JACC Vol. 8, No. 5
November 1986:1066–72

Myocardial Contrast Echocardiography in Humans: I. Safety—A Comparison With Routine Coronary Arteriography

CARL A. MOORE, MD, MARK L. SMUCKER, MD, FACC, SANJIV KAUL, MD, FACC

Charlottesville, Virginia

Myocardial contrast echocardiography is a new diagnostic cardiovascular imaging technique capable of defining perfusion zones of coronary vessels in vivo; ultimately, it may be used to measure absolute regional myocardial blood flow. However, before it can be used in humans, its safety must be clearly established. Accordingly, the electrocardiographic and hemodynamic effects of intracoronary injections of 2 cc of sonicated Renografin-76 were compared with 5 to 10 cc of nonsonicated Renografin-76 in 10 subjects with normal coronary arteries. Two cubic centimeters of sonicated Renografin provides optimal myocardial opacification during echocardiography, while 5 to 10 cc of Renografin is required for an adequate coronary arteriogram.

During coronary arteriography, heart rate decreased while PR and QT intervals and QRS duration increased as compared with baseline and myocardial contrast echocardiography ($p < 0.01$). Similarly, the decrease in aortic pressure and first derivative of left ventricular pressure (dP/dt) was significantly ($p < 0.01$) greater during routine coronary arteriography than during myocardial contrast echocardiography. Changes in left ventricular end-diastolic or pulmonary capillary wedge pressure were similar during myocardial contrast echocardiography and coronary angiography. There were no significant differences in the duration of electrocardiographic and hemodynamic changes between myocardial contrast echocardiography and coronary arteriography.

It is concluded that intracoronary injection of 2 cc of sonicated Renografin-76 provides optimal myocardial opacification. It is safe in humans, producing transient electrocardiographic and hemodynamic alterations that are less pronounced than those seen during routine coronary angiography.

(J Am Coll Cardiol 1986;8:1066–72)

Myocardial contrast echocardiography is a new diagnostic cardiovascular imaging technique capable of defining perfusion zones of coronary vessels in vivo; ultimately, it may be used to measure absolute regional myocardial blood flow (1–6). This technique has also been used to assess serially changes in total left ventricular "area at risk" during experimental myocardial infarction (7). It therefore has the potential for defining coronary perfusion beds before and after coronary angioplasty and determining the physiologic significance of coronary stenoses and the left ventricular "area at risk" for necrosis during acute myocardial infarction. However, before its use in human patients, its safety must be clearly established.

To produce contrast enhancement of the myocardium, microbubbles of air are produced in the contrast medium (8). To determine whether these microbubbles produce deleterious effects on the myocardium, brain and kidneys, Gillam et al. (9) injected a hand-agitated Renografin and saline mixture into the coronary, carotid and renal arteries of dogs and found no pathologic effects 24 hours later. They documented definite but transient changes in hemodynamics and left ventricular wall motion during contrast injections. In a preliminary report, Lang et al. (10) showed that transient alterations in left ventricular function during intracoronary injection of sonicated contrast agents in dogs are related to the contrast agents themselves, rather than to the presence of microbubbles.

Routine coronary arteriography in humans requires injection of an iodinated nonoxygen-carrying contrast agent into the epicardial coronary arteries. Transient hemodynamic, metabolic and electrocardiographic changes have been observed in humans during this procedure, probably

From the Division of Cardiology, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia. This study was supported in part by a grant-in-aid from the American Heart Association (Virginia Affiliate), Glen Allen, Virginia and United States Public Health Services Biomedical Development Grant No. 5S07-RR05431-23 from the National Institutes of Health, Bethesda, Maryland. Dr. Kaul is a recipient of the Clinical Investigator Award of the National Institutes of Health, Bethesda.

Manuscript received February 26, 1986; revised manuscript received May 12, 1986, accepted May 30, 1986.

Address for reprints: Sanjiv Kaul, MD, Division of Cardiology, Box 158, University of Virginia School of Medicine, Charlottesville, Virginia 22908.

0735-1097/86/$3.50

as a result of both a brief interruption in coronary blood flow and hyperosmolality of available contrast agents (11–16). Nevertheless, coronary arteriography is routinely employed for the diagnosis of coronary artery disease. The aim of the present study was to study the safety of myocardial contrast echocardiography in humans with normal coronary arteries, and to compare the hemodynamic and electrocardiographic effects of sonicated Renografin-76 used for myocardial contrast echocardiography with those of nonsonicated Renografin-76 used for routine coronary arteriography.

Methods

Study patients. Patients with chest pain and a low pretest likelihood of coronary artery disease (17) who were referred to our institution for cardiac catheterization were recruited for this study. All such patients gave informed consent to the protocol approved by the Human Investigation Committee at the University of Virginia School of Medicine. Myocardial contrast echocardiography was performed in the patients in this group who were found to have normal coronary arteries during coronary arteriography. Ten patients (three men and seven women) with a mean age of 53 ± 12 years (range 37 to 74) form the basis of this report.

Symptoms and signs. Occurrence of chest pain, visual disturbances or neurologic sequelae were monitored during and for 24 hours after the study.

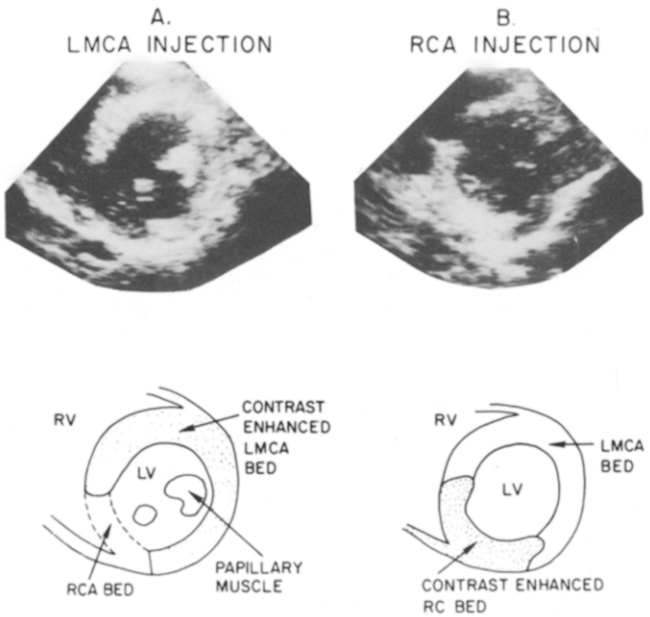
Hemodynamic measurements. All patients had routine coronary arteriography using the Judkins approach. The right femoral artery was used to introduce 7F left and right coronary catheters via an 8F arterial sheath placed in the femoral artery. In five patients, a Gensini catheter was introduced into the left ventricular cavity from the left femoral artery. A micromanometer-tipped catheter (Millar Mikro-tip, Millar Laboratories) was introduced through this catheter with the tip positioned just distal to the tip of the Gensini catheter. In four other patients, a Swan-Ganz pulmonary artery catheter was introduced through the right femoral vein to measure pulmonary capillary wedge pressure. In only one patient, neither left ventricular end-diastolic nor pulmonary capillary wedge pressure was measured during the study. Aortic pressure was measured in all 10 patients. All pressures were recorded on a commercially available recorder (Electronics for Medicine, model VR-12) using fluid-filled transducers (Gould P-50, Gould Inc.). Pressures were recorded before, during and after each coronary injection until they returned to baseline values.

Electrocardiographic measurements. Seven standard electrocardiographic leads were recorded (I, II, III, aVR, aVL, aVF and V_5). Other precordial leads were not used because echocardiographic images were obtained from acoustic windows in the parasternal region. Electrocardiographic recordings were obtained on a three-channel recorder (Hewlett Packard Corporation, model 1515B). Recordings of all seven leads were obtained before, during and for 5 seconds after injection, a time that roughly corresponded to the nadir of the hemodynamic changes. Lead II was recorded continuously throughout the study.

Echocardiographic recordings. Two-dimensional echocardiographic images were obtained using a phased array system (Hewlett Packard Corporation, model 77020A ultrasound system) with a 2.5 MHz transducer. Images were recorded on ½ inch (1.27 cm) videotapes using a commercially available video recorder (Panasonic, model AG-6300). All recordings were obtained in the parasternal short-axis projection at the mid-papillary muscle level with the patient in the supine position. Recordings were started approximately 10 seconds before injection of sonicated Renografin-76 and continued until contrast enhancement was no longer evident.

Two to three milliliters of sonicated Renografin-76 was used for each injection during myocardial contrast echocardiography. Our animal data and pilot studies in humans have demonstrated that this amount provides optimal myocardial opacification. Figure 1 is an example of such an injection in one of our patients, illustrating two short-axis views after left and right coronary injection of sonicated contrast agent. During contrast injection, approximately 1 cc enters the myocardium; the remainder fills the coronary catheter dead space. Larger amounts of contrast agent result in a "blooming" effect on the video screen and cause deterioration of images (18). Renografin-76 was sonicated us-

Figure 1. Contrast-enhanced echocardiograms with intracoronary injection of sonicated Renografin-76 (2 cc) in a subject with normal coronary arteries. The Renografin-76 produced optimal myocardial opacification of the left main coronary artery (LMCA) (**left**) and right coronary artery (RCA) (**right**) perfusion beds in a short-axis view at the mid-papillary muscle level. LV = left ventricle; RC = right coronary; RV = right ventricle.



ing a commercially available sonicator system (Heat Systems Ultrasonics, model W-375) (19). Five milliliters of Renografin-76 was sonicated at 20,000 cycles/s for 20 to 30 seconds at an energy output of 75 watts.

Protocol. After diagnostic catheterization, time was allowed for stabilization of hemodynamic variables. The left coronary artery was then injected with 8 to 10 ml of Renografin-76 for a left coronary angiogram. Electrocardiographic and hemodynamic data were obtained before, during and after this injection. Five minutes later, 2 to 3 ml of sonicated contrast agent was injected into the left coronary artery, and electrocardiographic, hemodynamic and echocardiographic data obtained before, during and after injection of the agent. In five patients, myocardial contrast echocardiography was repeated with hemodynamic and electrocardiographic monitoring. In 7 of the 10 patients, the right coronary artery was injected with 5 to 8 ml of Renografin-76 for a right coronary arteriogram, and electrocardiographic and hemodynamic data were recorded before, during and after the injection. Five minutes later, 2 to 3 ml of sonicated contrast agent was injected, and hemodynamic, electrocardiographic and echocardiographic data were recorded.

Statistical analysis. Data were analyzed using RS/1 (Bolt, Beraneck, and Newman, 1983) on a VAX 11/780 minicomputer (Digital Equipment Corporation). Comparisons of baseline data with data obtained during coronary arteriography and myocardial contrast echocardiography were made using Neuman-Keul's multiple comparison test whenever a significant ($p < 0.05$) difference was detected by the F test embodied in the analysis of variance (MULTICOMPARE).

Results

Seventeen injections of Renografin-76 were performed for routine coronary arteriography, and 24 injections of sonicated Renografin-76 were performed for myocardial contrast echocardiography.

Symptoms. Eight patients reported either no symptoms or vague substernal sensations that were less marked during myocardial contrast echocardiography than during coronary arteriography. One patient reported, during myocardial contrast echocardiography, chest tightness not previously noted during coronary arteriography; it resolved before the disappearance of contrast from the myocardium. Another patient reported, after completion of the experimental protocol, chest tightness that responded to sublingual nitroglycerin. No chest pain was reported in the next 24 hours by any patient. No neurologic or visual symptoms were reported or noted either during or after the study.

Electrocardiographic changes. Table 1 depicts the electrocardiographic changes during routine coronary arteriography and myocardial contrast echocardiography. There was no significant difference in the heart rate, PR interval and QRS duration between the baseline study and myocardial contrast echocardiography. In contrast, significant bradycardia and prolongation of the PR interval and QRS duration occurred during routine coronary arteriography.

Table 1. Electrocardiographic Changes During Intracoronary Injections of Nonsonicated and Sonicated Renografin-76 in 10 Patients

Variable	Baseline	Renografin-76	Sonicated Renografin-76	Overall p Value*
Heart rate (beats/min)	73 ± 14	58 ± 9	65 ± 10	0.02
		<0.05	<0.05	
			NS	
QRS axis (degrees)	48 ± 52	51 ± 52	52 ± 41	0.001
		<0.01	NS	
			<0.01	
PR interval (ms)	171 ± 10	182 ± 10	176 ± 10	0.001
		<0.01	<0.01	
			NS	
QRS duration (ms)	78 ± 10	91 ± 20	81 ± 10	0.001
		<0.01	<0.01	
			NS	
QT interval (ms)	424 ± 30	540 ± 70	480 ± 40	0.001
		<0.01	<0.01	
			p < 0.01	
ST depression (% patients)	40	70	47	0.20
T wave inversion (% patients)	10	82	82	0.001
		<0.01	NS	
			<0.01	
PVCs (% patients)	10	24	6	0.30

*Assessed using analysis of variance. NS = not significant; PVCs = premature ventricular complexes.

Table 2. Electrocardiographic Changes During Repeat Intracoronary Injection of Sonicated Renografin-76 in Five Patients

Variable	Injection 1	Injection 2	p Value
Heart rate (beats/min)	60 ± 3	58 ± 4	NS
QRS axis (degrees)	40 ± 48	40 ± 48	NS
PR interval (ms)	180 ± 40	180 ± 40	NS
QRS duration (ms)	840 ± 10	840 ± 10	NS
QT interval (ms)	480 ± 50	450 ± 50	NS
ST depression (% patients)	40	20	NS
T wave inversion (% patients)	60	60	NS
PVCs (% patients)	20	20	NS

NS = not significant; PVCs = premature ventricular complexes.

The QT interval was significantly longer during routine coronary arteriography than during myocardial contrast echocardiography. The shift in QRS axis and the incidence of transient T wave inversion were similar in the two studies. The incidence of premature ventricular beats and ST segment depression was similar during baseline study, myocardial contrast echocardiography and coronary arteriography.

Arrhythmias were noted in two patients during coronary arteriography and myocardial contrast echocardiography. One patient developed transient sinus arrest with a junctional escape rhythm (19 seconds during coronary arteriography and 13 seconds during myocardial contrast echocardiography) requiring intravenous atropine. The other patient developed transient (3 seconds) second and third degree block during an inadvertent rapid injection of 5 ml of sonicated Renografin-76 in the right coronary artery requiring intravenous atropine. Electrocardiographic changes were most marked at 3 to 10 seconds after injection of Renografin-76 (nonsonicated or sonicated) and abated by 10 to 90 seconds.

Electrocardiographic changes produced by repeat injection of the same amount of sonicated Renografin-76 in the same vessel in five patients were nearly identical (Table 2).

Hemodynamic changes. Effects of nonsonicated and sonicated Renografin-76 on aortic systolic pressure, left ventricular end-diastolic or pulmonary capillary wedge pressure and first derivative of the change in left ventricular pressure (dP/dt) in the nine patients in whom these measurements were recorded are depicted in Table 3. Although the aortic systolic pressure decreased significantly during both coronary arteriography and myocardial contrast echocardiography, the decrease was significantly greater with the former. Similar changes were noted in aortic diastolic and mean pressures (−23 ± 11 versus −9 ± 7% and −27 ± 5 versus −13 ± 5%, respectively). The left ventricular end-diastolic pressure and pulmonary capillary wedge pressure increased significantly during coronary arteriography and myocardial contrast echocardiography compared with baseline. Although the percent increase was larger during the former, this difference was not significant. Similarly, although the increase in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure lasted longer during coronary arteriography than during myocardial contrast echocardiography (24 ± 21 versus 14 ± 7 seconds), the difference was not significant. In the five patients in whom left ventricular dP/dt was measured, a significant decrease was noted during coronary arteriography, but not during myocardial contrast echocardiography. The duration of change in left ventricular dP/dt was similar during coronary arteriography and myocardial contrast echocardiography (20 ± 18 versus 17 ± 14 seconds).

Table 3. Hemodynamic Changes Noted During Intracoronary Injection of Nonsonicated and Sonicated Renografin-76 in Nine Patients

Variable	Control 1	Renografin-76	Change 1	Control 2	Sonicated Renografin-76	Change 2	Overall p Value*
ASP (mm Hg) (n = 9)	127 ± 23	96 ± 23	−25 ± 11%	130 ± 23	112 ± 24	−14 ± 9%	<0.0001
	<0.01			<0.05			
				<0.01			
PCWP or LVEDP (mm Hg) (n = 9)	11 ± 2	15 ± 3	34 ± 21%	12 ± 3	15 ± 2	20 ± 9%	<0.0001
	<0.01			<0.01			
				NS			
LV dP/dt (n = 5)	1686 ± 258	1247 ± 422	−25 ± 25%	1653 ± 264	1403 ± 331	−15 ± 16%	<0.0001
	<0.01			NS			
				NS			

*Assessed using analysis of variance. ASP = aortic systolic pressure; LV dP/dt = left ventricular dP/dt; LVEDP = left ventricular end-diastolic pressure; NS = not significant; PCWP = pulmonary capillary wedge pressure.

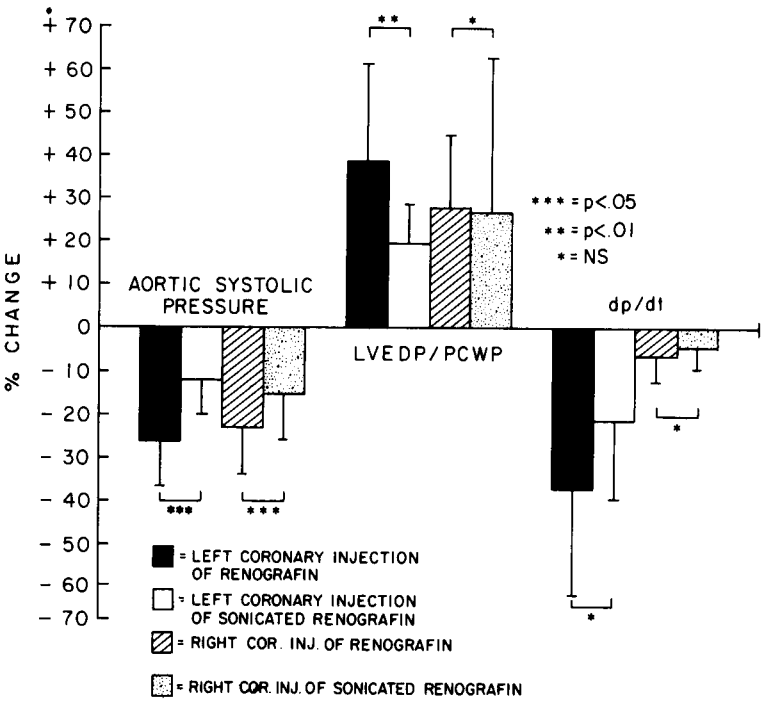


Figure 2. Hemodynamic variables at baseline study and during myocardial contrast echocardiography and coronary arteriography in 10 subjects with normal coronary arteries. COR. INJ. = coronary injection; dp/dt = first derivative of the change in left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; NS = not significant; PCWP = pulmonary capillary wedge pressure.

The effects of nonsonicated and sonicated Renografin-76 on aortic systolic pressure, left ventricular end-diastolic pressure or pulmonary capillary wedge pressure and left ventricular dP/dt were not significantly different between left and right coronary injections (Fig. 2). However, during left coronary injections, changes in aortic systolic pressure and left ventricular end-diastolic pressure or pulmonary capillary wedge pressure were significantly greater during coronary arteriography than during myocardial contrast echocardiography; changes in left ventricular dP/dt were similar. During right coronary injections, only changes in aortic systolic pressure were significantly greater during coronary arteriography than during myocardial contrast echocardiography.

Figure 3 illustrates the changes in aortic systolic pressure, left ventricular end-diastolic pressure and left ventricular dP/dt during a repeat injection of sonicated contrast agent in five patients. The hemodynamic variables and percent change in variables were almost identical. The duration of changes in left ventricular end-diastolic pressure and dP/dt was also similar (9 ± 3 versus 12 ± 2 seconds and 10 ± 3 versus 12 ± 8 seconds, respectively).

Echocardiographic changes. All echocardiograms were reviewed for myocardial opacification and wall motion changes during injection of sonicated Renografin-76. Myocardial opacification of left and right coronary vascular beds was optimal with injection of 2 to 3 cc of contrast agents. A "blooming" effect was noted when 5 cc of sonicated Renografin-76 was inadvertently injected into the right coronary artery of one patient. No significant wall motion abnormalities were noted after injection of sonicated Renografin-76. Wall motion was analyzed visually, and quantitative methods were not used.

Discussion

The present study demonstrates that selective intracoronary injections of sonicated Renografin-76 in amounts necessary to produce adequate and reproducible myocardial contrast enhancement during two-dimensional echocardiography appear to be safe in humans. The electrocardiographic and hemodynamic effects of injecting 2 ml of sonicated Renografin-76 (which is adequate to produce optimal myocardial opacification) are less than those associated with injecting 5 to 10 ml of nonsonicated Renografin-76 (which is required for a single injection during routine coronary arteriography). Although these results are based on a small number of patients with normal coronary arteries, our data suggest that myocardial contrast echocardiography may be safely used in patients undergoing routine coronary arteriography.

Electrocardiographic and hemodynamic effects of contrast agents. Transient but significant electrocardiographic and hemodynamic changes documented previously with iodinated contrast agents are probably related in part to transient ischemia of the sinoatrial node and myocardial cells, and in part to the viscosity, hypertonicity and calcium-chelating properties of iodinated contrast agents (11–16). Myocardial contrast echocardiography requires that microbubbles of air be produced in agents that are injected into the coronary vessels. It is therefore possible that addition

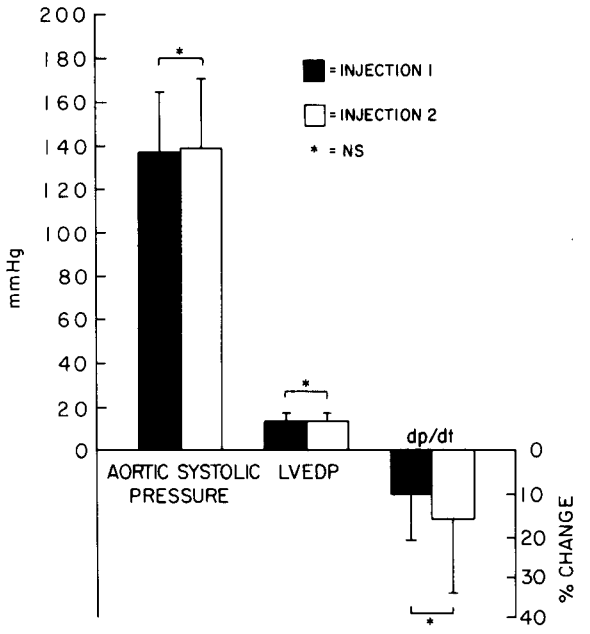


Figure 3. Hemodynamic variables during repeat injection of sonicated Renografin-76 in the left main coronary artery in five subjects with normal coronary arteries. Left ventricular dP/dt is depicted as percent change from baseline. Abbreviations as in Figure 2.

of such microbubbles may worsen the electrocardiographic and hemodynamic changes noted with these agents.

Previous studies using hand agitation to produce microbubbles have suggested that the microbubbles are predominantly responsible for the adverse effects on coronary blood flow and left ventricular function (20,21). Microbubbles produced by hand agitation are usually large (12 ± 7 μ in diameter) (9,19) and may become entrapped in the microcirculation, resulting in myocardial ischemia (22). When these agents are injected into the coronary circulation, the myocardial contrast effect noted on echocardiography usually lasts for 45 to 90 seconds (9). In contrast, sonication produces smaller microbubbles (5 ± 3 μ in diameter) (19), which do not become entrapped in the microcirculation (22). When these agents are injected into the coronary circulation, the myocardial contrast effect noted on echocardiography is shorter (15 to 20 seconds), implying faster coronary transit time. In a preliminary report, Lang et al. (10) injected sonicated and nonsonicated contrast agents into the coronary circulation of dogs and demonstrated that the effects of equal amounts of these agents on left ventricular function were similar. These data suggest that sonication produces smaller bubbles than hand agitation and that the bubbles do not produce adverse effects on left ventricular function in addition to those produced by the contrast agent itself.

The aim of our study was not to compare sonicated versus nonsonicated Renografin-76, but to compare the effects of the two techniques on left ventricular function. Two milliliters of sonicated Renografin required for adequate contrast enhancement of the myocardium during echocardiography was found to be safer than 5 to 10 ml of nonsonicated Renografin required for opacification of epicardial coronary arteries during routine coronary arteriography. However, the margin of safety may be narrower with sonicated versus nonsonicated contrast agents, as exemplified in the one patient in whom 5 ml of sonicated Renografin was inadvertently injected into the coronary circulation, producing transient complete heart block. Furthermore, these data are derived from patients with normal coronary arteries. Whether sonicated Renografin is safe in patients with reduced coronary blood flow has yet to be demonstrated. Since completion of this study, we have injected sonicated Renografin before and after coronary angioplasty with no adverse effects in 15 patients with coronary artery disease. However, this technique must be used in a larger number of patients and in different clinical situations before its safety can be clearly established. Our results suggest that it is probably safe to use sonicated Renografin-76 in humans undergoing routine coronary arteriography. Special emphasis, however, must be placed on the technique of microbubble production.

Using noniodinated contrast agents. Santoso et al. (23) recently reported that intracoronary injection of hand-agitated polygelin colloid solution is safe in humans. Interestingly, although they injected 5 ml of this substance into the coronary circulation, they did not observe any change in heart rate, systolic blood pressure or M-mode echocardiographic indexes of left ventricular contractility. The investigators attribute the lack of such changes to the chemical composition of the polygelin colloid solution which, unlike Renografin-76, is not hyperosmolar and does not have calcium-chelating properties. These data are somewhat surprising. First, injection of 5 ml of a nonoxygen-carrying substance into the coronary circulation should definitely interrupt coronary blood flow and, thus, produce hemodynamic changes. Second, as demonstrated by Levine et al. (21), hand agitation of even an oxygen-carrying medium such as fluosol produces effects on left ventricular function, probably as a result of microcapillary blockage produced by the large-sized microbubbles. We did not attempt to use noniodinated contrast agents, because they are expensive and not readily available. However, because they produce fewer hemodynamic effects, sonicated noniodinated contrast agents may be safer in patients with poor left ventricular function (24).

Limitation of the study. We did not quantitate regional myocardial function using two-dimensional echocardiography; echocardiographic images were acquired only during injection of the sonicated contrast agent. Although we did not see any significant changes in regional wall motion during injection of sonicated contrast agent, it is possible that transient but subtle changes could have occurred.

Conclusion. Ours is the first study demonstrating the safety of sonicated Renografin-76 in humans. The technique is at least as safe as routine coronary arteriography in subjects with normal coronary arteries. Although we have used this technique without any side effects in an additional 15 patients undergoing coronary angioplasty, it must be used in a larger number of patients with coronary artery disease before its safety as a routine adjunct to coronary arteriography can be clearly established. Our results, however, should provide an impetus to the use of this technique in humans. Apart from delineating perfusion zones of coronary vessels during acute myocardial infarction and before and after coronary angioplasty, this technique may be useful for measuring absolute regional myocardial blood flow and coronary vascular reserve.

We are grateful to Debra Peters for secretarial assistance and to Craig Harding for preparing the artwork.

References

1. DeMaria AN, Bommer WJ, Riggs K, et al. Echocardiographic visualization of myocardial perfusion by left heart and intracoronary injection of echo contrast agents (abstr). Circulation 1980:62(suppl III):III–143.
2. Bommer WJ, Resor J, Tickner D, et al. Quantitative regional myocardial perfusion scanning with contrast echocardiography (abstr). Am J Cardiol 1981;47:403.
3. Armstrong WF, Kinney EL, Mueller TM, Tickner EG, Dillon JC, Feigenbaum H. Assessment of myocardial perfusion abnormalities with contrast enhanced two-dimensional echocardiography. Circulation 1982;66:166–73.
4. Tei C, Sakamaki T, Shah PM, et al. Myocardial contrast echocardiography: a reproducible technique of myocardial opacification for identifying regional perfusion defects. Circulation 1983;67:585–93.
5. Kemper A, O'Boyle JE, Sharma S, et al. Hydrogen peroxide contrast-enhanced two-dimensional echocardiography: real-time in-vivo delineation of regional myocardial perfusion. Circulation 1983;68:603–11.
6. Kaul S, Pandian NG, Okada RD, Pohost GM, Weyman AE. Contrast echocardiography in acute myocardial ischemia. I. In-vivo determination of total left ventricular "area at risk." J Am Coll Cardiol 1984;4:1272–82.
7. Kaul S, Lutrario D, Pandian NG, Ruddy TD, Weyman AE, Okada RD. The optimal method of assessing left ventricular function during acute myocardial infarction: an experimental evaluation (abstr). Clin Res 1986;34:170A.
8. Feinstein SB, Ten Cate FJ, Zwehl W, et al. Two-dimensional contrast echocardiography. I. In-vitro development and quantitative analysis of echo contrast agents. J Am Coll Cardiol 1984;3:14–20.
9. Gillam LD, Kaul S, Fallon JT, et al. Functional and pathologic effects of multiple echocardiographic contrast injections on the myocardium, brain and kidney. J Am Coll Cardiol 1985;6:687–94.
10. Lang R, Borow KM, Neumann A, Feinstein SB. Echo contrast agents: effect of sonicated microbubbles and carrier solutions on left ventricular contractility (abstr). Circulation 1985;72(suppl III):III–58.
11. Gensini GG, DiGiorgi S. Myocardial toxicity of contrast agents used in angiography. Radiology 1964;82:24–33.
12. Friesinger GC, Schaffer J, Criley JM, Gaertner RA, Ross RS. Hemodynamic consequences of the injection of radiopaque material. Circulation 1965;31:730–40.
13. Benchimol A, McNally EM. Hemodynamic and electrocardiographic effects of selective coronary angiography in man. N Engl J Med 1966;274:1217–24.
14. Oppenheimer MH, Ascanio G, Henny GC, Caldwell E, Vinciguerra T. Metabolic and cardiovascular effects of selective intracoronary injections of contrast media. Invest Radiol 1973;8:13–21.
15. Guzman SV, West JW. Cardiac effects of intracoronary arterial injections of various roentgenographic contrast media. Am Heart J 1969;38:597–607.
16. Bassan M, Ganz W, Marcus HW, Swan HJC. The effect of intracoronary injection of contrast medium upon coronary blood flow. Circulation 1975;51:442–6.
17. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med 1979;300:1350–7.
18. Kaul S, Gillam LD, Weyman AE. Contrast echocardiography in acute myocardial ischemia. II. The effect of site of injection of contrast agent on the estimation of area at risk for necrosis after coronary occlusion. J Am Coll Cardiol 1985;6:825–30.
19. Keller MW, Feinstein SB. Laser analysis of sonicated echo contrast agents (abstr). J Ultrasound Med 1985;4:30.
20. Holt G, Reeves W, Rieder M, Daley L, Murthy V, Christensen C. Negative inotropic effects of intracoronary echo contrast agents (abstr). J Am Coll Cardiol 1985;5:474.
21. Levine RA, Gillam LD, Guerrero JL, Weyman AE. Wall motion abnormalities following myocardial echo contrast injection are caused by microbubbles (abstr). J Am Coll Cardiol 1985;5:474.
22. Feinstein SB, Shah PM, Bing RJ, et al. Microbubble dynamics visualized in the intact capillary circulation. J Am Coll Cardiol 1984;4:595–600.
23. Santoso T, Roelandt J, Mansyoer H, Abdurahman N, Meltzer RS, Hugenholtz PG. Myocardial perfusion imaging in humans by contrast echocardiography using polygelin colloid solution. J Am Coll Cardiol 1985;6:612–20.
24. Wineski JA, Gertz EW, Neese RA, Morris DL. Absence of myocardial biochemical toxicity with a non-ionic contrast agent (iopamidol). Am Heart J 1985;110:609–617.