Comparative Value of Dobutamine and Adenosine Stress in the Detection of Coronary Stenosis With Myocardial Contrast Echocardiography

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Background—Controversy continues as to whether adenosine or dobutamine is the superior pharmacological stress agent for myocardial contrast echocardiography (MCE).

Methods and Results—We compared real-time MCE refilling curves and wall thickening during adenosine and dobutamine stress in 14 open-chest dogs with left anterior descending and left circumflex coronary artery stenoses that reduced hyperemia by 40% to 60% and 70% to 90% (mild and severe non–flow-limiting stenosis, NFLS) and resting flow by 10% to 30% and 35% to 50% (mild and severe flow-limiting stenosis, FLS). MCE was performed with low-energy imaging during Optison infusion. After high-energy bubble destruction, time-intensity data from risk beds were fitted for an exponential function as $y = A(1 - e^{-bt})$, from which the rate of intensity increase ($b$) and maximal plateau intensity ($A$) were derived. Although severe NFLS and greater stenoses decreased $b$ with both dobutamine and adenosine, with mild NFLS it was reduced in 58% of animals with dobutamine versus 8% with adenosine. The absolute decrease in $b$, however, was greater for adenosine than dobutamine with FLS. The $A$ parameter was decreased with both adenosine and dobutamine only with the most severe FLS. Wall thickening was decreased with dobutamine in 33% of animals with severe NFLS and in all animals with any FLS; with adenosine, in all with severe FLS.

Conclusions—Both dobutamine and adenosine significantly reduce MCE refilling rates in the setting of severe stenosis and in the absence of contractile abnormalities. Dobutamine decreases refilling rate and wall thickening at a less reduced flow grade than adenosine, but adenosine produces a greater magnitude of change than dobutamine. (Circulation. 2001; 103:2724-2730.)

Key Words: contrast media • stress • echocardiography • dobutamine • adenosine

Myocardial opacification can now be achieved with real-time imaging after intravenous contrast agents. Moreover, measurement of the time course of reappearance of contrast intensity after high-energy bubble destruction provides a method to quantify coronary blood flow and thereby identify and quantify coronary stenoses. As is true of radionuclide methods, however, it is likely that the imposition of stress will be necessary to identify stenotic lesions by myocardial contrast echocardiography (MCE).

Pharmacological stress is well suited for echocardiography because it reduces movement artifacts and provides ample time to acquire contrast data. Two approaches have been used: inotropic stress with dobutamine and vasodilator stress with adenosine or dipyridamole. No data exist, however, comparing these 2 approaches in identifying perfusion abnormalities in conjunction with MCE. Therefore, this study systematically compared dobutamine versus adenosine in the detection of graded coronary stenoses by MCE.

Methods

Fourteen open-chest mongrel dogs were subjected to variable grades of coronary stenosis in accordance with the “Position of the American Heart Association on Research Animal Use” (Circulation. April 1985). A lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. An occluder was placed around the proximal left anterior descending coronary artery (LAD) in 12 dogs and around the left circumflex coronary artery (LCx) in 2, and an ultrasonic transit-time flow probe (2.0 to 2.5 mm) was placed proximal to the occluder and connected to a flowmeter (model T201, Transonic System Inc).

MCE was performed with a real-time ultrasound system (HD5000, ATL) capable of low-energy (0.1 to 0.2 mechanical index) MCE. Short-axis mid–papillary muscle images were obtained with the transducer fixed on a saline-filled latex bag positioned on the left ventricular anterior wall. The tomographic plane encompassing LAD and LCx perfusion territory distal to the occluder was identified by the lack of myocardial contrast during temporary coronary occlusion. Instrument settings were optimized and were subsequently held constant for each dog. Three high-energy fast, low-angle shot (FLASH) images were triggered every 15 cardiac
cycles to produce bubble destruction. Optison (Mallinckrodt Medical) was continuously infused at a rate of 12 mL/h by a gently agitated infusion pump.

Quantitative Image Analysis
The raw data were analyzed with HDI Laboratory (ATL) software. Two equal-sized regions of interest were manually traced in the midwall myocardium: 1 in the LAD perfusion bed (risk area, RA) and 1 in a control area (CA) equidistant from the transducer. MCE intensity throughout the imaging sequence was plotted against time and fitted to the exponential function $y = A(1 - e^{-t}) + c$, where $A$ was the plateau signal intensity, $b$ the rate of rise to the plateau, and $c$ the intercept at the origin. RA size was measured as the largest area with visually diminished opacification during refilling (nearly always at the beginning of the sequence) and was expressed as the percent total myocardial area from the same frames. Wall motion was measured as wall thickening (WT=end-systolic thickness−end-diastolic thickness/end-systolic thickness).

Qualitative Image Analysis
Myocardial perfusion was abnormal if either patchy/incomplete or absent and was scored as 0 if persistent throughout the sequence, 1 if present in 30% to 60% of the sequence, 2 if <30%, and 3 for no visualized defect. Qualitative analysis of both myocardial thickening and endocardial motion was scaled 0 for akinisia, 1 for severe hypokinesia or very low response, 2 for moderate hypokinesia or weak response, and 3 for normal response.

Myocardial Blood Flow Measurement and Dye Analysis
Myocardial blood flow was measured by standard techniques. Briefly, fluorescent microspheres were injected into the left atrium while reference blood samples were withdrawn from the femoral artery. At the end of the experiment, monastral blue dye was injected into the left atrium. The left ventricular cross-sectional slice corresponding to the echocardiographic short-axis image was photographed for RA size measurement. Then, the slice RA and CA were cut into 10 wedge-shaped transmural samples for blood flow analysis with a flow cytometer to count the microspheres.

Experimental Protocol
For each animal, hemodynamics, regional blood flow, flowmeter measurements, and real-time MCE were acquired at baseline. Subsequently, adenosine was infused at 140 ($\mu$mol/L)kg, and measurements were repeated. Fifteen minutes after adenosine parameters had returned to baseline, incremental 2.5 $\mu$mol/L kg-1 doses of dobutamine were infused at 3-minute intervals to reach a 60% to 70% and 70% to 90% (mild flow-limiting stenosis [FLS] and severe flow-limiting stenosis, respectively); and 2 grades that decreased resting coronary flow by 30% to 60% and 70% to 90% (mild non–flow-limiting stenosis [NFLS] and severe NFLS, respectively) were imposed by progressive constriction of a coronary stenosis were returned to baseline, incremental 2.5 $\mu$mol/L kg-1 doses of dobutamine were infused at 140 ($\mu$mol/L)kg, and measurements were repeated. Subsequently, 4 grades of coronary stenosis were imposed by progressive constriction of a coronary occluder: 2 grades that were non–flow-limiting stenosis (NFLS) at rest but decreased adenosine-induced hyperemic flow by 30% to 60% and 70% to 90% (mild NFLS and severe NFLS, respectively); and 2 grades that decreased resting coronary flow by 10% to 30% and 35% to 50% (mild flow-limiting stenosis [FLS] and severe FLS, respectively). At each stenosis, recordings were obtained before (rest) and after adenosine and dobutamine infusions.

Statistical Methods
Interobserver and intraobserver variabilities were assessed by 2 blinded observers by repeating quantitative and qualitative measurements during rest and adenosine and dobutamine infusions. Data were expressed as mean±SD. Comparisons of hemodynamics, myocardial blood flow, and MCE data were performed with repeated-measures ANOVA and Student’s t test. RA size by MCE was correlated with that by blue dye performed by linear regression analysis. A value of $P<0.05$ (2-sided) was considered significant. Reproducibility was assessed by ANOVA and Cohen test ($\kappa$-measurement).

Results
Two dogs had lethal ventricular fibrillation during dobutamine infusion with a severe FLS. FLASH transmission produced nearly complete microbubble destruction, which was followed by a gradual reappearance of dense generalized myocardial opacification over the 15-cycle sequence. A total of 180 sequences were analyzed, and 360 refilling curves were obtained. No difference was observed between LAD and LCx stenosis qualitatively (perfusion defects and contractile dysfunctions were detected at the same stenosis grades in both beds) or quantitatively (eg, the b parameter increased ~4-fold with adenosine and dobutamine in both beds and was decreased to 2-fold at severe NFLS) at individual flow states.

Hemodynamics, Myocardial Blood Flow, RA Size
During adenosine, a trend toward heart rate reduction was observed, and systolic and diastolic blood pressures were significantly decreased. At peak dobutamine infusion, heart rate and systolic and diastolic blood pressures increased (Table). No significant differences were observed for these parameters between baseline and coronary stenoses at rest.

In the presence of no stenoses or NFLS, coronary flow (flow probe) increased similarly with adenosine and dobutamine (from 23±8 to 74±22 and 62±14 mL/min, respectively, both $P<0.05$). The response of coronary flow differed with FLS: flow rate increased slightly (less than CA) with dobutamine for both mild FLS and severe FLS, whereas with adenosine, it was unchanged with mild FLS and was reduced (14±4 to 6±5 mL/min) with severe FLS lesions.

Microsphere measurements confirmed the decrease of RA blood flow during FLS, whereas no significant changes were observed with NFLS grades in either CA or RA. RA size with blue dye ranged from 18% to 73% of total myocardial area. Border zones with intermixed red- and blue-stained myocardium were identified in 6 dogs (50%) during coronary occlusion and increased the size of abnormal perfusion from 35% (RA) to 43% (RA+border zone).

Effects of Adenosine and Dobutamine on Baseline MCE
Qualitatively, contrast intensity appeared to be greater and more homogeneous during adenosine and dobutamine than baseline. Because dobutamine increased heart rate, the number of frames per cardiac cycle decreased proportionally (from 12±3 to 6±4 frames/cycle at 12 frames/s). Heart motion thereby yielded increased artifacts, manifested as patchy myocardial signals in frames immediately after FLASH. No similar change was observed during adenosine. The mean A parameter was 3.5±1.4 dB before drug, and it increased to 5.0±1.4 dB with dobutamine and to 5.4±1.3 dB with adenosine ($P<0.05$). Similarly, the b parameter increased significantly from 0.23±0.07 s$^{-1}$ without drug to 0.79±0.32 s$^{-1}$ with dobutamine and to 0.83±0.20 s$^{-1}$ with adenosine (Figure 1).

Qualitative Detection of Reduced Coronary Flow
Qualitative analysis was performed on interflash sequences rather than on single static images (Figure 2). Before drug
administration, visual analysis detected a grade 2 perfusion defect in 10 of 12 dogs (83%), each of which had an RA >40%, and only for the most severe stenosis (severe FLS). With dobutamine infusion, grade 2 MCE defects were observed in 7 dogs with mild NFLS and in 4 additional dogs with severe NFLS. The size of dobutamine-induced perfusion defects increased proportionally with higher grades of stenosis. Abnormal perfusion with adenosine was detected in only 2 dogs with mild NFLS and in 10 dogs during severe NFLS (grade 2 defect); defect size and intensity were similar to those with dobutamine. Conversely, FLS lesions were recognized more easily with adenosine than dobutamine, because the intensity difference between CA and RA was greater, and grade 0 defects were observed only with adenosine.

### Quantitative Detection of Coronary Flow Reduction

#### A and b Parameters

Before pharmacological stress, the A parameter was not altered by stenosis. Dobutamine produced a significant decrease of the A parameter only for the severe FLS ($5.0 \pm 1.4$ versus $2.9 \pm 1.2$ dB, $P<0.05$), whereas adenosine significantly decreased A at the mild FLS grade as well ($5.4 \pm 1.3$ versus $3.2 \pm 1.5$ dB, $P<0.05$). The b parameter was more sensitive to coronary stenoses than A. Before pharmacological stress, a significant decrease of b was observed only with severe FLS ($0.79 \pm 0.32$ versus $0.48 \pm 0.12$ s$^{-1}$, $P<0.05$). Dobutamine significantly decreased b even with mild NFLS ($0.79 \pm 0.32$ versus $0.48 \pm 0.12$ s$^{-1}$, $P<0.05$) (Figure 1). With adenosine, b was not significantly changed with mild NFLS but was decreased with severe NFLS ($0.83 \pm 0.20$ versus $0.42 \pm 0.17$ s$^{-1}$, $P<0.05$). The degree of decrease of b between grades was greater with adenosine than dobutamine (Figure 1). Thus, a significant difference in b was observed between mild NFLS and severe NFLS with adenosine but not dobutamine. Moreover, the magnitude of decrease in b was greater for adenosine than dobutamine for FLS, and a significant reduction between rest and stress was observed at the severe FLS grade only with adenosine (rest: $0.15 \pm 0.05$

### Hemodynamics and Myocardial Blood Flow

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BP indicates blood pressure; MBF, myocardial blood flow by microspheres.

Figure 1. A parameters (A) and b parameters (B) without any stressor and during adenosine and dobutamine at baseline, mild NFLS, severe NFLS, mild FLS, and severe FLS. NFL indicates NFLS.
s^{-1}; adenosine: 0.04±0.05 s^{-1}, P<0.05) and not with dobutamine (rest: 0.15±0.05 s^{-1}; dobutamine: 0.14±0.08 s^{-1}, P=NS).

**Difference in A and b Parameters Between CA and RA**
In the presence of NFLS, adenosine and dobutamine produced slight decreases in the RA/CA ratio only for the b parameter. In the presence of mild and severe FLS at rest, however, the ratio of b in RA to b in CA was significantly less with adenosine than dobutamine, but not for A at the last stage (Figure 3). These data provide the quantitative basis for the qualitative observation that identification of the hypoperfused RA was easier with adenosine than dobutamine during FLS.

**Determination of RA Size**
In the absence of stressor agents, correlation between MCE and blue-dye measures of RA size could be performed in the 10 dogs with defects during severe FLS grade and yielded a general correlation (r=0.71). Correlations were similar for dobutamine and adenosine for NFLS and mild FLS grade lesions. For the severe FLS grade, the correlation of MCE with blue-dye values for RA was close for both dobutamine and adenosine and was superior to rest (r=0.82 and r=0.94, respectively, both P<0.05).

**Wall Motion Analysis**
Without any stenosis, WT was 35±8% at rest, 55±6% during dobutamine (P<0.05), and 43±5% during adenosine.

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**Figure 2.** Representative images for each flow state and each agent. White arrows show perfusion defect. NFL indicates NFLS.

**Figure 3.** A and b parameter ratio between RA and CA for each agent and each flow state. NFL indicates NFLS.

**Figure 4.** WT in RA and CA for each flow state and agent. NFL indicates NFLS.
NS) (Figure 4). A significant WT decrease was observed only during dobutamine with severe NFLS and mild FLS in RA versus CA: severe NFLS, 46\% versus 55\% and mild FLS, 33\% versus 53\%, both P, 0.05. Finally, a greater WT decrease occurred with severe FLS for both dobutamine and adenosine in RA versus CA: 21\% versus 50\% and 15\% versus 40%, both P, 0.05, respectively (absolute values). Qualitative analysis of wall motion yielded similar findings. Figure 5 summarizes data both from qualitative wall motion and perfusion analysis showing high discordance between perfusion and contraction in 100% and 75% of animals for mild and severe NFLS, respectively, but not for severe stenoses.

**Reproducibility**

Concordance calculation for perfusion defect yielded a high k of 0.88 at rest and a slightly higher k of 0.82 with adenosine than 0.74 with dobutamine (P<0.05). Interobserver and intraobserver variabilities of refilling measurements were 15.4\% and 13.0\% for A and 12.5\% and 10.1\% for b, respectively. k for the wall motion analysis was 0.79, and interobserver and intraobserver variabilities were 7.5\% and 8.2\%, respectively.

**Discussion**

The present study is the first systematic comparison of the effects of dobutamine and adenosine on qualitative and quantitative parameters of myocardial perfusion and function in the setting of graded coronary stenoses. Our findings indicate that (1) without pharmacological stress, MCE enables detection of only severe reductions of coronary flow (severe FLS at rest) by either qualitative or quantitative analysis, (2) application of either dobutamine or adenosine enables MCE to identify lesions that do not reduce coronary flow at rest but do decrease coronary reserve, (3) both dobutamine and adenosine can produce perfusion abnormalities with grades of coronary stenosis that do not always result in contractile dysfunction, (4) dobutamine yields perfusion defects and wall motion abnormalities at lesser grades of stenosis than adenosine, and (5) adenosine yields images that both qualitatively and quantitatively more readily identify abnormal perfusion than dobutamine.

**Quantification of Perfusion by Real-Time MCE**

Visual analysis of MCE is limited by ultrasonic artifacts as well as subjectivity. The recognition that ultrasound destroys microbubbles has provided the basis for deriving destruction/refilling curves as a quantitative measure of perfusion. Because real-time MCE has greatly facilitated the clinical acquisition of these data, we used this technique to assess the ability of dobutamine and adenosine to identify graded coronary stenoses.

In contrast to previous triggered MCE studies, we observed an increased plateau signal intensity during both adenosine and dobutamine (Figure 1). This discrepancy is probably related to the multiple-pulse real-time MCE in this study.\(^6\) With a single-pulse technique such as gray-scale B-mode imaging, hyperemia would increase the rate of reappearance of opacification and not the peak steady-state intensity. The power-pulse inversion method used here applies autocorrelation analysis to measure the difference in the returning signal from consecutively transmitted interrogating impulses. Microbubbles can produce changes between pulses by moving, dissolving, or breaking into smaller bubbles. The power-pulse inversion method is therefore sensitive to both the concentration and the velocity of microbubbles, and both the refilling rate and peak intensity plateau reflect a combination of blood flow velocity and blood volume.

**Stress Agents in Perfusion Imaging**

Fung et al\(^6\) compared dobutamine echocardiography and dipyridamole scintigraphy in dogs and demonstrated a greater ratio of CA to RA blood flow induced by dipyridamole and a higher prevalence of contractile abnormalities with dobutamine. Consistent with Fung et al, with FLS at rest we observed a more clearly delineated defect and a greater decrease of intensity parameters during adenosine. Conversely, dobutamine induced both perfusion abnormalities and contractile dysfunction at lower grades of stenosis. In a large clinical study, Marvick et al\(^7\) did not observe a significant difference between dobutamine and adenosine single photon emission CT (SPECT), although adenosine yielded higher sensitivity. Porter et al\(^8\) demonstrated that adenosine and dobutamine can produce a perfusion defect with triggered-MCE imaging. Our study is the first, however, to systematically compare qualitative and quantitative evidence...
of perfusion and contraction at graded levels of stenosis using microbubble destruction/reperfusion analysis.

Adenosine infusion resulted in a major (~4-fold) increase in the b parameter at baseline and a lesser (<2-fold) increase in the A parameter. Thus, the major effect of adenosine was to increase blood flow velocity, with a smaller increase in microcirculatory volume, probably related to direct vasodilation. In response to progressive stenoses, the adenosine-induced increase in the A and b parameters was reduced and ultimately eliminated at severe grades, whereas the b parameter actually showed a reduction below baseline levels at the most severe stenoses, indicative of a coronary steal. At these severe grades, coronary steal (that is, a redistribution of blood flow toward normal areas via collaterals) decreases blood flow below resting values in the capillaries of the stenosed vessel. As a consequence, blood velocity in capillaries is then dramatically reduced, as demonstrated by the decrease of the b parameter.

In the absence of stenoses, the major effect of dobutamine was also to increase the b parameter, although only ~2-fold, with a proportionately smaller increase of the A parameter compared with adenosine. Similar results were observed in the CA under all conditions in our study. A comparable difference in the abilities of adenosine and dobutamine to augment coronary blood flow was found by Skopicki et al by PET imaging. Thus, although the major effect of dobutamine was to increase microcirculatory blood velocity, the agent also produced an increase in microcirculatory blood volume by vasodilatation due to the increased oxygen demand as well as perhaps the vasodilating effect of direct β-adrenergic receptor stimulation. The response of both the A and b parameters to dobutamine in the RA during ischemia was a diminution or elimination of the increase, although no steal phenomenon was observed.

Recent data have supported the concept that an adenosine-induced decrease of myocardial contrast intensity in ischemic beds is due to a reduction in the number of patent capillaries ("capillary derecruitment"4). This derecruitment occurs in an attempt to maintain capillary perfusion pressure in the face of diminished pressure in the precapillary arterioles. The mechanism for dobutamine-mediated reductions in myocardial perfusion has been less clear. The data in this study suggest that the impaired perfusion to the ischemic bed during dobutamine stress is related both to the inability to increase microcirculatory blood velocity as well as, to a small extent, a reduction in microcirculatory blood volume. Again, this may be related to capillary derecruitment, although dobutamine yields less reduction of poststenotic pressure than adenosine.10

Ischemic Detection Versus Perfusion Abnormality

This study demonstrated that real-time perfusion defects antedated contractile abnormalities, which were observed only with more severely abnormal NFLS and FLS (Figure 5). The discrepancy between perfusion and contraction abnormalities was probably emphasized by the ability of real-time MCE to detect slight blood velocity decreases in capillaries. During NFLS, defects were observed at the beginning of bubble refilling, rather than at the termination, which repre-

sents steady-state perfusion and is the condition evaluated by radionuclide, PET, and conventional MCE. A discordance between perfusion defects and contractile abnormalities has previously been reported in clinical11,12 and experimental13 studies, which were generally similar to ours in detecting dyssynergy at more advanced levels of flow reduction.11,13

Study Limitations

The use of open-chest dogs has implications for extrapolating the data to the clinical setting, but we believe that the findings established in this study remain valid. Drug interactions or the cumulative effect of the agents during the protocol could have influenced the response to subsequent doses. We analyzed both CA perfusion and contraction, however, and observed no significant variations in response between each grade of stenosis. Our protocol had the potential to induce stunning, but except for the most severe grade, no consequence of flow reduction was observed on myocardial contraction. Finally, we elected to set a 50% increase in heart rate as the goal for dobutamine infusion. This represents a smaller percentage increase in resting heart rate and resulted in a smaller dosage of dobutamine than is typically used clinically. A mean heart rate of 177 bpm was achieved, however, and even at this level, 2 of 14 animals experienced fatal ventricular fibrillation with the severe FLS. The artifacts seen with dobutamine-induced tachycardia would also most likely have been amplified at higher rates. Furthermore, larger doses of dobutamine probably would only have accentuated its advantages of producing abnormal perfusion and WT with lesser grades of stenosis and would not have altered the advantages of adenosine, which were related to reduced blood flow to the RA. Therefore, although a disparity exists between the doses used clinically and the doses used in this study for dobutamine but not adenosine, we believe that our findings depict the characteristics of these agents that will be experienced in patients.

Clinical Implications

As is evident from our findings, if MCE is to achieve a role in the clinical identification of coronary stenoses, some form of stress will be required. Although pharmacological stress provides longer imaging and reduces motion artifacts, it remains uncertain whether inotropes, such as dobutamine, or vasodilators, such as adenosine, will be superior for stress MCE. Our data document that both dobutamine and adenosine are effective agents in conjunction with MCE. Dobutamine is already widely used in stress echo and induces perfusion abnormalities and contractile dysfunction at lower grades of stenosis. Adenosine has the advantage of creating perfusion abnormalities that are more readily detectable by visual examination and of greater magnitude by quantitative analysis. At present, it is impossible to predict which stress agent will predominate in the clinical arena.

Acknowledgment

Dr Lafitte was supported by the French Federation of Cardiology.

References

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*Circulation.* 2001;103:2724-2730
doi: 10.1161/01.CIR.103.22.2724

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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