Myocardial Contrast Echocardiography for Simultaneous Assessment of Function and Perfusion in Real Time: A Technique Comes of Age

Running title: Senior et al.; Perfusion stress echocardiography and prognosis

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Contrast agents are now widely used in stress echocardiography (SE) to improve visualisation of the endocardial border, improve confidence in wall motion assessment and to reduce the number of uninterpretable images. The use of contrast agents in SE has also been shown to improve accuracy of wall motion assessment for the detection of coronary artery disease (CAD) compared to unenhanced SE images.\(^1\) Contrast stress echocardiography has been shown to impact positively on downstream costs.\(^2\) The ability of contrast agents, which contain microbubbles that mimic red blood cell rheology, to enable visualisation of myocardial perfusion resulted in rapid development of both microbubble and equipment technology that allowed the use of contrast echocardiography for the detection of myocardial perfusion in clinical cardiology.\(^3\) Numerous single and multicentre studies have proved that myocardial contrast perfusion stress echocardiography is now a clinical tool for the detection of CAD.\(^4\) The ability of myocardial contrast SE to assess function and perfusion simultaneously makes it a unique technique for the assessment of CAD.

The study by Gaibazzi \textit{et al} adds to the growing literature of the prognostic value of perfusion and function assessed simultaneously during high dose dipyridamole myocardial contrast perfusion SE for predicting hard outcomes over a mean period of 25 months in 1252 consecutive patients referred clinically for the evaluation of CAD.\(^5\) This study showed that perfusion and function assessed simultaneously during high dose dipyridamole, mostly without the addition of atropine, provided incremental prognostic information compared to clinical prognostic markers and resting left ventricular function data. However, myocardial perfusion data contained most of the prognostic information. Thus, normal perfusion and normal function during SE portended an excellent outcome (97.9\% 2 year event-free survival) but abnormal perfusion despite normal wall motion reduced event-free survival to 91.9\% (4-fold increase in
event rate). On the other hand, abnormal function (which was always accompanied by perfusion deficit) identified the highest risk patients (16% annual hard-event rate, a further 4-fold increase compared to abnormal perfusion but normal wall motion). To put it in simple clinical context, during myocardial contrast SE, completely normal perfusion is very reassuring (0.99% annual hard-event rate) while abnormal perfusion when it is accompanied by functional (wall motion) abnormalities identify very high risk patients (15% annual event rate). This highlights the clinical value of simultaneous assessment of perfusion and function during SE.

The pathophysiological basis of these findings is not complicated. Perfusion abnormalities appear earlier in the ischemic cascade, followed by wall motion abnormality during stress testing. This phenomenon accounts for the better sensitivity of perfusion compared to wall motion. Thus perfusion abnormalities may be the only abnormality in mild CAD during adequate stress and in patients with inadequate stress (inability to exercise well, premature termination of pharmacological stress due to side-effects or inability to reach target heart rate) even with moderate-severe CAD. Outcome in such patients is likely to be compromised despite normal wall motion. However, in patients with severe CAD, wall motion abnormality follows rapidly after perfusion deficit onset and therefore this combination identifies the worst CAD disease and hence worst outcome. Conversely, the specificity of myocardial perfusion during myocardial contrast SE is significantly poorer compared to wall motion for the detection of CAD. However, it is known that microcirculatory disorders occur with and without underlying myocardial disease in absence of significant CAD and prognosis in such patients is also compromised. As microbubbles assess the microvasculature directly, perfusion defects may represent prognostically significant microcirculatory disorders in absence of significant CAD.

However, one must be aware that in the study by Gaibazzi et al, dipyridamole – a
vasodilator, albeit in high dose (0.84mg/kg) – was utilised and in most cases (66%) without atropine. It is possible that many patients did not achieve 85% of target heart rate (data not shown) which is necessary to ensure adequate stress for demand ischemia which precipitates wall motion abnormality. However, perfusion deficit may occur during vasodilator stress in CAD without the need for increase in myocardial oxygen demand. Thus it may be argued that inadequate demand by the very nature of the stress test used may have impacted on the higher annual event rate of close to 1.5% seen with a normal wall motion. At least two large studies with pharmacological stress with dobutamine, which is commonly used during SE for wall motion assessment, have shown hard event rates varying between 1.1-1.3%, which is lower (though only marginally) than that seen in this study for wall motion assessment.9,10 Nevertheless, normal perfusion in this study portended a reassuring under 1% annual event rate mark (low-risk group). Another intriguing issue in this study was the lack of predictive value of multi-vessel ischemia for both perfusion and wall motion assessment. This is partly explained by the fact that all patients who underwent revascularization were those mostly likely to have multivessel SE abnormalities and they were censored.

In conclusion, myocardial contrast SE has now a plethora of data from diagnosis4 to prognosis (Table 1)5,11-21 in large patient cohorts from multiple investigators in patients with known and suspected CAD establishing its value in clinical cardiology. Its unique ability to assess function and perfusion simultaneously, both during rest and stress, combined with the significant advantages over other existing techniques in terms of availability, portability, lack of ionising radiation and cost should result in greater utilisation of myocardial contrast perfusion SE in clinical cardiology for the evaluation of CAD.

Conflict of Interest Disclosures: Dr Senior has received honoraria from Bracco diagnostics in the past 2 years and Dr Shah received a travel grant, also from Bracco, within the past 2 years.
References:


**Table 1.** Prognostic value of Myocardial contrast perfusion Stress Echocardiography for the prediction of all events and hard cardiac events (death and non-fatal myocardial infarction) in patients with suspected and/or known coronary artery disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Stress Method</th>
<th>Contrast Agent</th>
<th>Follow-Up (months)</th>
<th>Total Events (n)</th>
<th>Hard events (n)</th>
<th>Annual total event rate (%) Normal Scan</th>
<th>Annual total event rate (%) Abnormal Scan</th>
<th>Annual hard event rate (%) Normal Scan</th>
<th>Annual hard event rate (%) Abnormal Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaibazzi(^2) (2012)</td>
<td>1252</td>
<td>Dipyridamole</td>
<td>Sonovue</td>
<td>25</td>
<td>59</td>
<td>59</td>
<td>0.99</td>
<td>5.90</td>
<td>0.99</td>
<td>5.90</td>
</tr>
<tr>
<td>Anantharam(^1) (2011)</td>
<td>87</td>
<td>Dipyridamole</td>
<td>Sonovue</td>
<td>50 ± 19</td>
<td>28</td>
<td>28</td>
<td>2.53</td>
<td>11.76</td>
<td>2.53</td>
<td>11.76</td>
</tr>
<tr>
<td>Wejner-Mik(^3) (2011)</td>
<td>202</td>
<td>Dipyridamole</td>
<td>Optison</td>
<td>32 ± 11</td>
<td>109</td>
<td>26</td>
<td>3.47</td>
<td>26.35</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gaibazzi(^4) (2011)</td>
<td>545</td>
<td>Dipyridamole</td>
<td>Sonovue</td>
<td>12</td>
<td>25</td>
<td>12</td>
<td>0.86</td>
<td>11.28</td>
<td>0</td>
<td>6.15</td>
</tr>
<tr>
<td>Hong(^5) (2011)</td>
<td>513</td>
<td>Dobutamine</td>
<td>Definity</td>
<td>23</td>
<td>42</td>
<td>42</td>
<td>1.53</td>
<td>14.91</td>
<td>1.53</td>
<td>14.91</td>
</tr>
<tr>
<td>Dawson(^6) (2009)</td>
<td>261</td>
<td>Dipyridamole</td>
<td>Optison</td>
<td>14 ± 5</td>
<td>22</td>
<td>22</td>
<td>0.98</td>
<td>19.93</td>
<td>0.98</td>
<td>19.93</td>
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<tr>
<td>Miszalski-Janka(^7) (2009)</td>
<td>84</td>
<td>Exercise</td>
<td>Sonovue</td>
<td>48 ± 8</td>
<td>24</td>
<td>10</td>
<td>1.67</td>
<td>10.19</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tsutsui(^8) (2008)</td>
<td>399</td>
<td>Dobutamine</td>
<td>Optison &amp; Definity</td>
<td>21</td>
<td>46</td>
<td>46</td>
<td>1.85</td>
<td>12.18</td>
<td>1.85</td>
<td>12.18</td>
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<tr>
<td>Jeetley(^9) (2007)</td>
<td>145</td>
<td>Dipyridamole Dobutamine</td>
<td>Sonovue</td>
<td>8 ± 5</td>
<td>24</td>
<td>4</td>
<td>10.17</td>
<td>88.89</td>
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<td>N/A</td>
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<td>Basic(^10) (2006)</td>
<td>51</td>
<td>Dipyridamole</td>
<td>Optison &amp; Definity</td>
<td>29</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>19.70</td>
<td>0</td>
<td>3.94</td>
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<tr>
<td>Tsutsui(^11) (2005)</td>
<td>131</td>
<td>Dobutamine</td>
<td>Optison &amp; Definity</td>
<td>16</td>
<td>25</td>
<td>5</td>
<td>7.79</td>
<td>23.61</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Tsutsui(^12) (2005)</td>
<td>788</td>
<td>Dobutamine</td>
<td>Optison &amp; Definity</td>
<td>20</td>
<td>75</td>
<td>75</td>
<td>1.50</td>
<td>8.0</td>
<td>1.50</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>3206</strong></td>
<td></td>
<td></td>
<td><strong>273</strong></td>
<td><strong>479</strong></td>
<td><strong>272</strong></td>
<td><strong>2.59</strong></td>
<td><strong>18.86</strong></td>
<td><strong>1.37</strong></td>
<td><strong>10.25</strong></td>
</tr>
</tbody>
</table>

*Weighted mean percentages.

(N/A = Not Available (not possible to derive total and/or hard event rates from data presented in article or insufficient follow-up period)
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