Dobutamine echocardiography predicts functional outcome after revascularisation in patients with dysfunctional myocardium irrespective of the perfusion pattern on resting thallium-201 imaging

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Abstract

***Objective*—To evaluate whether the predictive value of dobutamine echocardiography for assessing contractile reserve was altered by differing patterns of regional myocardial perfusion.**

***Patients*—31 consecutive patients with symptomatic congestive heart failure (left ventricular ejection fraction < 35%) caused by coronary artery disease.**

***Setting*—A district general hospital.**

***Methods*—Thallium-201 perfusion imaging and low dose dobutamine (5–15 μg/kg/min) echocardiography were performed and resting echocardiography was repeated three months after revascularisation. Perfusion pattern and systolic wall thickening were compared using a 12 segment left ventricular model.**

***Results*—Of the 273 severely dysfunctional segments, 106 (39%) showed a normal perfusion and 167 (61%) an abnormal pattern. After revascularisation, recovery occurred in 71 of the segments with a normal perfusion pattern, and in these a dobutamine response was observed in 61 (86%); recovery also occurred in 56 segments with a mild to moderate abnormality of perfusion, and in these a dobutamine response was seen in 46 (81%) (NS). After revascularisation, the positive and negative predictive values for recovery of dysfunctional segments, where the majority were abnormally perfused, were 88% and 86%, respectively. Systolic wall thickening score indices improved from (mean (SD)) 3.21 (0.58) to 2.6 (0.66) ($p < 0.001$) after revascularisation in dobutamine responsive patients ($n = 24$) compared with patients who did not show a dobutamine response (2.86 (0.65) and 3.13 (0.56), $p = 0.61$, respectively).**

***Conclusions*—Dobutamine echocardiography predicted improvement of dysfunctional myocardium after revascularisation irrespective of the resting perfusion pattern seen.**

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Keywords: dobutamine echocardiography; perfusion; revascularisation

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In patients with coronary artery disease and severely dysfunctional myocardium, there may be an admixture of necrotic and viable but dysfunctional myocardium.[1–3] Dobutamine stimulation has been used to assess contractile reserve as an indicator of myocardial viability using echocardiographic techniques.[4–8] However, there has been controversy over the ability of dobutamine to elicit a contractile response in myocardial segments with an abnormal resting perfusion pattern.[8 9] Therefore, if this hypothesis is correct, dobutamine testing may be limited in the diagnosis of viable myocardium in patients with severe left ventricular dysfunction and coronary artery disease, where a reduced resting perfusion pattern is the predominant feature. It has been clearly shown that patients with severe left ventricular dysfunction and heart failure caused by coronary artery disease may benefit from revascularisation.[10 11] Recovery of systolic wall thickening in asynergic segments after such revascularisation is an important feature of viable myocardium.[1 4–8] Thus techniques are being developed to identify patients in whom there is the potential for improved revascularisation.

Thallium-201 uptake early after injection is an indirect marker of regional myocardial perfusion.[12] In this study we therefore examined the role of dobutamine echocardiography in predicting functional recovery of myocardial segments with varying patterns of myocardial perfusion early after thallium-201 administration in patients with chronic heart failure from ischaemic cardiomyopathy who were scheduled for revascularisation

Methods

PATIENT SELECTION

Patients with congestive heart failure (New York Heart Association (NYHA) functional class II–IV) with documented coronary artery disease and severe systolic wall thickening abnormalities (left ventricular ejection fraction < 35%) were evaluated for the study. Patients with significant valvar heart disease, acute myocardial infarction of less than four weeks' duration, unstable angina, and left bundle branch block were excluded. The study was approved by the hospital ethics committee and written consent was obtained.

DOBUTAMINE ECHOCARDIOGRAPHY

Echocardiography was performed using a digital ultrasound system (Advanced Technological Laboratories, HDI CV 3000, Bothell, Washington, USA) in the fundamental mode. Baseline echocardiography was performed in the parasternal long and short axis and in

apical four and two chamber views. Intravenous dobutamine was infused in incremental doses starting at a dose of 5 μg/kg/min. The last dose of 15 μg/kg/min was maintained for a further five minutes. Throughout the infusion the patients were monitored for symptoms, heart rate, and blood pressure and had continuous ECG recording. Echocardiography was also performed continuously throughout the study, but images were acquired at baseline and at the end of each infusion stage in a quad screen continuous loop display on the Image View system (Nova Microsonic, Mahwah, New Jersey, USA). Images were also recorded on videotape.

Images were analysed blind by two observers. Systolic wall thickening was assessed on a semiquantitative scale using the following scoring system: 1, normal; 2, mild reduction; 3, severe reduction; 4, absent wall thickening. A 12 segment left ventricular model was used, as described elsewhere.[6 13] Segments were considered analysable when wall thickening could be identified in at least 50% of each of the 12 segments. Contractile response in an asynergic segment during dobutamine infusion was defined as an improvement in systolic wall thickening by ≥ 1 grade. Similar improvement in an asynergic segment following revascularisation was defined as functional recovery or viable myocardium.[8] The systolic wall thickening index was calculated by adding the score in each segment and dividing the total score by 12. The left ventricular ejection fraction was also assessed using the modified Simpson technique.[14]

THALLIUM-201 SPECT

Imaging was performed 15 minutes after a 74 MBq injection of thallium-201 with pretreatment with 500 μg of glyceryl trinitrate. All images were obtained at the 80 keV photo peak with 30% window, and the digital data were stored on a 128 × 128 matrix. Single photon emission computed tomography (SPECT) imaging was performed in 32 projections (35 seconds for each projection) acquired over a 180° arc from 45° right anterior oblique to 45° left posterior oblique using a gamma camera equipped with a low energy, high resolution collimator. The images were divided into a matching 12 segment model. Each segment was classified quantitatively as having normal (grade 1), mildly reduced (grade 2), moderately reduced (grade 3), or severely reduced/absent thallium-201 uptake (grade 4) compared with the segment with maximum uptake. The images were analysed by two experienced observers who were blinded to clinical and echocardiographic data and any difference in scoring was resolved by consensus. All images were displayed simultaneously in the unprocessed and processed modes for comparison. An asynergic segment was classified as having normal perfusion pattern (thallium-201 score = 0), mild to moderately abnormal perfusion pattern (thallium-201 score $\geq 1 \leq 3$), or severely abnormal perfusion pattern (thallium-201 score = 4).

CORONARY ARTERIOGRAM

All patients underwent coronary arteriography in multiple projections within two months after the non-invasive studies. Significant coronary artery disease was identified when there was > 50% diameter stenosis in a major epicardial artery, and the films were reviewed independently of the non-invasive data.

REVASCULARISATION

Revascularisation was performed based on clinical grounds and coronary arteriography. During revascularisation procedures an attempt was made to revascularise all major epicardial vessels with > 50% diameter stenosis independent of the results of the imaging methods. The grafts were performed using intermittent cross clamp fibrillation techniques at 32.5°C. The left internal mammary artery was used to graft the left anterior descending arteries in all patients. All patients underwent echocardiography at rest only, three months after revascularisation, for assessment of functional recovery of the asynergic segments.

STATISTICAL ANALYSIS

Continuous variables are presented as mean (SD), while discrete variables are shown as proportions or percentages. Comparison of quantitative variables was accomplished by using analysis of variance for repeated measures. The χ^2 test was also used when appropriate. Significance of changes was analysed by the McNemar's test for paired data. A p value < 0.05 was considered significant.

Results

PATIENTS

Thirty one patients were studied, of whom 29 were male and two female, mean age 63 (8) years (range 42 to 82). Twenty eight patients had a history of previous myocardial infarction, 15 had a history of hypertension, and 11 had diabetes. All the patients had congestive heart failure: 16 were in NYHA functional class II, 14 in class III, and one in class IV. Angina was present in five patients. The mean (SD) left ventricular ejection fraction was 24 (10)%. Thirty patients were on diuretics, six on digoxin, 28 on angiotensin converting enzyme inhibitors, and 10 on long acting nitrates. Significant multivessel coronary artery disease was present in 27 patients (90%), of whom 19 had three vessel disease. There was no mortality three months after revascularisation when resting echocardiography was performed.

RESTING SYSTOLIC WALL THICKENING AND PERFUSION PATTERN BY THALLIUM-201

Of a total of 372 possible segments in 31 patients (12 segment model), 56 (15%) showed normal systolic wall thickening at rest, and of these 53 (95%) showed a normal perfusion pattern. Forty three (12%) of 372 segments showed mildly reduced wall thickening; of these 38 (88%) showed a normal to moderately abnormal perfusion pattern. However, 273 (73%) of 372 segments showed a severe reduction in wall thickening (grade ≥ 3), and of these 106 (39%) had a normal

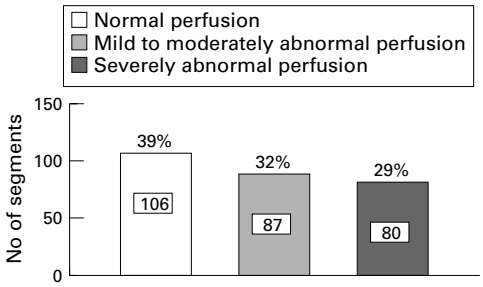

Figure 1 Patterns of perfusion in severely dysfunctional segments.

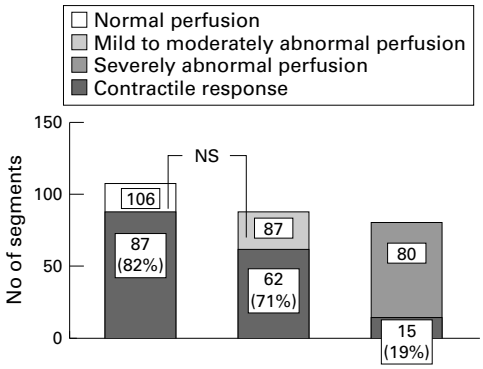

Figure 2 Contractile response in dysfunctional segments (n = 273) with varying perfusion patterns.

perfusion pattern, 87 (32%) a mild to moderate abnormality in perfusion, and 80 (29%) a severely abnormal perfusion pattern (fig 1). Thus 61% of the myocardial segments had an abnormal perfusion pattern (Tl-201 uptake grade ⩾ 2).

CONTRACTILE RESPONSE DURING DOBUTAMINE INFUSION IN SEGMENTS WITH A SEVERE REDUCTION IN SYSTOLIC WALL THICKENING AT REST

Of 273 severely dysfunctional segments, 164 (60%) showed a contractile response. The majority of these (120 (73%)) improved at a dobutamine dose of 5 μg/kg/min, 33 (20%) improved at 10 μg/kg/min, and 11 (7%) at 15 μg/kg/min. Of the 164 segments showing a contractile response, 87 (53%) had a normal perfusion pattern and 62 (38%) a mild to moderately abnormal pattern. (NS). However, only 15 segments with a severely abnormal perfusion pattern (9%) showed a contractile response (fig 2).

THALLIUM UPTAKE IN PATIENTS IN THE INFARCTED AND NON-INFARCTED SEVERELY ASYNERGIC SEGMENTS

There were 28 patients with a history of a previous myocardial infarction, of whom seven suffered infarction in more than one vascular territory. The thallium uptake score in the infarcted and non-infarcted severely asynergic segments was 2.4 (1.1) and 1.5 (1.2), respectively ($p < 0.01$) (table 1).

POST-REVASCULARISATION

After revascularisation, functional improvement occurred in 127 (47%) of the 273 segments with a severe reduction in wall thickening at rest. Of these 127 segments, 71 (56%) had a normal perfusion pattern with thallium-201, and 61 of these (86%) had shown a contractile response during dobutamine infusion before revascularisation; the remaining 56 (44%) of the 127 segments had an abnormal perfusion pattern which improved after revascularisation, and 46 of these (81%) had shown a contractile response to dobutamine (fig 3). The proportion of positive dobutamine responses did not differ significantly in these two groups. Of the remaining 146 severely dysfunctional segments that did not improve after revascularisation, 40 (27%) had shown a normal perfusion pattern before revascularisation, and of these 26 (65%) had shown a contractile response during dobutamine. However, among the 106 segments with an abnormal perfusion pattern that did not improve after revascularisation, only 30 (28%) had shown a contractile response ($p < 001$).

Twenty two (71%) of the 31 patients showed improvement in wall thickening in at least two severely asynergic segments. Dobutamine echocardiography had shown a contractile response in 21 of these patients (95%). Conversely, of the nine patients who did not show improvement after revascularisation in at

Table 1 Thallium score in the infarcted and non-infarcted severely asynergic segments

	Thallium score in severely asynergic segments	
Patient	*Infarct site*	*Non-infarct site*
1	1.10	3.40
2	1.00	2.40
3	3.00	1.00
4	3.80	1.50
5	2.25	1.00
6	3.80	2.33
7	2.00	0.00
8	2.70	1.45
9	2.95	0.00
10	1.80	4.00
11	4.00	1.25
12	1.80	0.00
13	1.95	1.00
14	1.25	0.00
15	4.00	2.10
16	3.25	2.00
17	3.20	2.20
18	1.00	2.60
19	4.00	1.67
20	1.06	0.00
21	2.00	0.00
22	1.00	1.30
23	2.00	1.30
24	1.00	0.50
25	2.20	0.70
26	3.63	2.00
27	4.40	1.94
Mean (SD)	2.40 (1.13)	1.50 (1.20)*

*p<0.01

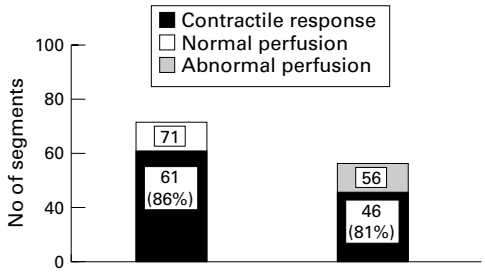

Figure 3 Contractile response in dysfunctional segments with different thallium-201 perfusion patterns that recovered function after revascularisation (n = 127)

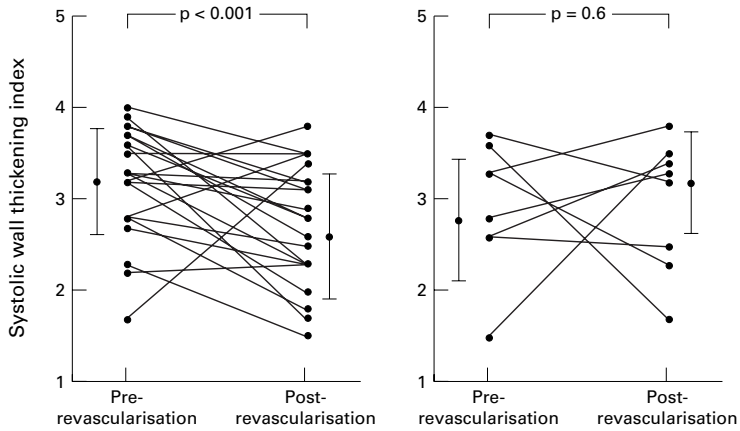

Figure 4 Effect of revascularisation on systolic wall thickening indices in patients with (left) and without (right) a dobutamine response.

least two asynergic segments, dobutamine echocardiography had shown lack of contractile response in six. Thus the positive and negative predictive values of dobutamine echocardiography for functional improvement after revascularisation were 88% and 85%, respectively. Furthermore, the systolic wall thickening index at rest improved from 3.21 (0.58) to 2.61 (0.66) ($p < 0.001$) after revascularisation in patients who showed a contractile response during dobutamine echocardiography. Conversely, in patients who showed a lack of contractile response, there were no significant changes in systolic wall thickening indices before (2.86 (0.65)) and after revascularisation (3.13 (0.56)) (fig 4). Regional thallium-201 uptake (normal to moderately abnormal) in at least two asynergic segments was observed in 23 patients, of whom 18 (78%) showed improvement in wall thickening in at least two of these segments after revascularisation. Conversely of the eight patients with normal to moderately abnormal thallium-201 uptake in less than two asynergic segments, only two showed improvement in wall thickening following revascularisation. Thus the positive and negative predictive values of early thallium-201 uptake for functional improvement after revascularisation were 78% and 75%, respectively (NS *v* dobutamine echocardiography).

Discussion

Low dose dobutamine echocardiography has previously been shown to predict improvement of dysfunctional but viable myocardium after revascularisation.[4 6 7 15] Dobutamine is a synthetic β_1 agonist with additional α_1 and β_2 stimulating properties.[16] At low dose it detects contractile reserve in dysfunctional myocardium by recruiting contractile proteins. However, it has been suggested that where there is a severely compromised coronary flow reserve, it is likely that stimulation of the myocardium by even low doses of dobutamine may precipitate myocardial ischaemia.[17] In this situation, augmentation of contractility may be prevented by a critical reduction in oxygen supply. However, Sun *et al* have recently shown that dobutamine increases coronary blood flow, and thus detection of contractile response in hypoperfused myocardium may not be compromised.[18]

In this study, we selected patients with symptomatic congestive cardiac failure and severe left ventricular dysfunction secondary to extensive coronary artery disease who underwent early thallium-201 imaging to assess their myocardial perfusion pattern and low dose dobutamine echocardiography to evaluate the contractile response before revascularisation. We showed that in this group of patients the perfusion pattern was normal in 39%, mild to moderately abnormal in 32%, and severely abnormal in 29% of the segments showing severe dysfunction. Sawada *et al* similarly found an admixture of dysfunctional and viable myocardium with different patterns of perfusion[9]; however, in that study there was a higher prevalence of normally perfused but dysfunctional myocardium. The higher prevalence of segments with abnormal perfusion pattern in our study may be explained by the fact that our patients had more severely compromised left ventricular function (left ventricular ejection fraction 24% *v* 32%), with a higher prevalence of previous myocardial infarction (90% *v* 72%) and multivessel disease (90% *v* 84%) than in the study by Sawada *et al*.

Although many earlier studies using positron emission tomography reported a substantial decrease in myocardial blood flow in patients with chronic ischaemic left ventricular dysfunction, in more recent studies the blood flow has been found to be normal or near normal in such patients.[1–3 19–22] In our study, 29% of the segments showed severe abnormalities of perfusion by thallium-201 imaging, and in the majority this was not caused by a partial volume effect as only 9% of these segments had a contractile response during dobutamine administration.

The results of our study support the view that the myocardial blood flow pattern at rest is abnormal in many segments, leading to asynergy in the setting of chronic ischaemic left ventricular dysfunction.

The dobutamine induced contractile response in segments with a normal perfusion pattern and in those with a mild to moderately abnormal pattern did not differ significantly, although more segments with a normal perfusion pattern showed a contractile response. Baumgartner *et al*, on the other hand, found a significantly smaller contractile response during dobutamine stimulation in segments with less than 50% viable cells on histology but where thallium-201 imaging showed viability.[23] One reason for this might be that the dose of dobutamine used by Baumgartner was smaller than in our study and therefore elicited a smaller contractile response. Furthermore in our study thallium-201 SPECT was performed early rather than late, and this may result in lower thallium uptake. However, there was a significant reduction in contractile response in dysfunctional segments with severe abnormalities of perfusion pattern. Our findings confirmed those of Sawada *et al*,[9] who showed that improvement in wall motion during dobutamine stimulation was more commonly

observed in myocardial segments with normal perfusion than in those with reduced perfusion. Similarly, Panza *et al* reported that improvement with dobutamine declined in proportion to the severity of the perfusion abnormalities.[24] These findings are consistent with the view that in chronic states of regional dysfunction and hypoperfusion—often referred to as "hibernation"—the myocardium contains degenerated myocytes with loss of myofibrils among myocytes with persisting metabolic activity.[25] The contractile response will depend on the relative prevalence of necrotic and viable myocardium.

In contrast to our finding that the dysfunctional segments which improved after revascularisation had a similar dobutamine response irrespective of the pattern of perfusion, Sawada *et al* showed the response to be reduced in dysfunctional and viable but hypoperfused myocardium compared with dysfunctional but normally perfused segments.[9] Sawada used positron emission tomography to assess viability, while we used recovery after revascularisation as the standard for viability. This could explain the difference in our results, as positron emission tomography has been shown to overestimate myocardial viability when response to revascularisation is used as the gold standard.[26] It is conceivable that viable myocardium surrounded by a large area of extensive fibrosis may show metabolic activity but fail to respond to dobutamine or recover function after revascularisation. However, in the present study we also found that about 65% of normally perfused but dysfunctional segments which failed to improve after revascularisation had a contractile response during dobutamine administration. These could represent viable myocardium which did not show functional recovery, probably because necrosis affected the subendocardial myocardium which contributes most to myocardial systolic thickening.[27] However, as coronary arteriography was not performed after revascularisation, it is not possible to exclude occluded grafts as a cause of lack of improvement in these segments.

In a population with a high prevalence of dysfunctional myocardium with an abnormal perfusion pattern, the positive and negative predictive accuracy of dobutamine echocardiography for the recovery of myocardial function after revascularisation is high, at 88% and 86% respectively. Our study also showed that patients with a dobutamine response had a significant improvement in global left ventricular function after revascularisation compared with those who did not have a response. This is in agreement with the findings of Perrone-Fillardi *et al*, who evaluated patients with hypoperfused and dysfunctional myocardium.[28]

The mechanism by which dobutamine stimulation elicits a contractile response in hypoperfused dysfunctional segments without precipitating ischaemia has been demonstrated by Sun and co-workers.[18] Using positron emission tomography and echocardiography, they clearly showed that the improvement in contractile function during dobutamine infusion was associated with a concomitant increase in myocardial blood flow. The percentage increase in blood flow during dobutamine infusion in the dysfunctional myocardium approached that in normal myocardial regions. This was confirmed by Krivokapich *et al*.[29] The increase in myocardial blood flow occurs because there is persistence of coronary flow reserve distal to a stenosis despite reduction in myocardial blood flow, which dobutamine may exploit.[30] However, prolonged stimulation by dobutamine of a dysfunctional myocardium is known to precipitate ischaemia and even myocardial infarction.[16 31] The standard protocol for dobutamine infusion for the assessment of contractile response, however, has a considerably shorter infusion time. Another potential mechanism whereby the contractile response may be elicited during dobutamine despite reduced resting myocardial flow is through the peripheral vasodilator effect of dobutamine, which causes reduction in left ventricular size and end systolic wall stress, thus increasing systolic wall thickening for the same myocardial blood flow.[7] A transient improvement in the percentage of wall thickening has been shown with dobutamine in a model of short term hibernation without concomitant increase in myocardial blood flow.[31]

In conclusion, low dose dobutamine echocardiography predicts improvement of dysfunctional segments after revascularisation irrespective of the resting perfusion pattern. This technique may be reliably used to assess patients with ischaemic cardiomyopathy for revascularisation.

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