Myocardial contrast echocardiography and quantitative videointensity analysis after myocardial infarction: correlation between residual myocardial perfusion, contractile reserve and long-term remodeling

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Key words:
Blood volume; Contrast media; Echocardiography; Ventricular remodeling.

Background. **Previous studies have shown the important role played by intracoronary myocardial contrast echocardiography (MCE) in predicting the long-term remodeling and function after myocardial infarction. The left ventricular volume is an important determinant of the clinical outcome following an acute event. No data, however, are available on the role of intravenous MCE in this regard.**

Methods. **Ten consecutive patients with an anterior myocardial infarction were studied using low-dose dobutamine stress echocardiography (Dob) and intravenous MCE 8 ± 4 days after the acute event. In all patients the left anterior descending coronary artery (LAD) was identified as the infarct-related vessel. A LAD score was generated using the percent residual stenosis and its location (proximal, mid, distal portion). Quantitative myocardial videointensity plots were then generated for each of the 12 ventricular segments analyzed, while the volumes were assessed during Dob and after 8 ± 4 months. A higher peak intensity in the dysfunctioning muscle, during intravenous MCE infusion, was assumed to reflect a greater myocardial blood volume.**

Results. **Despite no change in the wall motion score index (WMSI), the percentage changes in systolic volumes during inotropic stimulation showed a linear relation with the LAD score. Furthermore, a normalized myocardial gray level in the asynergic region, taken as the plateau value of the videointensity time curve, showed an inverse relationship with the percentage changes in systolic volumes at follow-up.**

Conclusions. **The residual microcirculation in the dysfunctioning muscle, quantitatively assessed at intravenous MCE 8 ± 4 days after the acute event, has the potential of predicting chronic remodeling following an anterior myocardial infarction, irrespective of changes in the WMSI. The product of the degree of the residual infarct-related artery stenosis and its proximity predicts the ventricular volume response during low-dose Dob.**

(Ital Heart J 2002; 3 (11): 650-655)

Received May 22, 2002;
revision received September 30, 2002;
accepted October 2, 2002.

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Introduction

Several papers have shown the importance of intracoronary myocardial contrast echocardiography (MCE) in predicting the time course of the microvascular damage within the risk region after an acute myocardial infarction and its effects on subsequent ventricular remodeling[1,2]. More recently, intravenous MCE has been used to predict the time course[3]. If the residual myocardial perfusion is related to microvascular integrity and viability[4], it may be the key to predicting the long-term post-myocardial infarction changes in regional function and ventricular volume.

The reserve microcirculation within the risk region, however, might exert beneficial chamber effects even in the absence of evidence of viability, and this might be related to the scaffolding effect exerted by a patent microcirculation[5,6]. In a recent angiographic study we have shown that patients with proven post-myocardial infarction residual myocardial blood volume in the risk region exhibit a reduction in ventricular volumes over time, comparable with that of other patients having the same final conditions of coronary patency and extent of regional dysfunction[7].

The aim of the present study was to evaluate the potential relation between the gray level in the infarct region, taken as an index of the regional myocardial blood volume and quantitatively assessed after intravenous administration of an echocontrast

agent, the extent of the residual contractile reserve as assessed by low-dose dobutamine stress echocardiography (Dob) early after a myocardial infarction, and chronic ventricular remodeling.

Methods

Ten consecutive patients, with good quality echocardiographic images from the apical approach, who had been admitted for an acute, transmural, anterior myocardial infarction were included in this prospective study. They were studied using Dob and MCE with an intravenous infusion of microbubbles of galactose (Levovist, Schering, Berlin, Germany) 8 ± 4 days after the acute event, when stunning of the microcirculation should have at least partially declined. Coronary angiography was performed 1.2 ± 2.8 days after Dob and MCE. In each patient the infarct-related vessel was identified on the basis of the available electrocardiograms and of the location of the asynergic wall motion on the ventriculogram. The left anterior descending coronary artery (LAD) was identified as the infarct-related vessel in all patients. Their clinical characteristics are detailed in table I. The visually assessed residual stenosis of the infarct-related vessel averaged 87 ± 16%. For each patient, a LAD score was generated by multiplying the percentage of residual stenosis by a coefficient of 1, if the lesion was proximal, by 0.66 if it was located at the mid segment and by 0.33 if at the distal segment of the vessel. In the only patient who exhibited angiographic collaterals to the LAD, in the presence of a proximally occluded vessel, a coefficient of 0.50 was used.

Echocardiography. At baseline, during low-dose Dob (10 γ/kg/min) and at follow-up, the ventricular volumes and ejection fraction were measured using the biplane modified Simpson's method. The qualitative wall motion score index (WMSI) was calculated using the 16-segment American Society of Echocardiography model, classifying the segments as normal, hypokinetic or akinetic[8]. Levovist was infused over 2 min at a concentration of 400 mg/ml and at an infusion rate of 4 ml/min; this was preceded by a 2 ml bolus. The images were acquired using second harmonic gray scale imaging with a high mechanical index and an intermittent 1:4 end-systolic trigger, over regular time intervals (15, 45, 90, 150, and 210 s). Three end-systolic images at each step were digitally stored and the quantitative analysis was performed off-line on the first frame of each step. The whole procedure was performed in the apical 4-chamber view and repeated in the apical 3-chamber view as well.

Quantitative analysis of the videointensity level (gray level) was performed off-line on the digitized images using a specific software package (Scion Image, Scion Corporation, MD, USA) and assuming that a higher peak intensity of dye contrast in a region of interest (ROI) reflects a greater myocardial blood volume[9]. The ROIs (20 × 20 pixel matrix) were placed over the mid-myocardium and, for each ventricular segment, the videointensity was measured by averaging two such ROIs and subtracting the background. The videointensity in the left ventricular cavity was also analyzed and used to normalize the myocardial signal. Videointensity plots were thus generated, using the 4- and 3-chamber views, for each of the 12 segments into which the original 16 ventricular segments used for the qualitative analysis had been collapsed. The results were then fitted to an exponential function $y = a \cdot [1-\exp(-b \cdot x)]$ expressing the videointensity as a function of time. Only segments with positive and plateauing values for a, which reflects the myocardial blood volume in the interrogated region[10], were accepted for the final analysis. Examples of curves in a patient with contrast enhancement in the risk region and in a patient with no such effect are shown in figures 1 and 2.

Follow-up. Three patients, who exhibited an isolated, significant residual stenosis of the proximal-medium LAD, underwent coronary angioplasty and stenting immediately after diagnostic coronary angiography, irrespective of the demonstration or otherwise of viability in the infarct region. One patient underwent surgical revascularization within 2 months because of three-vessel disease and evidence of inducible ischemia. All the remaining patients were managed conservatively and discharged on maximal medical therapy with an optimized dosage of ACE-inhibitors and beta-blockers. A follow-up examination and a resting echocardiogram were obtained at a mean of 8 ± 4 months in all patients, except for one who had moved abroad and could not be traced. Two patients experienced residual angina (the same site as the previous myocardial infarction in one case, a remote site in the other) during the follow-up period and in both cases minimal enzyme release was documented in one occasion. In both cases, it was decided not to submit the patient to a revascularization procedure.

Table I. Patients' clinical characteristics.

No. patients	10
Age (years)	58.8 ± 13.2
Sex (M/F)	7/3
Anterior myocardial infarction	10
Sinus rhythm	10
Stenosis of the anterior descending artery (%)	87 ± 16
LAD score	76 ± 19
Single-vessel disease	4
Two-vessel disease	2
Three-vessel disease	4
No. patients submitted to revascularization	
PTCA	3
CABG	1

CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; PTCA = coronary angioplasty.

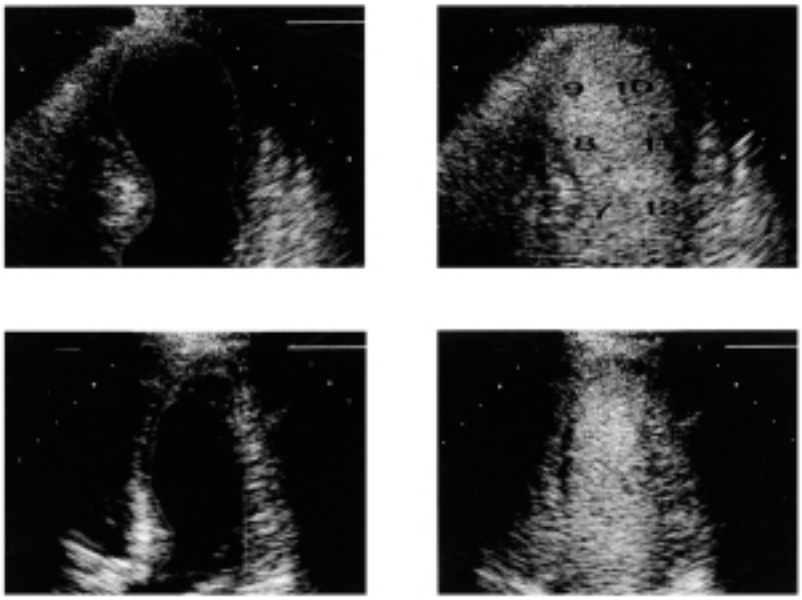

Figure 1. Top: *apical 3-chamber view of the heart of a patient showing reserve of microcirculation in the risk region (anteroseptal and apical areas) before* (left) *and after* (right) *contrast infusion. The ventricular endocardial border has been traced on the baseline image. The numbers refer to the segments in the model adopted for the regional wall motion and videointensity analyses.* Bottom: *apical 3-chamber view of the heart of a patient with a comparable area of dysfunction* (left) *and the absence of a myocardial contrast effect after Levovist* (right). *In this case the endocardial border has been traced on the pre-contrast image.*

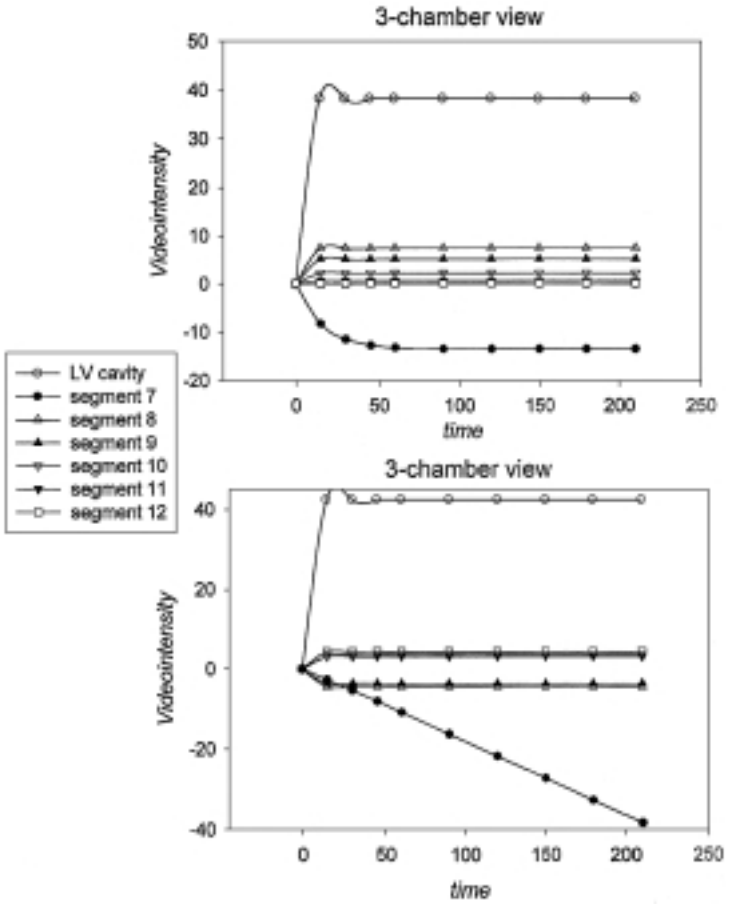

Figure 2. Top: *quantitative analysis of the heart shown in figure 1* (top). *Fitted curves are shown. Segments 8, 9 and to a lesser extent segment 10, demonstrate an increase in videointensity with the infusion. The gray level does not increase in segments 11-12. Segment 7 shows a significant decrease in videointensity, suggesting attenuation. At follow-up, the systolic ventricular volume had decreased by 7% in this patient.* Bottom: *quantitative analysis of the heart shown in figure 1* (bottom). *Fitted curves are shown. The videointensity does not increase in segments 8 and 9, while it increases only modestly in the remaining part of the ventricle. The videointensity in segment 7 does not reach a plateau and thus is not considered for the final analysis. In this patient, the ventricular volume increased by 27% at follow-up. LV = left ventricular.*

Statistical analysis. Data are expressed as mean 1 ± SD. Differences in means were assessed by the Student's t-tests for paired and unpaired data, as appropriate. Contingency table analysis was performed for categorical variables. Multivariate analysis was also used in order to identify which of the following variables (gray level in the dysfunctioning area, the LAD score, the number of asynergic segments) predicted changes in ventricular volumes during Dob and at follow-up.

Results

Heart rate, left ventricular volumes, ejection fraction and WMSI at baseline, during Dob, and at follow-up are shown in table II. The volumes did not change significantly during Dob, while they increased to a limited extent during 8 months of follow-up. The ejection fraction remained stable over the study period. Only the heart rate increased significantly during inotropic stimulation (+37 ± 27%, p = 0.002) and decreased at follow-up (-18 ± 17%, p = 0.01). In comparison to the baseline values, there were no changes in the WMSI during Dob and at follow-up.

It was possible to analyze MCE in each patient. In just one patient, the images from the 4-chamber view during contrast echocardiography were unsuitable for quantitative analysis and thus data from the 3-chamber view only were used. Stable and positive values for *a* were present in 55 out of a total of 114 segments analyzed (48%). Negative values, reflecting shadowing or attenuation, were found in 28 out of 114 segments (25%). Non-plateauing values accounted for 31 segments (27%), evenly distributed across the various ventricular segments. The normalized gray level in the asynergic region averaged 0.09 ± 0.02 in those patients whose systolic ventricular volume increased by more than 15% (+35.7 ± 20.0%) at follow-up. The corresponding value in non-dilating ventricles (-2.1 ± 4.7% vs baseline) averaged 0.13 ± 0.03 (p = 0.06). Comparable results were obtained for the non-normalized videointensity data (4.2 ± 1.3 vs 6.3 ± 1.1, p = 0.04), although the extent of gray level in the remote region (6.7 ± 4.1 vs 4.5 ± 5.1, p = 0.63) and the WMSI (1.9 ± 0.2 vs 2.1 ± 0.2, p = 0.25) of the two groups were not different. A multivariate analysis was performed in order to determine which variable among the average gray level in the dysfunctioning area, the LAD score and the number of baseline asynergic segments actually predicted the percentage systolic ventricular volume changes (as compared to baseline) during Dob (Table III). The LAD score was found to be the only predictor (p = 0.003, Fig. 3). The normalized gray level across the asynergic region, on the other hand, was the only significant determinant of the changes in systolic volumes at follow-up (p = 0.04, Fig. 4, Table III).

Table II. Heart rate and volume data at baseline, during low-dose dobutamine echocardiography and at follow-up.

Baseline	
Heart rate (b/min)	75 ± 11
End-diastolic volume (ml/m^2)	81 ± 10
End-systolic volume (ml/m^2)	49 ± 10
Ejection fraction (%)	40 ± 10
Wall motion score index	2.0 ± 0.2
Low-dose dobutamine	
Heart rate (b/min)	103 ± 25*
End-diastolic volume (ml/m^2)	78 ± 16
End-systolic volume (ml/m^2)	46 ± 18
Ejection fraction (%)	43 ± 13
Wall motion score index	2.0 ± 0.02
Follow-up (9 patients)	
Heart rate (b/min)	60 ± 7**
End-diastolic volume (ml/m^2)	89 ± 23§
End-systolic volume (ml/m^2)	52 ± 15
Ejection fraction (%)	42 ± 5
Wall motion score index	2.0 ± 0.2

* = p = 0.002 vs baseline; ** = p = 0.01 vs baseline; § = p = 0.032 vs low-dose dobutamine.

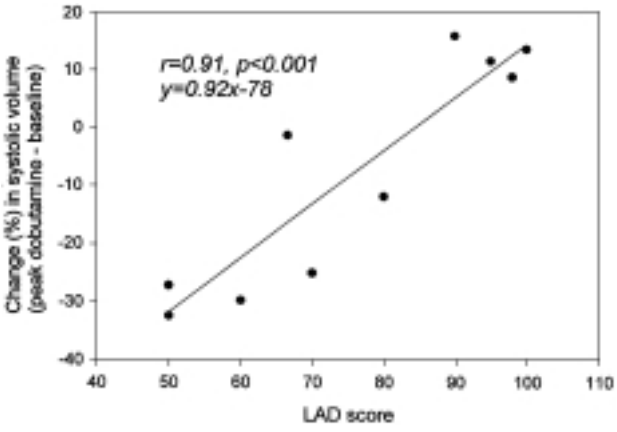

Figure 3. *Direct relation between the left anterior descending coronary artery (LAD) score and the percentage changes in end-systolic volumes (peak dobutamine minus baseline) in our patient population.*

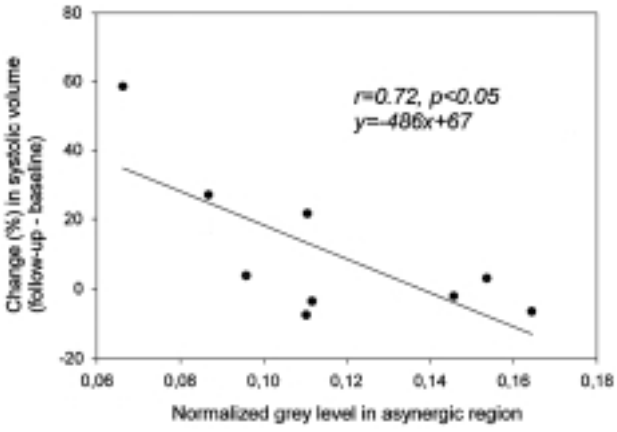

Figure 4. *Inverse relation between the changes in the end-systolic volumes at 6 months (follow-up minus baseline) and the normalized gray level in the asynergic region.*

Table III. Results of multivariate analysis of the percentage changes in systolic ventricular volume during dobutamine echocardiography and at follow-up.

	Coefficient	Standard error	p
During dobutamine echocardiography			
LAD score	0.746	0.158	0.003
Extent of asynergy	4.291	2.591	NS
Gray level in the risk area	-110.3	85.52	NS
At follow-up			
LAD score	-0.288	0.354	NS
Extent of asynergy	-1.009	6.405	NS
Gray level in the risk area	-527.9	191.9	0.04

LAD = left anterior descending coronary artery.

Discussion

There is much documentation in the literature regarding the use of contrast echocardiography for the evaluation of the myocardial viability, as revealed by the integrity of the microvascular capillaries during intracoronary contrast injections in patients with acute or chronic ischemic heart disease[1-4,11,12]. In a clinical model of anterior myocardial infarction, the angiographic demonstration of the perfusion in the area at risk, after angioplasty had resolved the residual stenosis of the culprit vessel, was associated with a better post-infarction remodeling than that in patients who did not show a microcirculation reserve[7]. In particular, the effect of limiting the increase in the ventricular volume at follow-up was achieved even in the absence of significant recovery of the regional systolic function. These data, which highlight the impact on the volumetric post-infarction changes deriving from the presence of a preserved microvascular bed in the risk area, are supported by those of the present study. The residual myocardial blood volume in the dysfunctional region, as calculated on the basis of the plateau phase of the segmental videointensity plots after intravenous MCE, contributes to the prevention of ventricular remodeling irrespective of the recovery of the regional systolic function. Whether this is associated with the persistence, within the damaged tissue, of some viability capable of counteracting the abnormally increased wall stress although unable to promote contraction, or whether it is an expression of the restraining effects of a blood-filled coronary microcirculation[13], is impossible to judge on the basis of our data alone. The WMSI, almost exclusively composed of akinetic vs hypokinetic segments (62 vs 2), remained unmodified during the course of the study. In our patient population this regional parameter showed no sensitivity in detecting the subliminal changes in ventricular volume which were observed during low-dose Dob and at follow-up.

Inotropic challenge and ventricular volume changes. It is well-known that beyond a 20-40% transmural necrosis, no thickening is detectable in the affected segment at rest[14]. Although the inotropic reserve can be elicited by increasing the dose of dobutamine, with a response in thickening that is dictated by the degree of transmural involvement[15], the presence of a residual flow-limiting stenosis may blunt such a relationship, so that a no thickening response may be elicited, even in the presence of viable muscle and a high inotropic stimulation[16]. In our study, 10 γ/kg/min Dob, in the presence of a tight residual stenosis, failed to demonstrate a regional contractile reserve in the dysfunctional, akinetic region, with no recovery in function detectable even at follow-up. It is possible, in fact, that some degree of ischemia in the risk territory had been generated by the inotropic challenge itself, given the increment in systolic ventricular volume that developed in those patients with a high LAD score, in whom the culprit lesion was very tight (97 ± 4%) and proximal (Fig. 3). These findings underline the difficulty in detecting subtle ischemia by the human eye in the presence of a preexisting profound asynergy and point out the risk of underestimating the benefit not necessarily mediated by the recovery of the regional systolic function[17].

Limitations of the study. The present study is burdened by several limitations which are mainly related to the small group of patients imaged using this intravenous contrast quantitative approach. It is difficult to find patients with the same clinical characteristics, especially when the patient number, for a given laboratory, is not very high and subjects with more than single-vessel disease have to be included. However, in this very early post-myocardial infarction phase no worsening in the non-infarcted muscle was evident, in our patient population, during low-dose Dob, potentially excluding remote ischemia, at least at a low threshold. Furthermore, the persistence of residual stenosis in the culprit vessel in some patients might have contributed to an unfavorable remodeling, thus diluting our results. Such persistent lesions, however, should not have influenced the potential of the contrast technique to image the residual microcirculation in the risk region, as long as triggering acquisition was delayed enough. In a recent paper, in fact, Swinburn et al.[18], using 1:5 and

1:10 triggering intervals, have shown that the gray level potentiation of the post-myocardial infarction dysfunctioning muscle by intravenous MCE is independent of the presence of residual stenosis. In our study we used a 1:4 time interval, coupled, however, with a quantitative rather than a qualitative analysis and a contrast infusion instead of a bolus. These factors should have compensated for the shorter interval.

In conclusion, the myocardial blood volume in the asynergic region, as assessed on the basis of the normalized myocardial gray level obtained from that same region during intravenous infusion of an echocontrast agent, has the potential of predicting chronic remodeling in patients following an anterior myocardial infarction. This result, which appears to be independent of the viability as assessed at low-dose Dob and of the recovery of the regional systolic function, underlines the beneficial role of the residual microcirculation in counteracting the ventricular volume increase in the months following the acute event, further supporting the "open artery hypothesis".

References

1. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of "no-reflow" phenomenon: a predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation 1996; 93: 223-8.
2. Brochet E, Czitrom D, Karila-Cohen D, et al. Early changes in myocardial perfusion patterns after myocardial infarction: relation with contractile reserve and functional recovery. J Am Coll Cardiol 2001; 32: 2011-7.
3. Rocchi G, Kasprzak JD, Galema TW, de Jong N, Ten Cate FJ. Usefulness of power Doppler contrast echocardiography to identify reperfusion after acute myocardial infarction. Am J Cardiol 2001; 87: 278-82.
4. Ragosta M, Camarano G, Kaul S, Powers ER, Sarembock IJ, Gimple LW. Microvascular integrity indicates myocellular viability in patients with recent myocardial infarction: new insights using myocardial contrast echocardiography. Circulation 1994; 89: 2562-9.
5. Kim CB, Braunwald E. Potential benefits of late reperfusion of infarcted myocardium. The open artery hypothesis. Circulation 1993; 88: 2426-36.
6. Anselmi M, Bolognese L, Chierchia S, Maggioni A, Marino P. The role of myocardial viability in deriving benefit from reestablishing infarct-related artery flow after acute myocardial infarction. Prog Cardiovasc Dis 2000; 42: 455-70.
7. Destro G, Marino P, Barbieri E, et al. Postinfarctional remodeling: increased dye intensity in the myocardial risk area after angioplasty of infarct-related coronary artery is associated with reduction of ventricular volumes. J Am Coll Cardiol 2001; 37: 1239-45.
8. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989; 2: 358-67.
9. Kaul S. Clinical applications of myocardial contrast echocardiography. In: Braunwald E, ed. Heart disease. A textbook of cardiovascular medicine. Update 1. Philadelphia, PA: WB Saunders, 1997: 304-13.
10. Wei K, Jayaweera AR, Firozaan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998; 97: 473-83.
11. Agati L, Voci P, Bilotta F, et al. Influence of residual perfusion within the infarct zone on the natural history of left ventricular dysfunction after acute myocardial infarction: a myocardial contrast echocardiographic study. J Am Coll Cardiol 1994; 24: 336-42.
12. Bolognese L, Antoniucci D, Rovai D, et al. Myocardial contrast echocardiography versus dobutamine echocardiography for predicting functional recovery after acute myocardial infarction treated with primary coronary angioplasty. J Am Coll Cardiol 1996; 28: 1677-83.
13. Mc Culloch AD, Hunter PJ, Smaill BH. Mechanical effects of coronary perfusion in the passive canine left ventricle. Am J Physiol 1992; 262: H523-H530.
14. Lieberman AN, Weiss JL, Jugdutt BI, et al. Two-dimensional echocardiography and infarct size: relationship of regional wall motion and thickening to the extent of myocardial infarction in the dogs. Circulation 1981; 63: 739-45.
15. Sklenar J, Ismail S, Villanueva FS, et al. Dobutamine echocardiography for determining the extent of myocardial salvage after reperfusion: an experimental evaluation. Circulation 1994; 90: 1502-12.
16. Kaul S. Response of dysfunctional myocardium to dobutamine. "The eyes see what the mind knows". J Am Coll Cardiol 1996; 27: 1608-11.
17. Beller GA. Comparison of ^{201}TI scintigraphy and low-dose dobutamine echocardiography for the noninvasive assessment of myocardial viability. Circulation 1996; 94: 2681-4.
18. Swinburn JM, Lahiri A, Senior R. Intravenous myocardial contrast echocardiography predicts recovery of dyssynergic myocardium early after acute myocardial infarction. J Am Coll Cardiol 2001; 38: 19-25.