



# Real Time Contrast Echocardiography — A New Bedside Technique to Predict Contractile Reserve Early After Acute Myocardial Infarction

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**Aims:** Power pulse inversion echocardiography is a new technique by which contrast microbubbles can be visualised in real time within the myocardium, enabling simultaneous assessment of myocardial function and microvascular integrity, which is a prerequisite for myocardial viability. We aimed to determine whether microvascular integrity using power pulse inversion can be used to predict contractile reserve early after myocardial infarction.

**Methods and Results:** We studied 19 stable patients 5.1(1.6) days after presentation using low dose dobutamine stress echocardiography and power pulse inversion using slow bolus intravenous injections of Optison. A 16-segment left ventricular model was used to define wall thickening at baseline and following low dose dobutamine infusion (1, normal; 2, reduced; 3, absent), and contrast opacification (1, homogeneous; 2, heterogenous or reduced; 3, absent). The techniques were compared on a segment-by-segment basis to determine whether microvascular integrity (contrast opacification score of 1 or 2) could predict contractile reserve (any improvement during low dose dobutamine infusion) in segments that were akinetic at rest. Follow-up echocardiography was performed one month later.

**Results:** Ninety-four (31%) of the 304 segments were akinetic at rest, and 22 (23%) of these demonstrated contractile reserve. In 87 (92%) of the resting akinetic segments contrast opacification could be adequately determined, and of these 20 (23%) showed microvascular integrity. The negative and positive predictive value of microvascular integrity for determining contractile reserve was 90% and 65%, respectively, and 92% and 59% respectively for predicting recovery of function.

**Conclusion:** Power pulse inversion can be used at rest to determine myocardial function and simultaneously to predict contractile reserve of akinetic segments in patients early after myocardial infarction. This technique has the potential to provide a bedside assessment of myocardial viability.

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**Key Words:** contrast echocardiography; myocardial infarction; dobutamine echocardiography; myocardial viability.

## Background

Myocardial contrast echocardiography can be used to accurately assess myocardial microcirculation, a prerequisite for myocardial viability<sup>[1,2]</sup>. However, until recently the use of intravenous contrast agents required intermittent imaging techniques, and consequent loss of simultaneous functional information, because microbubbles are destroyed at high power outputs<sup>[3,4]</sup>.

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Intermittent imaging may require long triggering intervals to achieve optimal contrast visualization, since myocardial blood flow may be reduced distal to an occluded or tightly stenosed coronary artery<sup>[5]</sup>. This makes it a technically difficult and time-consuming procedure. Furthermore, strong tissue harmonic signals are produced when high power outputs are used<sup>[6]</sup>, with the additional disadvantage that it can be difficult to distinguish echoes produced by microbubbles in the microcirculation from those resulting from the surrounding tissue. Recent technical advances have enabled detection of sufficient harmonic echoes from microbubbles when using very low power outputs. This overcomes the aforementioned difficulties. First, microbubbles resonate but do not burst, second, very few

tissue harmonic signals are produced<sup>[6]</sup>, and finally several cycles can be obtained quickly, allowing bubble visualisation even in low flow states. Power pulse inversion imaging is a new technique which uses low power outputs to visualize contrast in real time, permitting simultaneous integration of perfusion and wall thickening information<sup>[7]</sup>. However, there is no published data on the use of this technique for the prediction of myocardial viability after acute myocardial infarction. Thus, in this study we compared the value of real time myocardial contrast echocardiography with low dose dobutamine echocardiography, a standard technique for the assessment of myocardial viability. Follow-up data for recovery of function were also obtained.

## Methods

Stable patients with documented myocardial infarction were included in this study. All patients gave prior consent, and the study was approved by the local ethical committee. Patients underwent low dose dobutamine echocardiography and myocardial contrast echocardiography during hospital admission but at least 3 days after myocardial infarction. All patients also underwent follow-up echocardiography 1 month later.

### *Low Dose Dobutamine Echocardiography*

Baseline images were acquired using tissue harmonic imaging with a broad-band transducer (4–2 MHz) (HDI5000, ATL, Bothell, Washington, U.S.A.) in standard apical and parasternal views. An intravenous dobutamine infusion was started and further images were captured after 5 min at each stage of 5, 10 and 15 micrograms/kg/min. Images were digitized and all stages of each view were displayed side-by-side for subsequent wall thickening analysis. Systolic wall thickening was scored using the American Society of Echocardiography 16-segment left ventricular model by two experienced observers who were blinded to the clinical details of the patients using a three point scale: 1, normal, 2, reduced, 3, absent. Disagreements were resolved by consensus. Only segments with a score of 3 at rest were analysed, and contractile reserve was said to be present if this improved to 2 or 1 following dobutamine infusion.

### *Contrast Echocardiography*

Following acquisition of the baseline echocardiographic images the power pulse inversion mode was activated. Two-dimensional gains were set so that minimal tissue signal was seen. The colour gains were then adjusted so that no Doppler signal was seen except at the mitral valve and proximal to the apex. Intravenous boluses of 0.3 ml Optison were injected followed by a slow flush

**Table 1.** Patient demographics.

Age	60 ± 13 years
Sex (male)	13 (68%)
Previous MI	4 (21%)
Diabetes	4 (21%)
Hypertension	7 (37%)
Smokers	5 (26%)
Ant MI	13 (68%)
Wall motion score index	1.5 ± 0.4
Thrombolysis	12 (63%)
Peak creatine kinase	1740 ± 1794 iu/L
Peak creatine kinase-MB	164 ± 169 iu/L

over 20 s. Imaging was performed using a mechanical index of 0.11 to 0.14. The focus was set at the mitral valve level, but was moved towards the apex if there was concern about a contrast defect in that area. Two or three injections of contrast were given in each of the three apical views (four, two and three chamber) as required. Flash echo at a mechanical index of 0.9 was performed when contrast appeared in the left ventricular cavity following each Optison injection. This is used to destroy any microbubbles in the myocardium and to observe refilling of myocardium with contrast microbubbles. The same 16-segment left ventricular model was used to assess contrast opacification using a semi-quantitative scoring system: 1, normal, homogeneous opacification; 2, reduced, heterogeneous opacification; 3, minimal or no contrast opacification. A segment with no resting wall thickening was defined as viable if the contrast opacification score was 1 or 2. Analysis of contractile reserve, contrast perfusion and recovery of function were performed independently of each other and the observer (RS) was also blinded to the clinical data.

## Results

Nineteen patients were studied an average of 5 (1–6) days after the presenting myocardial infarction. The mean age of the cohort was 60 years, and 13 (68%) were male. The demographic details are presented in [Table 1](#).

Of the total of 304 segments, 94 (31%) were akinetic at rest and 22 (23%) of these demonstrated contractile reserve. The presence or absence of contrast opacification could be adequately determined in 251 (83%) of all segments and in 87 (92%) of the resting akinetic segments. Of the 53 segments which could not be analysed, 32 (60%) occurred at the base of the heart and were subject to attenuation and shadowing artefacts. Of the 87 interpretable segments, which were akinetic at rest, 20 (22%) showed contrast evidence of myocardial viability and 67 (77%) showed minimal or absence of contrast. [Table 2](#) shows the correlation of viability assessed by contrast echocardiography and contractile reserve for all segments. The agreement between myocardial contrast echocardiography and low dose dobutamine echocardiography for defining viability was 84% ( $\kappa=0.55$ ,

**Table 2.** Relationship between viability detected by myocardial contrast echocardiography and contractile reserve.

	Contrast echocardiography	
	Non-viable	Viable
Contractile reserve		
Absent	60	7
Present	7	13

Concordance 84%; kappa 0.55 (95% CI 0.34–0.76).

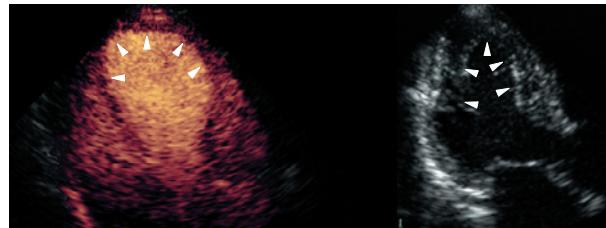
**Table 3.** Contingency table showing contractile reserve and contrast opacification score for segments, which were akinetic at rest.

	Contrast opacification score		
	3	2	1
Contractile reserve			
Absent	60	6	1
Present	7	6	7

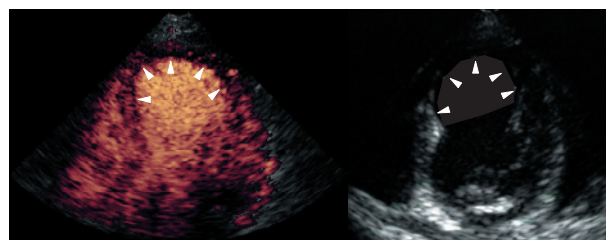
95% CI 0.34 to 0.76). The sensitivity and specificity for predicting contractile reserve was 65% and 90% respectively. Positive and negative predictive values were 65% and 90%.

Table 3 shows the relationship between contractile reserve and contrast opacification score. A contrast opacification score of 3 identified 90% of segments with no contractile reserve, and a score of 1 identified 88% of segments with contractile reserve. However, a score of 2 did not discriminate between segments with and without contractile reserve. At follow-up, 19 of the 87 akinetic segments showed recovery of function. Sensitivities of contrast and dobutamine echocardiography for recovery of function were 68% and 58%, and specificities were 88% and 85%. The positive and negative predictive values of contrast echocardiography for recovery of function was 59% and 92%, while that of dobutamine echocardiography was 50% and 89%, respectively.

Figure 1 shows an example from a patient who sustained apical–septal infarction. Echocardiography showed akinetic distal septum and apex (apical three chamber view). Power pulse inversion imaging showed good contrast opacification of the akinetic segments, which suggest significant microvascular integrity. Contractile response during dobutamine infusion was present in these segments. Figure 2 is another example of a patient with anterior infarction. Echocardiography showed akinetic apex and distal septum and distal lateral wall and no contrast opacification was seen during power pulse inversion imaging in the apex and distal lateral wall while distal septum showed reduced contrast. Contractile response was absent in these segments during dobutamine infusion.



**Figure 1.** Apical three chamber view showing contrast opacification during power pulse inversion imaging in akinetic segments (mid-distal septum and apex) (Panel A). These segments improved during dobutamine infusion (arrows) (Panel B).



**Figure 2.** Apical chamber view showing absence of contrast in apex and distal lateral wall and reduced opacification in distal septum during power pulse inversion imaging (Panel A). These segments did not show any contractile response during dobutamine infusion (Panel B).

## Discussion

Several studies have demonstrated the value of contrast echocardiography for the identification of viable myocardium. The presence of microbubbles in the myocardium suggests microvascular integrity, which is a pre-requisite for myocardial viability. The paradox of contrast echocardiography, however, is that the interaction of the ultrasound beam with the microbubble contrast agent results, at standard power outputs, in the destruction of the microbubble<sup>[3]</sup>. This has not posed a major problem to the assessment of myocardial blood flow during intra-coronary injection of contrast agents since the concentration of contrast is sufficiently high to result in adequate ultrasound backscatter despite microbubble destruction. With the introduction of agents which were capable of trans-pulmonary transit and could be injected intravenously, however, the much lower concentrations of contrast achieved in the coronary beds required intermittent imaging to allow build up of contrast over time to alleviate the problem of bubble destruction and facilitate opacification of the myocardium<sup>[8–10]</sup>. In low flow states, such as in patients with hibernating myocardium, long pulsing intervals are required to optimize the detection of viable myocardium<sup>[5]</sup>. However, this technique resulted in the loss of real time wall thickening information. Furthermore, at standard power outputs it can be difficult to distinguish contrast signal from that resulting from tissue.

Power pulse inversion imaging is a new development which allows imaging of contrast agent in the myocardial beds in real time<sup>[7]</sup>. This is achieved by imaging using an ultrasound beam with an output power almost ten times less than that used for conventional imaging, which does not cause significant bubble destruction. At these pressures microbubbles oscillate non-linearly and produce significant harmonic backscatter, while tissue produces very little harmonic response, permitting selective visualization of contrast microbubbles<sup>[11]</sup>. This allows simultaneous assessment of myocardial function and microvascular perfusion, and enables several cardiac cycles to be obtained relatively rapidly, permitting adequate microbubble visualization even in low flow states.

We analysed only segments that were akinetic. We excluded hypokinetic segments because by definition they are viable as they retain contractile function, although reduced. We and others have previously shown that triggered contrast echocardiography at standard power outputs has the potential to predict functional recovery after myocardial infarction<sup>[5,9]</sup>. The present study is the first study to demonstrate that power pulse inversion imaging has the potential to predict contractile reserve in this setting. Real time imaging with this technique has a high negative predictive value for contractile reserve, in keeping with accepted wisdom that intact microvasculature is essential for myocardial function<sup>[12-15]</sup>. The positive predictive value of real time imaging is, however, less good. This can be explained, at least in part, by the fact that these two techniques assess different aspects of myocardial physiology, perfusion and function, and that these do not necessarily parallel one another. For example, the subendocardium is responsible for 80% of wall thickening<sup>[16]</sup>, so infarction of this region results in loss of local myocardial contractility, despite significant viability and perfusion of the rest of the myocardial wall. Furthermore, viability may also exist in the absence of a contractile response to dobutamine if there is insufficient mass of viable myocardium for the response to be observed, or if the viable myocardium is subtended by a critical stenosis that may result in ischaemia before a contractile response can be mounted because of a very narrow supply-demand ratio. Thus, the concordance between the two techniques is modest and the major disagreement between the two techniques is in the segments with contrast opacification where contractile reserve is not always present.

### Limitations

This was a small study designed to determine whether this new technique could be used practically to assess myocardial perfusion, and should now provide the basis for further investigation into this field. We used a bolus injection of contrast rather than an infusion. While the latter is the ideal choice of administration when quantifying tissue perfusion using contrast echocardiography, a slow bolus allows for sufficiently stable levels of contrast to be achieved for qualitative assessment.

This study was conducted using a semi-quantitative scoring system for contrast opacification. We found that a score of 2 was not discriminatory for the presence or absence of contractile reserve. Further study using quantitative techniques may yield an acoustic cut-off below which viability is deemed not to be present.

Attention to technical detail is also essential to the success of this technique. We have experienced a pronounced learning curve in its use. As with all forms of echocardiography, and contrast echocardiography in particular, artefacts and attenuation are important considerations when using this technique. Potential defects at the apex can be reinterrogated by imaging with the focus set closer to the area of interest, and this often resulted in filling in of such a 'defect'. The more problematic areas are at the base of the heart. In this study 60% of uninterpretable segments were situated at the cardiac base, and were probably caused by insufficient power at the far lateral field to elicit bubble resonance. However, in most cases this can be overcome by moving the transducer to bring the region of interest into the centre of the beam. It is crucial that particular attention is paid to slow but steady injection of contrast, which is best assessed by observing a bright yellow streak in the right ventricle. Failure to see myocardial opacification after the first injection is common, and presumably relates to lack of sufficient contrast concentration in the microvasculature. Thus two or three injections may be required before deciding that myocardial opacification is absent.

Finally, coronary arteriography in these patients were not performed at discharge as all these patients were stable. The decision to perform coronary arteriography in these patients will be after an exercise test performed 6 weeks after acute myocardial infarction.

## Conclusion

Power pulse inversion contrast echocardiography can be used at rest to determine myocardial function and simultaneously to predict contractile reserve of akinetic segments in patients early after myocardial infarction. This technique has the potential to provide a bedside assessment of myocardial viability.

## References

- [1] Firschke C, Lindner JR, Wei K *et al.* Myocardial perfusion imaging in the setting of coronary artery stenosis and acute myocardial infarction using venous injection of a second-generation echocardiographic contrast agent. *Circulation* 1997; **96** (3): 959-967.
- [2] Ragosta M, Camarano G, Kaul S *et al.* Microvascular integrity indicates myocellular viability in patients with recent myocardial infarction. New insights using myocardial contrast echocardiography. *Circulation* 1994; **89** (6): 2562-2569.

- [3] Wei K, Skyba DM, Firschke C *et al.* Interactions between microbubbles and ultrasound: in vitro and in vivo observations. *J Am Coll Cardiol* 1997; **29** (5): 1081–1088.
- [4] Porter TR, Xie F, Li S *et al.* Increased ultrasound contrast and decreased microbubble destruction rates with triggered ultrasound imaging. *J Am Soc Echocardiogr* 1996; **9** (5): 599–605.
- [5] Swinburn JMA, Lahiri A, Senior R. Intravenous myocardial contrast echocardiography Predicts recovery of dysynergic myocardium early after acute myocardial infarction. *J Am Coll Cardiol* 2001; **38**: 19–25.
- [6] Burns PN. Harmonic imaging with ultrasound contrast agents. *Clin Radiol* 1996; **51** (Suppl 1): 50–55.
- [7] Tiemann K, Lohmeier S, Kuntz S *et al.* Real-time contrast echo assessment of myocardial perfusion at low emission power: First experimental and clinical results using Power Pulse Inversion Imaging. *Echocardiography* 1999; **16** (8): 799–809.
- [8] Wei K, Jayaweera AR, Firoozan S *et al.* Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation* 1998; **97** (5): 473–483.
- [9] Lepper W, Hoffmann R, Kamp O *et al.* Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction. *Circulation* 2000; **101** (20): 2368–2374.
- [10] Kaul S. Myocardial contrast echocardiography: 15 years of research and development. *Circulation* 1997; **96** (10): 3745–3760.
- [11] Burns PN. Contrast imaging for echocardiography—principles and instrumentation In: Becher H, Burns PN eds. *Handbook of Contrast Echo*, 1st Edition. Frankfurt: Springer Verlag, 2000.
- [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** (7): 1677–1683.
- [13] Iliceto S, Galiuto L, Marchese A *et al.* Analysis of microvascular integrity, contractile reserve, and myocardial viability after acute myocardial infarction by dobutamine echocardiography and myocardial contrast echocardiography. *Am J Cardiol* 1996; **77** (7): 441–445.
- [14] 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* **32**: 2011–2017.
- [15] Myers JH, Stirling MC, Choy M *et al.* Direct measurement of inner and outer wall thickening dynamics with epicardial echocardiography. *Circulation* 1986; **74** (1): 164–72.
- [16] 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 echocardiography study. *J Am Coll Cardiol* 1994; **24**: 336–342.