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Residual myocardial perfusion in reversibly damaged myocardium by dipyridamole contrast echocardiography

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In patients with previous myocardial infarction and left ventricular asynergy, dipyridamole infusion may have the capacity to unmask myocardial viability through transient recovery of contractile function in asynergic segments. The purpose of this study was to assess simultaneous changes in myocardial perfusion and LV function — elicited by dipyridamole infusion — in infarcted, asynergic segments. The echo contrast agent Albunex was injected into the left coronary artery of 19 patients (17 males, age 49–70 years) with previous myocardial infarction and baseline left ventricular asynergy, both before and after dipyridamole infusion (up to 0·56 mg . kg^{-1}, i.v.). Analysis was not possible in three patients due to inadequate image quality and in two due to weak contrast. There were no major adverse events, or changes in vital signs or demonstrated on the electrocardiogram. After dipyridamole, 7/14 patients, showed an improvement in regional function of asynergic segments ('responders'), whereas seven patients did not ('non-responders'). Among non-responders, five had a myocardial perfusion deficit corresponding to 41% of the total left ventricular area before dipyridamole and to 38% after dipyridamole. No baseline perfusion deficits were observed in the remaining two non-responders; one of these, however, developed transient asynergy and perfusion deficit after dipyridamole. Among responders, five showed a normal perfusion pattern, both before and after dipyridamole, while the remaining two showed a perfusion deficit which markedly decreased after dipyridamole (from 32% to 13% of total left ventricular area). Thus, residual contractile reserve of asynergic, infarcted ventricular segments appears to be associated with myocardial perfusion either preserved at baseline or recruitable by a coronary dilator stimulus.
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Key Words: Echocardiography, coronary circulation, myocardial perfusion, myocardial viability, dipyridamole.

Introduction

In patients with coronary artery disease, persistent regional impairment of ventricular function does not necessarily result in myocardial infarction with subsequent scarring. In fact, asynergic segments may recover their contractile function either spontaneously or after stimuli[1,2], such as post-extrasystolic potentiation[3] or infusion of low doses of sympathomimetic amine[4,5]. This functional improvement is commonly considered to be a sign of myocardial viability, and its absence as necrosis. Recently, dipyridamole infusion has been shown to enhance the contractile function of asynergic segments[6]. The transient inotropic pre-ischaemic effect of dipyridamole has been attributed to increased coronary blood flow[7], but direct clinical evidence supporting this hypothesis is missing. Thus, the purpose of this study was to simultaneously assess changes in myocardial perfusion and ventricular function — induced by dipyridamole infusion — in patients with previous myocardial infarction and baseline ventricular asynergy. To exploit the high spatial and temporal resolution of ultrasound, myocardial perfusion was evaluated by contrast echocardiography.

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Methods

Study population

The study was performed in 19 patients with previous myocardial infarction. Mean age was 59 years (range 49–70 years), 17 patients were males and two females.

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The infarction was at least 3 months old in all patients and was the first infarction; it was a Q-wave infarction in 12 patients and a non-Q infarction in seven. The Q waves were located in the antero-lateral leads in six patients and in the inferior leads in the remaining six patients. The patients underwent coronary angiography (Judkins technique) either because of post-infarction angina (16 patients) or dyspnoea on effort (three patients). Mean angiographic left ventricular ejection fraction was 45%, ranging from 23% to 60%. Coronary stenoses (>50% diameter narrowing by visual analysis) involving one, two or three major coronary vessels were observed in two, seven and nine patients, respectively. One patient with a previous non-Q myocardial infarction and antero-lateral hypokinesis was shown to have an apparently normal coronary angiogram. Wash out of medication was not performed during the study. All patients were informed of the investigative nature of the study and signed an informed consent form.

Echocardiographic examination

Two-dimensional echocardiographic images were retrieved by either electronic (SSA 270, Toshiba and Sonos 1500, Hewlett Packard) or mechanical sector scanners (SIM 7000, Esaote Biomedica), operating at 3·75, 3·5 and 2·5 MHz, respectively. The patients were examined in a partial left lateral decubitus position, on the cardiac catheterization table. An apical approach was chosen in each patient, orienting the transducer so as to obtain the best delineation of asynergic left ventricular walls. After achieving the optimal gray scale image in each patient, gain setting controls were kept constant. The echocardiographic images were monitored throughout the study and stored on a 0·5 inch VHS video tape recorder.

Echocardiographic contrast agent

Air-filled human serum albumin microspheres (Albunex, Nycomed Imaging AS, Norway and MBI, U.S.A.) were used as the echocardiographic contrast agent in each patient[8]. Albunex is prepared from plasma collected from healthy donors who have been tested and found negative for hepatitis B surface antigen and antibodies to HIV. The agent, which has a concentration of 4×10^8 microspheres/ml with a mean diameter of 4 μm, was kept in a refrigerator and returned to room temperature before the study. It was injected into the left coronary artery of each patient, manually, at a rate of approximately 0·5 ml . s^{-1}. A volume corresponding to the dead space of the catheter was added to the injected dose each time. After each injection, any contrast agent remaining inside the catheter was withdrawn.

Study protocol

The study was performed immediately after routine coronary angiography. A dose of 2 ml of contrast agent — after one-to-one dilution with 5% human serum albumin — was initially injected into the left coronary artery. If the myocardial echo contrast appeared to be adequate, one additional injection of contrast — at the same dose and concentration — was performed. If the contrast appeared to be insufficient, the undiluted solution was injected, keeping the volume at 2 ml. After baseline contrast injections, dipyridamole was infused intravenously up to the dose of 0·56 mg . kg^{-1} over 4 min, but the infusion was interrupted if changes in regional wall motion occurred, including either improvement or deterioration in left ventricular function. After dipyridamole, the contrast agent was again injected into the left coronary artery at the same dose and concentration as the injection before dipyridamole. Finally, aminophylline (up to 3 ml) was injected i.v. to counteract the effects of dipyridamole.

Echographic data analysis

To evaluate regional ventricular wall motion, each study was analysed by two contemporary observers. For each injection, the left ventricle was divided into 16 segments[9], and each segment was scored as normal (score 1), hypokinetic (score 2), akinetic (score 3) or dyskinetic (score 4) to derive a wall motion score index. Whenever a disagreement occurred, the study was re-examined and a consensus reached. To evaluate global left ventricular function, the echocardiographic images were digitized by a computer for image processing (Mipron, Kontron, Germany); before contrast, three end-diastolic and three end-systolic images were sampled for each injection and left ventricular ejection fraction was measured by the Modified Simpson's rule[10]. To evaluate myocardial perfusion, three end-diastolic images before contrast and three at peak myocardial echo contrast, in the same echocardiographic view, were sampled for each injection. The area of perfused myocardium (i.e. the area of myocardium showing apparent contrast enhancement) was planimetred in each of the three contrast images, and the area of total left ventricular myocardium was measured in each of three pre-contrast images. The percentage of perfused myocardium was derived for each injection as the ratio between mean area of opacified myocardium and mean left ventricular area. The percentage of underperfused, or markedly hypoperfused myocardium was obtained by subtraction. To evaluate within- and between-observer variability, myocardial perfusion measurements were repeated a second time by the original observer and by another observer.

Safety

All patients underwent physical examination and 12 lead ECG before and the day following the study. During and immediately after the injections of contrast agent, patients were requested to report any symptoms. One ECG lead and two-dimensional echocardiographic images were monitored throughout the study.

Statistical analysis

The variability of measurements of perfusion deficits was evaluated by the analysis-of-variance, through the study of the variability between-frames within-injections, the variability between-injections within-patients and the variability between patients. The results are based on ratios between mean squared error in the different models. The within- and between-observers variability was evaluated by comparing the variation when including the observers in the model against the total variation. The pre-performance planned hypothesis to be tested was to compare pre- and post-dipyridamole perfusion deficits. This was tested with Student's paired t-test. Subgroup comparisons were done with Student's two-group t-test. *P*-values <0.05 are considered significant.

Results

The study was completed in all 19 enrolled patients. Dipyridamole infusion was interrupted after 2 to 4 min. Five patients could not be analysed: three because of poor image quality and two because of the inadequate contrast effect.

Ventricular function

At baseline, the two-dimensional echocardiogram showed abnormal left ventricular function in each patient — a regional hypokinesis, akinesis or dyskinesis being present in one, 12 and one patient(s), respectively. After dipyridamole, seven patients showed no improvement in regional wall motion of asynergic ventricular segments ('non-responders'), while seven patients showed a transient reduction in the magnitude and extent of left ventricular asynergies ('responders'). Among the non-responders, the wall motion score index after dipyridamole (1.8 ± 0.2, mean ± SD) was not statistically different from baseline (1.7 ± 0.1). Echocardiographic left ventricular ejection fraction was also unchanged during the study: $40 \pm 14\%$ and $38 \pm 9\%$ before the two baseline contrast injections and $38 \pm 6\%$ after dipyridamole. Among the responders, the wall motion score index after dipyridamole (1.2 ± 0.2) was significantly lower than at baseline (1.5 ± 0.3, $P<0.05$). Similarly, left ventricular ejection fraction ($32 \pm 5\%$ and $33 \pm 9\%$ before the two baseline contrast injections) was significantly higher after dipyridamole ($45 \pm 12\%$ $P<0.001$). An example of improved left ventricular function after dipyridamole is illustrated in Fig. 1.

All the seven non-responders to dipyridamole had a Q wave myocardial infarction, while five of the seven patient responders to dipyridamole had a non-Q myocardial infarction. The degree of coronary stenoses in the infarct-related artery was not significantly different between the responders (area stenosis = $78\% \pm 35\%$) and the non-responders to dipyridamole (area stenosis = $84\% \pm 19$).

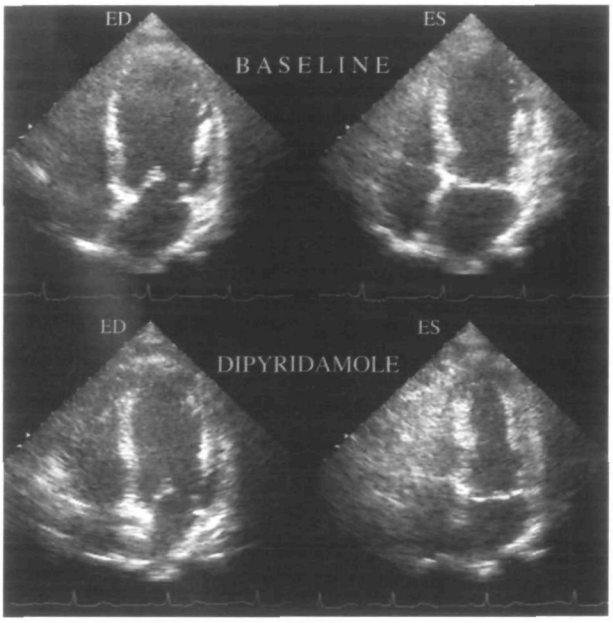

Figure 1 **Effects of dipyridamole on myocardial perfusion and function in a patient with previous infarction. Under baseline conditions (upper panels) the apex and the distal lateral wall of the left ventricle appear asynergic and present a perfusion deficit. After dipyridamole (lower panels) left ventricular global and regional function improve and the perfusion deficit decreases. ED = end-diastole, ES = end-systole.**

Myocardial perfusion

Out of the seven non-responders, five showed a perfusion deficit at baseline. The extent of these deficits corresponded to 41% of total left ventricular area before, and to 38% after dipyridamole ($P<0.05$). The remaining two non-responders showed no perfusion deficit at baseline; however, one of these patients developed transient asynergy and a perfusion deficit after dipyridamole. Out of the seven responders, five showed preserved myocardial perfusion (no perfusion deficits), both before and after dipyridamole, whereas two showed a perfusion deficit at baseline. The extent of these deficits corresponded to 29% and 35% of the total left ventricular area before, and was markedly reduced to 16% and 10% of left ventricular area, after dipyridamole, respectively (Fig. 1).

Reproducibility of measurements

Analysis-of-variance showed that the reproducibility of planimetric measurements of perfused myocardium was good. As regards total variability, frame-to-frame, injection-to-injection and dipyridamole variability accounted for 5%, intra- and inter-observer variability for 4.1% and 1.2%, respectively, while patient differences accounted for 89.7%.

Safety

The test was safe in all enrolled patients. Adverse events occurred in two patients, who complained of headache or shortness of breath. Both symptoms appeared after dipyridamole, were described as mild and did not require specific treatment. No significant changes in heart rate, systolic or diastolic blood pressure were observed the day following the study.

Discussion

Myocardial perfusion was assessed by contrast echocardiography in asynergic, infarcted ventricular segments, both before and after coronary dilation by low dose dipyridamole infusion. The asynergic ventricular walls with improved regional function after dipyridamole showed that myocardial perfusion could be either preserved at baseline or recruitable by vasodilation.

Preserved myocardial perfusion in asynergic segments

One half of our patients with previous myocardial infarction showed no perfusion deficit when studied by contrast echocardiography in resting conditions. This observation has already been reported in previous studies. In fact, even in the presence of a recent infarction and complete coronary occlusion, Sabia *et al.*[11] reported that myocardial perfusion demonstrated by contrast echocardiography may be preserved in the asynergic ventricular segment. This is made possible by the presence of collaterals, and has important clinical implications. Patients with a recent infarction and preserved myocardial perfusion were more likely to have less depressed ventricular function[11] and a greater improvement in function after successful angioplasty[12] than patients with perfusion deficits demonstrated by contrast echocardiography. The above studies support the hypothesis that residual perfusion preserves myocardial viability in infarcted segments. This concept appears to be further supported by the present study, as patients with residual perfusion in infarcted segments were more likely to show transient functional recovery after vasodilation — commonly considered to be the echocardiographic landmark of myocardial viability[5,6].

Recruitable myocardial perfusion in asynergic segments

The second point of this study refers to the dynamic nature of perfusion deficits in patients with previous myocardial infarction. The spatial extent of perfusion deficits decreased after dipyridamole; this improvement was considerable in responders (although not statistically significant due to the small number of responders with baseline perfusion deficits) and was mild, but still present, in non-responders. A residual coronary flow reserve, despite decreased resting coronary blood flow, has been recently demonstrated in man. To determine whether resting myocardial hypo-perfusion indicates exhausted coronary flow reserve, Parodi *et al.*[13] injected radionuclide labelled microspheres into the left ventricular cavity of patients with isolated left anterior descending coronary artery stenosis and no previous myocardial infarction. Despite the presence of perfusion defects at rest, nine patients showed a papaverine-recruitable coronary reserve in the same areas, in agreement with a similar observation by positron emission tomography[14] and with previous experimental studies, where a transmural vasodilator reserve could be identified in the face of depressed resting myocardial perfusion[15–17].

Differential effects of dipyridamole

In patients with coronary artery disease, dipyridamole infusion has two different effects on myocardial perfusion. At an early phase, dipyridamole has a beneficial inotropic effect, whereas later on during the infusion it may induce myocardial ischaemia and ventricular asynergy[18,19]. In this study, the infusion was stopped 2 to 4 min after it was started and beneficial inotropic effects were prominent. Our data are consistent with experimental studies showing that even very low doses of dipyridamole can evoke contractile recovery in asynergic but viable segments[20], and with clinical data suggesting that a substantial increase in coronary flow is obtained after a few minutes of dipyridamole infusion[21]. The primary effect of dipyridamole is adenosine A_2-receptor mediated vasodilation on the coronary arteriole smooth muscle cell, leading to an increase in flow[22]. At this point, an increase in function is to be expected on the basis of the known relationship between myocardial contractility and coronary perfusion[23] as originally described by Gregg[7].

Limitations of the study

The study has several limitations. The number of enrolled patients was limited, and in about one fourth of them it was not possible to analyse the results due to inadequate image quality. Future studies should comprise larger and more homogeneous categories of patients, and possibly involve therapeutic wash out. Dipyridamole-induced changes in ventricular function and perfusion were attributed to the effects of the drug on coronary circulation, while haemodynamic variables were not measured in this study. However, when the effects of dipyridamole on heart rate, and left and right ventricular pressures were measured, the changes were not statistically significant in patients in whom myocardial ischaemia was not induced[24]. The analysis of a greater number of echo sections would have made the results more precise, increasing, however, the number of

injections and prolonging the duration of the examination. The extent of myocardial perfusion deficits at baseline was smaller in responders than in non-responders, suggesting a smaller infarction in the responder group; this way also indicated by the higher incidence of non-Q infarctions in this group of patients. The contrast agent was only injected into the left coronary artery, but right-to-left collateral circulation might have been evaluated if the agent had been injected into the right coronary artery as well[11,12]. Due to difficulties in the quantitation of coronary blood flow by contrast echocardiography[25], myocardial perfusion was scored according to a binary system: i.e. as present or absent, although perfusion is rarely totally abolished, even in the presence of a myocardial infarction. Finally, the assessment of myocardial perfusion by Albunex still requires the direct injection of the contrast agent into the coronary arteries, making the study invasive.

Safety

This study shows that intracoronary injections of Albunex can be safely performed in patients with coronary artery disease and previous myocardial infarction. Observed side effects were minor, and were probably due to dipyridamole infusion. Thus, although caution is recommended as with all intracoronary injections, Albunex can be safely injected intracoronarily in man.

Implications

As this study generated various hypotheses definite conclusions cannot be drawn. However, substantial agreement was shown between improvement in regional wall motion and myocardial perfusion induced by dipyridamole in infarcted, asynergic ventricular segments. It is tempting to speculate that the combined information on myocardial viability — detected as contractile reserve by pharmacological stress echo and as myocardial perfusion by myocardial contrast echocardiography — might help to better characterize viable myocardium as 'stunned' (normal perfusion) or 'hibernating' (low perfusion). Such distinction is of great interest, but is currently obtainable only by expensive and sophisticated positron emission tomography techniques, combining myocardial blood flow and metabolism. Recent studies have shown the possibility of assessing myocardial perfusion non-invasively, after an intravenous injection of echo contrast agents[26–28]. When this opportunity becomes available in the clinical setting, the study of myocardial perfusion by contrast echocardiography might be routinely included in stress echocardiography, probably improving its diagnostic accuracy.

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References

[1] Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982; 66: 1146–9.
[2] Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the 'Hibernating Myocardium'. J Am Coll Cardiol 1986; 8: 1467–70.
[3] Popio KA, Gorlin R, Bechtel D, Levine JA. Postextrasystolic potentiation as a predictor of potential myocardial viability: preoperative analyses compared with studies after coronary bypass surgery. Am J Cardiol 1977; 39: 944–53.
[4] Nesto RW, Cohn LH, Collins JJ Jr, Wynne J, Holman L, Cohn PF. Inotropic contractile reserve: a useful predictor of increased 5 year survival and improved postoperative left ventricular function in patients with coronary artery disease and reduced ejection fraction. Am J Cardiol 1982; 50: 39–44.
[5] Piérard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. J Am Coll Cardiol 1990; 15: 1021–31.
[6] Picano E, Marzullo P, Gigli G *et al.* Identification of viable myocardium by dipyridamole-induced improvement in regional left ventricular function assessed by echocardiography in myocardial infarction and comparison with thallium scintigraphy at rest. Am J Cardiol 1992; 70: 703–9.
[7] Gregg DE. Effect of coronary perfusion pressure or coronary flow on oxygen usage of myocardium. Circ Res 1963; 13: 497–500.
[8] Keller MW, Glasheen W, Kaul S. Albunex: a safe and effective commercially produced agent for myocardial contrast echocardiography. J Am Soc Echocardiogr 1989; 2: 48–52.
[9] American Society of Echocardiography Committee on standards, subcommittee on quantitation of two-dimensional echocardiograms: Schiller NB, Shah PM, Crawford M *et al.* Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echo 1989; 2: 358–67.
[10] Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. Circulation 1979; 60: 760–6.
[11] Sabia PJ, Powers ER, Jayaweera AR, Ragosta M, Kaul S. Functional significance of collateral blood flow in patients with recent acute myocardial infarction: a study using myocardial contrast echocardiography. Circulation 1992; 85: 2080–9.
[12] Sabia PJ, Powers ER, Ragosta M, Sarembock IJ, Burwell RL, Kaul S. An association between collateral blood flow and myocardial viability in patients with recent myocardial infarction. N Engl J Med 1992; 327: 1825–30.
[13] Parodi O, Sambuceti G, Roghi A *et al.* Residual coronary reserve despite decreased resting blood flow in patients with critical coronary lesions. Circulation 1993; 87: 330–43.
[14] Sambuceti G, Parodi O, Marzullo P *et al.* Regional myocardial blood flow in stable angina pectoris associated with isolated significant narrowing of either the left anterior descending or left circumflex coronary artery. Am J Cardiol 1993; 72: 990–4.
[15] Gould KL, Lipscomb K, Calvert C. Compensatory changes of the distal vascular bed during progressive coronary constriction. Circulation 1975; 51: 1085–94.
[16] Canty JM, Klocke FJ. Reduced regional myocardial perfusion in the presence of pharmacologic vasodilator reserve. Circulation 1985; 71: 370–7.
[17] Aversano T, Becker LC. Persistence of coronary vasodilator reserve despite functionally significant flow reduction. Am J Physiol 1985; 248: H403–11.
[18] Picano E, Lattanzi F, Masini M, Distante A, L'Abbate A. High dose dipyridamole echocardiography test in effort angina pectoris. J Am Coll Cardiol 1986; 8: 848–54.

[19] Bolognese L, Sarasso G, Bongo AS *et al.* Dipyridamole echocardiography test. A new tool for detecting jeopardized myocardium after thrombolytic therapy. Circulation 1991; 84: 1100–6.
[20] Stahl LD, Aversano TR, Becker LC. Selective enhancement of function of stunned myocardium by increased flow. Circulation 1986; 74: 843–51.
[21] Wilson RF, White CW. Intracoronary papaverine: an ideal coronary vasodilator for studies of the coronary circulation in humans. Circulation 1986; 73: 444.
[22] Ely SW, Berne RM. Protective effects of adenosine in myocardial ischemia. Circulation 1992; 85: 893–904.
[23] Dole WP. Autoregulation of the coronary circulation. Prog Cardiovasc Dis 1987; 29: 293–323.
[24] Picano E, Simonetti I, Carpeggiani C *et al.* Regional and global biventricular function during dipyridamole stress testing. Am J Cardiol 1989; 63: 429–32.
[25] Rovai D, Ghelardini G, Trivella MG *et al.* Intracoronary air-filled albumin microspheres for myocardial blood flow measurement. J Am Coll Cardiol 1993; 22: 2014–21.
[26] Villanueva FS, Glasheen WP, Sklenar J, Jayaweera AR, Kaul S. Successful and reproducible myocardial opacification during two-dimensional echocardiography from right atrial injection of contrast. Circulation 1992; 85: 1557–64.
[27] Monaghan MJ, Metcalfe JM, Odunlami S, Waaler A, Jewitt DE. Digital radiofrequency echocardiography in the detection of myocardial contrast following intravenous administration of Albunex. Eur H J 1993; 14: 1–10.
[28] DeMaria AN, Dittrich H, Kwuan OL, Kimura B. Myocardial opacification produced by peripheral venous injection of a new ultrasonic contrast agent. Circulation 1993; 88 (Suppl): 1–401.