); the inferior wall, the distal segment of the posterior and lateral wall and the distal septum were also well discriminated (rate of concordance of 73.3, 73.3, 73.3 and 73.3%, respectively), whereas the mid and basal septum was poorly discriminated (rate of concordance of 66.6 and 33.3%, respectively). Therefore, the comparison between MCE and myocardial scintigraphy showed a very low rate of concordance (33.3%) in the discrimination of the basal segment of the interventricular septum.

Figure 3 shows the rate of concordance between MCE and myocardial scintigraphy in both groups of patients evaluated for myocardial perfusion. The rate of concordance greatly decreased, especially in septal discrimination, being MCE highly more specific than scintigraphy. MCE and myocardial scintigraphy showed a great concordance in all myocardial segments of the anterior wall (rate of concordance of 86.6% for basal, 86.6% mid, and 80% distal segments, respectively). Furthermore, the inferior wall, the distal segments of posterior and lateral wall were also evaluated, with a rate of concordance of 86.6% for the inferior wall and 83.3% for the posterior and lateral walls. Conversely,

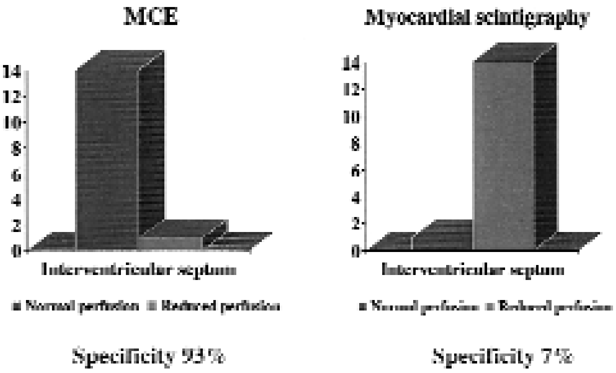

Figure 1. *Comparison between myocardial contrast echocardiography (MCE) and rest myocardial scintigraphy: assessment of myocardial septal perfusion related to the presence or absence of anteroseptal myocardial infarction or ischemia (defined as diseased left anterior descending coronary artery at coronary angiography) in the 30 patients with left bundle branch block.*

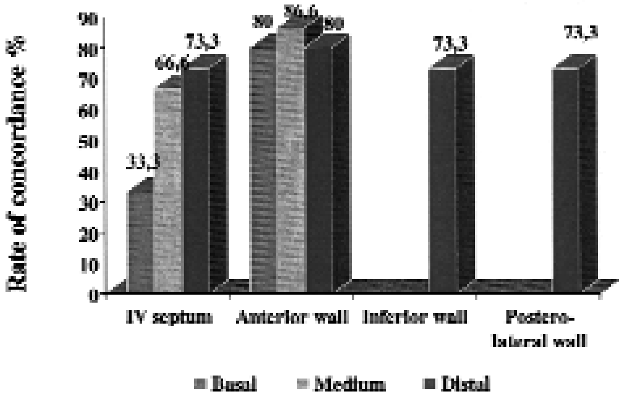

Figure 2. *Rate of concordance between myocardial contrast echocardiography and myocardial scintigraphy in the assessment of perfusion for each myocardial segment in group 2. IV = interventricular.*

Table I. Results in all 30 patients with left bundle branch block.

	Group 1 (n=15)	Group 2 (n=15)	Specificity (%)	Sensitivity (%)
CA LAD disease in MI	0	+		
MCE	VN 14, FP 1	VP 4, FN 1	93	93
Thallium-201 SPECT	FP 14, VN 1	VP 5, FN 0	7	100

CA = coronary angiography; FN = false negative; FP = false positive; LAD = left anterior descending coronary artery; MI = myocardial infarction; MCE = myocardial contrast echocardiography; SPECT = single photon emission computed tomography; VN = very negative; VP = very positive.

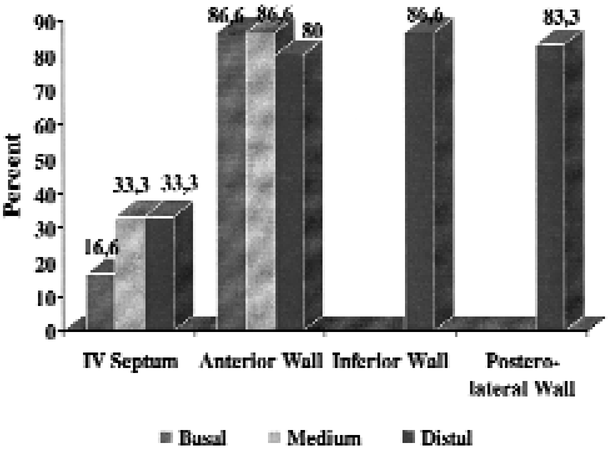

Figure 3. *Rate of concordance between myocardial contrast echocardiography and myocardial scintigraphy in both groups of patients evaluated for myocardial perfusion. IV = interventricular.*

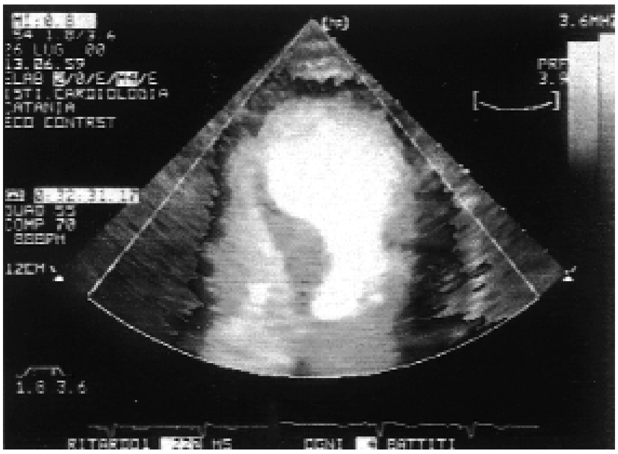

Figure 4. *Myocardial contrast echocardiography demonstrated a normal septal perfusion in a patient with left bundle branch block and normal coronary arteries.*

septal perfusion was poorly discriminated in basal, mid and distal septum (rate of concordance of 16.6, 33.3 and 33.3%, respectively).

Discussion

Our study demonstrated for the first time the utility of MCE in patients with LBBB. MCE allows a diagnostic benefit in the detection of microvascular damage in patients with LBBB without a clear knowledge of the status of the coronary artery, also where the accuracy of thallium-201 myocardial scintigraphy is quite poor, due to false-positive myocardial perfusion defects in the interventricular septum.

We found that in patients with LBBB, but normal coronary arteries, MCE showed normal perfusion, whereas rest thallium-201 myocardial scintigraphy demonstrated a septal or anteroseptal defect in 73% of patients with LBBB, detecting significant LAD only in 42%[10] (Figs. 4 and 5). Only in one subject, MCE showed an impairment of septal perfusion, but this patient was suffering from hypertrophic cardiomyopathy. In this setting, the perfusion defect was probably caused by localized mid-ventricular septal hypertrophy.

The mechanisms of false-positive septal perfusion scintigraphic defects in patients with LBBB are not completely understood. Several hypotheses have been postulated, based on experimental animal studies[18-20], but no studies of this mechanism have been reported in humans. Three principal pathophysiological mechanisms involved in perfusion defects related to LBBB could be suggested: 1) functional ischemia caused by delayed and asynchronous ventricular contraction with septal contraction in the late systolic or early diastolic period (downregulation of the coronary vasomotor tone)[21]; 2) ischemia after exercise related to small vessel fibrodegenerative disease[22]; 3) transmural compression of intramyocardial septal vessels due to delayed and asynchronous contraction, during systole and release of the compressive force during diastole (mechanic factor)[13,23]. At this time, a full explanation for the presence of perfusion scintigraphic defects in patients with LBBB is missing. However, the above mechanisms could justify the high percentage of rest thallium-201 scintigraphic false-positive perfusion defects, localized in the interventricular septum from the apex to the base, observed at scintigraphy in patients without coronary artery disease.

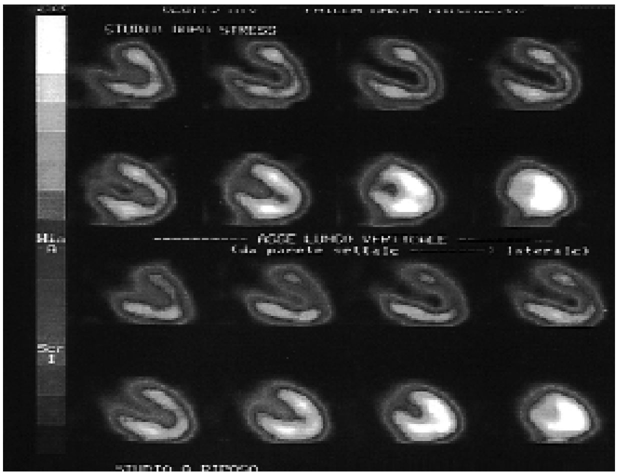

Figure 5. *Myocardial scintigraphy showed an impaired septal perfusion in the same patient as figure 4 with left bundle branch block and normal coronary arteries.*

Furthermore, scintigraphy requires pharmacologic stress test to improve its specificity. Data collected by previous studies have demonstrated that scintigraphic specificity varies from 30%, combined with exercise stress test, to 81% with pharmacologic stress test (adenosine or dipyridamole) Thereby, pharmacologic stress with dobutamine[13], dipyridamole[8-11] or adenosine[12,13] is associated with higher specificity than that of exercise, but there are still false-positive results due to dyskinesia of the interventricular septum, secondary to LBBB. Moreover, the use of thallium-201 SPECT scintigraphy is still unclear and previous data disagree about positive threshold criteria for myocardial perfusion.

Clearly, new refinements of MCE allowed to investigate myocardial perfusion better than in the past. Because of the characteristics and action of radiotracers, basically different from those used in other imaging techniques and little specific in LBBB, MCE probably will be able to provide crucial information over the next years. Thus, thanks to the widespread clinical application of MCE in patients with LBBB, a significant decrease in false-positive perfusion defects and an improved accuracy in the prognostic evaluation could be hypothesized in the LBBB setting.

In conclusion, our data indicate that MCE allows a diagnostic benefit in the detection of microvascular damage in patients with LBBB and unknown coronary artery disease, also when the accuracy of thallium-201 myocardial scintigraphy is quite poor, due to false-positive myocardial perfusion defects in the interventricular septum.

Therefore, intravenous MCE could be used as a noninvasive technique to screen, among patients with LBBB, those at high risk for coronary artery disease.

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