METHODS

Contrast Echocardiography During Coronary Arteriography in Humans: Perfusion and Anatomic Studies

STEVEN B. FEINSTEIN, MD, ROBERTO M. LANG, MD, CANDACE DICK, MD, ALEX NEUMANN, BS, JAFAR AL-SADIR, MD, FACC, K.G. CHUA, MD, FACC, JOHN CARROLL, MD, TED FELDMAN, MD, KENNETH M. BOROW, MD, FACC

Chicago, Illinois

In humans, the physiologic relation between myocardial blood flow and epicardial coronary artery anatomy remains poorly defined. With the recent development of sonicated microbubble contrast agents, it is now possible to use contrast echocardiography to assess myocardial perfusion and to correlate blood flow with angiographically identified coronary artery anatomy. The purpose of the current study was to determine myocardial perfusion patterns in patients without significant coronary artery disease. These results may be used as a reference to analyze myocardial blood flow in patients with coronary artery disease.

Sonicated meglumine diatrizoate solution (Renografin-76), which contains microbubbles measuring 4.5 ± 2.8 μm in diameter by laser analysis, was used as the echocardiographic contrast agent during elective coronary arteriography in 14 patients without significant coronary artery disease. Patients received intracoronary injections of 1.5 to 2 ml of sonicated Renografin-76 without complications. Perfusion characteristics were studied by visual assessment of the two-dimensional echocardiographic images obtained after individual injections. In patients found to be free of significant coronary artery disease by arteriography, the left coronary system always supplied the anteroseptal, anterior, anterolateral and posterior regions of the left ventricle at the mid-papillary, cross-sectional level. The right coronary artery system perfused the inferior and interseptal regions in 89% of the patients identified with a right dominant system. The anterolateral papillary muscle was perfused from the left coronary system in all cases. The posteromedial papillary muscle was perfused from the left coronary system in 58% of the patients and from the right system in 42% of the patients. The mid portion of the intraventricular septum was variably perfused from both coronary systems.

These results indicate that in patients free of significant coronary artery disease, the general perfusion pattern may be anticipated from the epicardial vessel distribution. However, for a specific patient, individual regional perfusion patterns vary. Thus, data are now available in humans correlating normal myocardial perfusion and angiographically determined coronary anatomy. Contrast echocardiography, when used in conjunction with cardiac catheterization, provides a rapid, safe and effective method for the clinical evaluation of regional myocardial blood flow.

(I Am Coll Cardiol 1988;11:59-65)

Conventional imaging techniques used to assess ischemic heart disease are limited in their ability to quantify myocardial perfusion (1). Although the most widely used imaging modality, coronary arteriography, provides qualitative planar images of the lumen of major coronary arteries, it does not allow direct evaluation of myocardial tissue perfusion (2-4). Newer imaging techniques (positron emission tomography and nuclear magnetic resonance imaging) now being developed will incorporate functional and anatomic descriptors to facilitate the clinical evaluation of patients with ischemic heart disease (1). In general, myocardial perfusion patterns are anatomically defined by a complex vascular network. Furthermore, transmural myocardial perfusion is affected by regional stress, status of the underlying vascular anatomy and the viability of the cardiac tissue. Currently, the degree of coronary artery stenosis and the analysis of

This work was presented in part at the 36th Annual Scientific Session of the American College of Cardiology, March 8 to 12, 1987, New Orleans, Louisiana. It was supported in part by the Goldsmith Research Foundation and by the Chicago Heart Association Grant-in-Aid award 1985 to 87. Dr. Feinstein is the recipient of the Amoco Foundation Fellowship for 1985 to 1987 at the University of Chicago. Roberto M. Lang, MD is the recipient of a National Institute of Health Research Award T53-GM 07337-02.

Manuscript received April 15, 1987; revised manuscript received July 22, 1987, accepted August 3, 1987.

Address for reprints: Steven B. Feinstein, MD, Section of Cardiology, University of Chicago Medical Center, 5841 South Maryland Avenue, Box 44, Chicago, Illinois 60637.

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regional wall motion by standard two-dimensional echocardiography do not adequately define the status of tissue blood flow and viability. An ideal technique for assessing such perfusion would acquire data in a real time format while not disturbing either intrinsic vascular flow characteristics or ventricular contractile state. Experimental and clinical studies suggest that contrast echocardiographic techniques may fulfill these criteria (5–27).

Sonication of meglumine sodium diatrizoate solution (Renografin-76) reproducibly creates stable microbubbles with an average diameter similar to that of red blood cells (5,6,28). These microbubbles flow through the microvessels without occlusion (29,30) and, according to videodensitometric analyses, reflect physiologic myocardial transit times (8,19). Studies of the effects of sonicated Renografin-76 on left ventricular contractility in dogs (14) have shown that the solution rather than the presence of microbubbles affects left ventricular function. Similarly, studies (15,22) in patients receiving intracoronary injections of sonicated microbubbles of Renografin-76 (1.5 to 2 ml) revealed that left ventricular contractile state was not significantly altered by the presence of the sonicated microbubbles. In addition, initial clinical studies using contrast echocardiography in the catheterization laboratory (20) and the operating room (21) have described the safety of injecting small volumes of agitated microbubble solutions into the aortic root or directly into the coronary arteries to identify regional perfusion defects.

However, as contrast echocardiography becomes a useful procedure for assessing myocardial perfusion, it becomes necessary to establish references for blood flow distribution patterns in patients free of coronary artery disease. Accordingly, this report correlates myocardial perfusion determined by contrast echocardiography with coronary artery anatomy as identified by arteriography in patients without significant coronary stenosis.

Methods

Patient selection. A total of 50 patients participated in a protocol approved by the University of Chicago Clinical Investigation Committee for the study of myocardial perfusion using contrast echocardiography during coronary arteriography. Patients diagnosed as having critical aortic or mitral stenosis, critical and unstable ischemic heart disease, a recent cerebrovascular accident (within 2 months) or endocarditis were excluded from the overall study. Of the 50 patients evaluated, 18 were identified by arteriography as having no significant coronary artery disease. These patients were used as a reference group to establish normal contrast perfusion data and constituted the study group for this report.

Coronary arteriography. Routine informed consent for cardiac catheterization was obtained and all standard preca-
cross-sectional view obtained at the papillary muscle level was the most commonly recorded view and therefore, was chosen for the regional perfusion analysis. The two-dimensional cross-sectional view was divided into 10 regions, modified from the Report of the American Society of Echocardiography Committee on Nomenclature and Standards (31) (Fig. 2).

Regions 1 through 10 were labeled in a clockwise manner as follows: anterior, anterolateral, posterolateral, posterior, inferior, inferoseptal, mid-septal, anteroseptal and the anterolateral and posteromedial papillary muscles. For regions with echocardiographic "drop out," or loss of lateral border resolution, no assessment of perfusion was made. In areas supplied by both the left and right coronary arteries, dominance of perfusion was established if >50% of an area was estimated to be perfused from the selective arterial injection.

Results

Coronary arteriography in the patients without significant coronary artery disease. Of the initial 50 patients studied, 18 did not have significant coronary artery disease. Four of these 18 patients were excluded from further analysis—three because a parasternal, cross-sectional two-dimensional echocardiographic view was not available and one because the contrast effect was inadequate. (The latter patient was the first subject studied in our protocol and the microbubble solution was diluted before the intracoronary injections.) A right dominant coronary system was noted in 12 of the 14 patients without significant coronary artery disease; the remaining 2 patients demonstrated a left dominant system. In several of the patients classified as having a right dominant system, the left circumflex coronary artery supplied arterial branches to the posterolateral aspect of the left ventricle. No patient studied developed complications during or after the catheterization procedure. In patients in whom hemodynamic variables were assessed throughout the contrast echocardiographic portion of the study, only minor, transient alterations were noted in the heart rate, blood pressure and electrocardiogram (ECG) during the intracoronary injections. Our findings, previously reported (12-15,25), are consistent with recent clinical data from other laboratories (20-22,24,26,27).

Contrast echocardiography. The contrast echocardiographic perfusion studies in the 14 patients employed a total of 70 intracoronary injections (1.5 to 2 ml each) of sonicated Renografin-76. The number of injections per patient ranged from four to eight, and the echocardiographic views obtained per patient varied between one and three, with the parasternal long-axis and cross-sectional views used in 64 (91%) of 70 injections.

Of the 140 regions visually analyzed (10 regions in 14 patients), 3 regions in one patient were considered inadequate for analysis purposes. In three patients, no right coronary artery injection of microbubbles was performed because of difficulty in attaining a stable catheter position. Accordingly, perfusion characteristics were analyzed only for the left coronary injections in those three patients.

Assessment of regional myocardial perfusion in patients without significant coronary artery disease (Fig. 3). Regional perfusion based on videointensity was analyzed in each patient using a two-dimensional echocardiographic parasternal...
nal cross-sectional view obtained at the papillary muscle level. Figure 3 illustrates the cross-sectional echocardiographic video images from one patient study. From the still frame photographs, it was possible to identify the endocardial and epicardial borders as well as the two papillary muscles. The baseline image is shown in Figure 3A. After a 1.5 to 2 ml injection of sonicated Renografin-76 microbubbles into the right coronary artery (Fig. 3B), dense white opacification was noted in the inferoseptal and inferior regions. The posteromedial papillary muscle was also visually enhanced after the injection. Figure 3C demonstrates the tissue distribution of the microbubbles after a 1.5 to 2.0 ml left main intracoronary injection of sonicated Renografin-76; the areas of echo contrast enhancement from the left coronary injection complemented those regions not receiving microbubble perfusion after the right coronary injection. The left injection perfused the anteroseptal, anterior, anterolateral, posterolateral, and posterior regions. The anterolateral papillary muscle was also perfused from the left coronary injection.
Right dominant coronary artery system (Fig. 4). In all 12 patients with a right dominant coronary system, the left coronary artery perfused the anteroseptal, anterior, anterolateral, posterolateral and posterior regions of the left ventricle. The anterolateral papillary muscle was consistently perfused by the left coronary distribution. The right coronary artery perfused the inferior and inferoseptal areas in 89% of cases, the mid-septal area in 17% and the posteromedial papillary muscle in 42%.

Left dominant coronary artery system. In the two patients with normal coronary arteries and a left dominant system, both papillary muscles were supplied from the left system. However, the inferior and inferoseptal regions were supplied from the left coronary system in one patient and from the right coronary system in the other patient.

Variability of perfusion. Of the 14 patients analyzed, 8 had two or more (range two to five) sequential intracoronary injections of sonicated Renografin-76 with simultaneous two-dimensional echocardiograms performed at the cross-sectional papillary muscle level. The perfusion distribution patterns noted after each injection were separately analyzed by two observers several months later. There was no variation noted in the regional patterns in any case when serial injections were compared.

Discussion

Regional coronary perfusion patterns assessed by contrast echocardiography. This report describes the successful clinical use of real-time contrast echocardiography to assess myocardial perfusion in humans at the time of coronary arteriography. These studies demonstrated the feasibility of using contrast echocardiography with sonicated Renografin-76 to identify regional perfusion at the papillary muscle level within myocardial tissue. The myocardial perfusion data available in this study were not obtained using arteriography or conventional two-dimensional echocardiography.

Overall, in the patients without significant coronary artery disease, the variation noted in the regional blood flow at the level of the papillary muscle was limited primarily to the interventricular septum, the inferior wall and the posteromedial papillary muscle. However, in an individual patient, the actual extent of perfusion could not readily be predicted from the epicardial coronary anatomy.

The variation noted when comparing anatomy and perfusion among patients may arise from a variety of factors: the simplified coronary anatomic description used; the presence of collateral vessels; the influence of non-ECG-gated, manual intracoronary injections, or simply a variation in individual perfusion patterns. However, the importance of identifying regional perfusion patterns at the time of coronary arteriography needs to be stressed. Today, a detailed analysis of myocardial perfusion has not been possible with coronary arteriography or standard two-dimensional echocardiographic images. By combining these two imaging modalities at the time of cardiac catheterization and introducing microbubbles as an intravascular, non-diffusible tracer, a real-time, tomographic perfusion index can be developed. Thus, despite the complex vascular network within the myocardium and the variations in transmural flow characteristics due to coronary stenosis, myocardial infarction or interventional therapy, contrast echocardiographic techniques may prove to be a valuable tool for the immediate assessment of myocardial blood flow.

Previous studies. Before the development of sonicated microbubble ultrasound agents, contrast echocardiography employed hand-agitated microbubbles that were relatively large, variable in size and unable to pass through the capillary bed without obstruction (29,30,32). Despite the large size of microbubbles in hand-agitated contrast solutions, no histologic abnormalities attributable to vascular occlusion in the brain, heart or kidney have been noted in animal studies (33). In human studies, hand-agitated microbubbles have been injected from both the left and right sides of the heart since 1968 for the qualitative assessment of valvular regurgitation (34), cavity dimensions (35) and intracardiac shunts (36-38). These studies have been performed without significant clinical complications (20,21,34-39).

However, the recent development of small, uniform-sized sonicated Renografin-76 microbubbles has allowed tracking of echocorrelative tracers through the microvasculature within physiologic transit times (8,18,19). We have previously determined the effects of sonicated microbubbles on left ventricular contractility in animals using a sensitive
noninvasive index of myocardial function (14). Alterations in contractile state noted in that study were attributed to the particular carrier solution or to the presence of the larger hand-agitated bubble solution and not to the presence of the sonicated microbubbles of Renografin-76 solution (23). This work recently has been expanded into clinical trials (15). In humans, intracoronary injections of small volumes (1.5 to 2 ml) of sonicated microbubbles in Renografin-76 did not adversely affect contractility. This was true even though intracoronary injection of large volumes (7 to 9 ml) of Renografin-76 transiently depressed contractile state.

Methodologic considerations. For this initial study of perfusion in patients at the time of cardiac catheterization, we limited the total echocardiographic imaging time to approximately 10 to 15 min. This was done to avoid unnecessary delays in performing the catheterization procedure. Therefore, we did not attempt to fully characterize the left ventricular myocardial perfusion. Our efforts revealed that the parasternal short-axis view was the most commonly obtained image and, hence, we chose to analyze only that level of perfusion in each patient. Because of the clinical utility of assessing myocardial perfusion in conjunction with coronary angiography, in subsequent studies we have extended the imaging time to permit more views of the myocardium.

With regard to the image quality and yield of the parasternal short-axis views, contrast echocardiographic techniques offer several advantages over those of standard two-dimensional echocardiograms. First, the use of microbubbles enhances the signal to noise ratio; thus the quality of the two-dimensional image is improved, permitting clearer identification of endocardial and epicardial surfaces. Consequently, measurements of wall thickness and cavity dimensions are easily performed. The enhanced ultrasound signals should complement and promote the use of quantitative two-dimensional echocardiography for the evaluation of left ventricular performance (40,41). In addition, the enhanced border identification may facilitate the use of computer-assisted, automated edge detection algorithms, ultimately permitting three-dimensional reconstruction of perfusion within the myocardium.

Second, using contrast echocardiographic techniques in conjunction with coronary angiography, it is possible to "target" areas of interest in the myocardium. Specifically, if a clinical question exists regarding the perfusion distribution associated with the left anterior descending artery, the ultrasound investigation can be directed to the anteroseptal, anterior and anterolateral regions of the myocardium. By identifying the region of interest we can improve the yield of clinical information, using contrast echocardiography at the time of the cardiac catheterization. In future studies, by devoting more time to ultrasound imaging in the catheterization laboratory, we could obtain several views of the myocardium and, consequently, more thoroughly characterize the myocardial blood flow.

With regard to the individual variability associated with intramyocardial blood flow, several factors may contribute. The nonstandardized manual intracoronary injections of contrast agents may have resulted in the recruitment of capillary vessels, thus disturbing the native blood flow patterns within the tissue. The use of a hyperosmolar, biologically active solution (Renografin-76) may alter the autoregulation of the vasculature. In addition, the timing of the injection often extended beyond a single cardiac cycle. Thus, the spatial, temporal heterogeneity of regional flow is likely to be altered (42). In the future, an ECG-gated, volume- and pressure-controlled mechanical injector may reduce the effects of the injection process on the native coronary blood flow (43) and the use of newly developed air-filled, albumin microspheres should reduce the variability and biologic activity of the current ultrasound contrast agents (44-46).

Conclusions. This initial study suggests that contrast echocardiography utilizing sonicated Renografin-76 microbubbles is a safe, efficacious and physiologic means of determining regional myocardial perfusion. Further validation and testing will be required to determine the clinical utility of performing contrast echocardiographic studies to assess tissue blood flow. With the increasing clinical use of interventional therapies, the need to demonstrate the severity of coronary artery lesions and their physiologic significance is critical (1). This study suggests that important clinical issues regarding coronary artery anatomy and myocardial perfusion can be addressed in a single setting. Used at the time of cardiac catheterization during coronary angioplasty or cardiac revascularization surgery, contrast echocardiography may provide an improved understanding of the physiology of blood flow within the myocardium. Subsequent therapy and management decisions could then be approached in a quantifiable manner, perhaps ultimately resulting in improved management of patients with ischemic heart disease.

We thank David James for his expertise in preparing the manuscript and the accompanying graphics. We also thank Patricia Walley, Paulette Nizynski, Carolyn Hughes, Martin Perez and Stephen Ginger for their support and assistance in performing these studies.

References


