Detection of regional temporal abnormalities in left ventricular function during acute myocardial ischemia

VICTOR MOR-AVI, KEITH A. COLLINS, CLAUDIA E. KORCARZ, MILIND SHAH, KIRK T. SPENCER, AND ROBERTO M. LANG

The Noninvasive Cardiac Imaging Laboratory, University of Chicago, Chicago, Illinois 60637

Received 2 August 2000; accepted in final form 15 November 2000

Detection of regional temporal abnormalities in left ventricular function during acute myocardial ischemia. Am J Physiol Heart Circ Physiol 280: H1770–H1781, 2001.—Echocardiographic diagnosis of myocardial ischemia is based on visualizing hypokinesis, which occurs late in the ischemic cascade. We hypothesized that temporal changes in endocardial motion may constitute sensitive early markers of ischemia. Two protocols were performed in 19 anesthetized pigs. Protocol 1 included 54 intracoronary balloon occlusions. Transthoracic images were acquired at baseline and every 15 s during 5 min of occlusion and reperfusion. In protocol 2, ischemia was induced in 12 animals by use of graded dobutamine infusion, after creating significant partial occlusions without a resting wall motion abnormality. Systolic and diastolic endocardial motion was color encoded using color kinesis and analyzed using custom software. All ischemic episodes caused detectable and reversible changes. The earliest sign of ischemia was tardokinesis in 31/54 occlusions, whereas hypokinesis appeared first in 23/54 cases. Dobutamine-induced ischemia caused tardokinesis first in 9/12 and hypokinesis in 3/12 animals. Reversible ischemic changes in regional left ventricular performance can be objectively detected using analysis of echocardiographic images and will likely improve the early noninvasive diagnosis of acute ischemia.

ultrasound imaging; ventricular function; endocardial motion; color kinesis

ECHOCARDIOGRAPHIC DIAGNOSIS of myocardial ischemia is based on visualizing a regional decrease in systolic endocardial motion and myocardial thickening. The sensitivity of this subjective methodology is known to be limited when ischemia is not severe enough to result in visibly reduced wall motion. Temporal changes in regional systolic and, in particular, diastolic endocardial motion, which have been suggested as potentially more sensitive early markers of ischemia (9), are currently not evaluated in clinical practice because they are extremely difficult to characterize using conventional technologies. We hypothesized that these temporal changes could be detected from echocardiographic images. A recently developed real-time imaging technique based on acoustic quantification color encodes left ventricular systolic and diastolic endocardial motion by using different colors to represent consecutive time frames (16). This color-coded display, known as color kinesis images, provides quantifiable information on both magnitude and timing of regional endocardial motion.

We have previously described a method of quantitative segmental analysis of color kinesis images (19), which allowed us to objectively detect resting as well as stress-induced wall motion abnormalities (12, 16) in patients with coronary arterial disease. Although studies by our group and other investigators strongly suggest that color kinesis is a useful aid in detecting reduced wall motion (7, 8, 14, 17, 26, 31, 34), this methodology has not been previously used to evaluate altered timing of wall motion as an early marker of ischemia (2, 35). To directly correlate temporal changes in regional wall motion with ischemia, we designed a controlled study, where such changes could be observed as they develop in an animal model of regional ischemia and gradually resolve during reperfusion. If confirmed, this relationship would establish the basis for clinical use of these indexes for the diagnosis of ischemia.

Accordingly, our aims were to determine 1) whether the variations in magnitude and timing of regional systolic and diastolic endocardial motion caused by acute myocardial ischemia are detectable using analysis of echocardiographic images, 2) whether a pattern of changes exists that could be related to the progression of ischemia and its reversal, and 3) which specific changes are the earliest to appear during ischemia. These goals were tested in two models of ischemia, including variable degrees of coronary flow restriction at rest and a combination of subcritical coronary occlusions with pharmacologically induced stress.

METHODS

Animal preparation. Experiments were carried out in 19 male farm pigs (20–30 kg). The protocol was approved by the Institutional Animal Care and Use Committee, in accordance with the guidelines of the National Institutes of Health.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Animals were pretreated with telazol (2.2 mg/kg im) and atropine sulfate (0.05 mg/kg im). After intubation, pigs were mechanically ventilated (Drager, Telford, PA) and anesthetized with isoflurane (0.5–2.5% mixed with 100% oxygen). Respiration rates were 20–30 strokes/min with a tidal volume of 12–18 ml/kg. Animals were restrained in a supine position. Electrocardiogram (ECG), body temperature, non-invasive blood pressure, and expiratory gases were monitored throughout the experiment with the use of a Cardiocap II monitoring system (Datex, Tewksbury, MA). Ear veins were used for intravenous lines. Lidocaine was administered as a bolus (1 mg/kg iv) and then continuously infused (4 mg·kg⁻¹·h⁻¹) throughout the experiment to prevent ventricular arrhythmias. In addition, a bolus injection of bretyllum (5 mg/kg iv) was given 15 min later, with repeated injections given every 30 min if persistent arrhythmias occurred.

An intracoronary balloon catheter (2.5-mm balloon diameter by 20-mm length; Guidant, Santa Clara, CA) was introduced via the right femoral artery into either the left anterior descending (LAD) or left circumflex (LCX) coronary artery under fluoroscopic guidance. In either case, the balloon was positioned near the origin of the artery to maximize the perfusion territory affected by balloon inflations. To roughly calibrate coronary flow restriction, distal coronary flow was visually assessed by a series of intracoronary renografin injections (Hypaque-76; Nycomed, Princeton, NJ) during brief balloon inflations at variable pressures. These balloon inflations were limited to <5 s in duration with recovery intervals of at least 30 s to avoid ischemia.

Image acquisition. Transthoracic images were obtained using an S4 transducer (SONOS 5500, Hewlett-Packard) operating in a frequency range of 2–4 MHz. Right parasternal short-axis views were obtained at the level of the papillary muscle tips. After optimization of image quality and gain settings for endocardial tracking by acoustic quantification (3), color kinesis was activated to alternately color encode systolic and diastolic endocardial motion within a region of interest surrounding the left ventricular (LV) cavity. For improved temporal resolution, we used prototype high-frame rate color kinesis software, which allowed color-encoded imaging at 60 frames/s. Image sequences were acquired during end expiration and stored on magneto-optical disk for offline analysis. The duration of color encoding of systolic endocardial motion was set to be equal to the duration of LV ejection period plus four additional frames (66 ms) to allow color encoding of possible delayed regional contraction during isovolumic contraction. These indexes included incremental fractional area change and filling fraction, which were expressed in percentage of regional end-systolic area and displayed as stacked color histograms, where different colors correspond to consecutive time frames (16). The temporal aspects of regional wall motion were expressed by the following indexes (calculated for each segment): 1) mean time of ejection and mean time of filling and 2) percentage of regional ejection at 50% ejection time and percentage of regional filling at 50% filling time.

Hypokinesis was defined as a 40% or greater decrease in regional fractional area change after coronary occlusion. Systolic or diastolic tardokinesis was defined as an increase in mean time of ejection or filling >15% associated with a decrease of >20% in percentage of ejection or filling at half times, without concurrent hypokinesis.

Statistical analysis. Regional fractional area change and filling fraction data were averaged for each group of animals undergoing coronary occlusion in the same artery. In each group, average systolic and diastolic histograms were generated for each representative phase of ischemia. Also, in each short-axis segment, mean ejection and filling times as well as percentage of ejection and percentage of filling at one-half ejection and filling times were averaged for each group of animals. In addition, to allow intersegment and interanimal comparison, the indexes obtained during different phases of ischemia and reperfusion were normalized by their control values, and normalized indexes were then averaged. Data were displayed as means ± SD of all animals in each group over different phases of ischemia. Two-way analysis of variance with repeated measures was used to test significance of differences between segments and phases in each group of animals. Indexes that resulted in significant overall differences between segments and phases were then subjected to two separate t-tests: 1) comparison between ischemic versus nonischemic segments within the same phase and 2) compar-
RESULTS

Protocol 1 included 54 coronary occlusions, 29 of which were in the LAD (17 partial and 12 complete) in 11 pigs and 25 in the LCX (14 partial and 11 complete) in 8 pigs. In this protocol, no significant ischemia-induced changes were observed in either blood pressure or heart rate. Of these 19 pigs, 12 recovered to undergo protocol 2, 6 from the LAD group and 6 from the LCX group. The total number of images acquired and analyzed in the two protocols was 3,467.

Figure 1 shows an example of end-systolic and end-diastolic color kinesis images and corresponding regional fractional area changes and filling fractions at baseline, during complete LAD occlusion and reperfusion. Color kinesis images obtained 2 min after occlusion showed thinning of the color band in the anteroseptal wall in both systole and diastole, reflecting hypokinesis. Images acquired 0.5 min after coronary occlusion showed no visible difference in the thickness of the color bands. However, subtle changes in the color distribution within this segment in both systolic and diastolic images may be noted before hypokinesis becomes apparent. In particular, the relative contribution of early colors (orange tones in systole and blue tones in diastole) was reduced compared with control images. These variations in color distribution in the ischemic segment reflect the increased role of late...
ejection and late filling during early ischemia (systolic and diastolic tardokinesis). These changes were gradually resolved during reperfusion.

The histograms corresponding to each image demonstrated the gradual changes during ischemia and reperfusion in a quantitative manner. In the histograms obtained 0.5 min after LAD occlusion, tardokinesis is visualized as a wedge of late colors in the anteroseptal segment, resulting from a lack of colors representing early motion without a change in overall magnitude of motion in that segment. After 2 min of coronary occlusion, hypokinesis in this segment is visualized as a “well,” reflecting a marked regional decrease in the magnitude of wall motion.

Figure 2 shows an example of similar data obtained in an animal that underwent LCX occlusion. Similarly, 2 min after coronary occlusion, a significant thinning of the color band is noted in the posterior segment in both systole and diastole. Hypokinesis may be visualized again as a well in the posterior segment in the histograms. In this case, there was no clear evidence of tardokinesis detectable on either color kinesis images or the corresponding histograms, before hypokinesis, in either systole or diastole. Balloon deflation resulted in wall motion patterns similar to control.

In Fig. 3, images from two animals before and after intracorony contrast injections are shown with the segmentation schemes superimposed on the peak contrast images. Injection into the LAD resulted in dense opacification of the anteroseptal and a less pronounced contrast effect in the anterior segment. Injection of Optison in the LCX caused contrast enhancement in the posterior wall, with some minor enhancement in the adjacent inferior and lateral segments. These findings corroborated the location of wall motion abnormalities induced by occlusion of each coronary artery in its respective perfusion territory.

The type of response to coronary occlusions, i.e., hypokinesis and tardokinesis, varied between animals. Both tardokinesis and hypokinesis were visualized in 24/54 occlusions, and 30/54 occlusions resulted in either type of response. Accordingly, Figs. 4 and 5
represent the summary of data averaged for the subset of 16 animals that responded with systolic and diastolic tardokinesis followed by hypokinesis (10 in the LAD group and 6 in the LCX group) in at least one ischemic episode. In addition, the time of occurrence of each response after coronary flow restriction varied widely. Thus data were not averaged at a specific time postocclusion, but rather at the time when each response was observed in each animal.

Regional fractional area changes and filling fractions averaged in this manner for this subgroup of animals are presented in Fig. 4, separately for the LAD and LCX occlusions. Compared with control histograms, tardokinesis can be seen as a wedge of late colors in the anteroseptal segment in the LAD-occluded animals and in the posterior wall in animals that underwent LCX occlusions. Hypokinesis can be visualized as a well in the specific artery-related regions. These responses to coronary flow restriction were resolved during reperfusion, which resulted in patterns of wall motion nearly identical to controls.

Figure 5 shows the mean ejection and filling times as well as percentage of ejection and percentage of filling at one-half ejection and filling times averaged for this group of animals. In the LAD-occluded animals, only the anteroseptal segment showed significant increases in mean ejection and filling times (119 ± 30 and 134 ± 35% of control values, respectively; P < 0.05 for both), reflecting increased dependency on late ejection and filling in the ischemic segments. In contrast, all other segments showed the opposite trends. These findings quantitatively confirmed the delayed systolic and diastolic function in the ischemic segments before hypokinesis. Similar changes in the temporal indexes were observed in the posterior wall as a result of LCX occlusions. The posterior segment showed increases in mean ejection and filling times (119 ± 16%, P < 0.05, and 105 ± 11%, not significant, of control values, respectively) and decreases in percent ejection and filling at half times (75 ± 13 and 78 ± 13% of control values, respectively; P < 0.05 for both). In addition, the diastolic temporal indexes of the adjacent inferior segment were affected (mean filling time, 110 ± 20%; percent filling at one-half filling time, 66 ± 41% of control values; P < 0.05 for both). All these indexes returned to their control values after reperfusion of both LAD and LCX territories.

On the basis of our quantitative definitions of hypokinesis, the frequency of each type of response as a first sign of ischemia was determined. Figure 6 shows that over one-half (31/54 occlusions) of the first ischemic responses were either systolic or diastolic tardokinesis (16 vs. 15) in complete as well as partial occlusions. The incidence of tardokinesis as the first sign of ischemia was higher in the LAD compared with the LCX territory (69 vs. 44%) and was not different between complete and partial occlusions in either artery (67 vs. 70% in the LAD; 45 vs. 42% in the LCX). Hypokinesis as the sole sign of ischemia was observed in only 23/54 occlusions, was less frequently observed in the LAD-dependent segments compared with LCX regions (31 vs. 56%), and showed no marked difference between complete and partial occlusions (33 vs. 29% in the LAD; 55 vs. 57% in the LCX).

In protocol 2, all 12 animals with partial coronary occlusions responded to dobutamine infusion with changes in heart rate and wall motion patterns. Figure 7 shows one example of such changes induced by dobutamine. Increasing infusion rates resulted in a gradual increase in heart rate from 109 beats/min (bpm) at rest to 156 bpm at the highest dose of dobutamine. With the increasing dose of dobutamine, one can see a gradual increase in the thickness of the color band, reflecting increased endocardial motion in all segments. In parallel, the relative contribution of early colors progressively increased, reflecting augmented endocardial motion during early systole and early diastole. At peak dose of dobutamine, the anteroseptal wall became nearly akinetic, as reflected by a severely narrowed color band in both systolic and diastolic images. Whereas the histograms corresponding to these images quantitatively confirmed the initial increase in endocardial motion followed by a regional hypokinesis in the ischemic segment, they also revealed gradual temporal changes in this particular segment, which occurred before hypokinesis. Interestingly, in this example, diastolic tardokinesis seemed to appear at lower doses of dobutamine than systolic tardokinesis.
As Fig. 8 shows, diastolic tardokinesis preceded systolic tardokinesis or hypokinesis in 5/12 cases, and systolic tardokinesis was first to appear in 4/12 cases. Only 3/12 animals responded with hypokinesis without presenting with preceding tardokinesis. Importantly, 2/12 animals responded with tardokinesis, which did not develop into hypokinesis.

DISCUSSION

Although echocardiography is one of the major noninvasive tools routinely used in the diagnosis of coronary arterial disease, the detection of resting as well as stress-induced wall motion abnormalities is based on subjective visual interpretation (23, 24). The sensitivity of this methodology is severely limited when coronary stenosis is not sufficient to result in visible wall motion abnormalities. Accordingly, a strong need exists for a technique capable of extracting more subtle information on regional wall motion from ultrasound images that may provide additional insight into regional ventricular function and thus improve the sensitivity of echocardiographic diagnosis of ischemia. In addition to subtle changes in magnitude of wall motion, this less-readily visualized information may include altered temporal aspects of systolic as well as diastolic LV function.

One of the recent developments in ultrasound imaging of LV function that has the potential to address this issue is real-time color encoding of endocardial motion, using color kinesis technology. Several groups of researchers have demonstrated the value of this technique for the objective evaluation of regional wall motion (7, 8, 12, 14, 16, 17, 26, 31, 34). We developed computer software for segmental analysis of the color-coded images that quantifies multiple indexes of magnitude and timing of regional LV endocardial motion (19). We found that these indexes provided additional clinically relevant information in different disease...

Fig. 4. RFAC and FF histograms obtained by averaging data from 16 animals that initially responded to coronary occlusions with tardokinesis and then hypokinesis (LAD, top, n = 10; LCX, bottom, n = 6). These changes are highlighted by arrows and resolved during recovery. Segment notations are the same as in Fig. 1. Standard deviations used for statistical analysis were not graphed for clarity of presentation; ↑P < 0.05 compared with control.
states, including coronary arterial disease (12, 16), LV hypertrophy (32), dilated cardiomyopathy (6), and others (33).

However, to determine the relevance of these indexes to the diagnosis of myocardial ischemia with certainty, a clear connection had to be established between the onset and progression of ischemia and variations in magnitude and timing of wall motion extracted from color-encoded images. Specifically, we were interested in testing the hypothesis that during acute ischemia, temporal changes occur earlier than changes in the magnitude of wall motion. This goal was achieved in an animal model of induced myocardial ischemia to avoid the multiple confounding factors inevitable in human studies. We induced variable degrees of ischemia in different areas of ventricular myocardium by creating coronary flow restrictions in two major coronary arteries in pigs.

The effects of these interventions on noninvasively obtained parameters of regional LV function were studied under resting conditions and during pharmacological stress. We found that acute ischemia resulted...
in reproducible, gradual, and reversible changes in multiple indexes of regional ventricular wall motion, which were easily detected and quantified by use of noninvasive color-encoded imaging with simple computer analysis. In particular, temporal changes most often occurred before visually detectable resting as well as stress-induced wall motion abnormalities. Despite the currently accepted tenet that, in the ischemic cascade, diastolic changes precede contractile dysfunction (27), in our study, the frequency of ischemia-induced temporal changes was nearly equal for systole and diastole. These findings reinforce the basis for the diagnostic use of temporal measures of LV wall motion for the early detection of ischemia.

**Imaging technique.** Color encoding of endocardial motion is a recent development that provides information...
tion on the timing of endocardial motion, which can be quantified using offline analysis. High frame rate color encoding was essential to allow accurate assessment of temporal changes in LV performance at heart rates typically observed in pigs, particularly with dobutamine. Our study demonstrated that with this modification, this technique offers online access to new markers of ischemia.

Because one of our goals was to determine whether descriptors of regional wall motion follow a certain pattern of changes during ischemia, systolic and diastolic images were acquired alternately during each balloon inflation. This strategy was necessary to answer the question of whether systole or diastole is affected by ischemia first. Setting the duration of systolic color encoding beyond that of LV ejection period was essential for demonstrating systolic tardokinesis, because previous studies suggested that ischemic segments may continue their contraction while areas of normally perfused myocardium enter the relaxation phase (21). The adjustments in the timing of diastolic color coding were particularly relevant during graded dobutamine infusion because of the changes in heart rate.

Interpretation of results. Protocol 1 was designed to study the effects of acute ischemia on quantitative indexes of magnitude and timing of regional LV wall motion. More specifically, we focused on early changes that could eventually be used for the detection of myocardial ischemia caused by coronary flow obstructions that do not manifest in wall motion abnormalities. Because we expected the effects of partial coronary occlusions to be subtle and difficult to detect, complete occlusions were also performed to better define and characterize ischemia-induced temporal changes.

We studied several systolic and diastolic indexes on the assumption that they may be affected to a different extent at different stages of the ischemic cascade. Several previous publications have presented strong evidence that diastolic performance is affected before systolic dysfunction. These included an experimental study in which sonomicrometers were used to assess regional LV function in a canine model of chronic myocardial ischemia (27) as well as several clinical studies in which the effects of transient ischemia were assessed by Doppler echocardiography during balloon angioplasty (15) and by radionuclide ventriculography during pacing-induced ischemia (1). However, others have found that ischemia caused simultaneous changes in both systolic and diastolic function in open-chest pigs during coronary occlusions, as assessed by tissue Doppler imaging and validated by ultrasonic crystals (5). Furthermore, Ihara et al. (10), who used similar techniques, reported that that this sequence of events was reversed during coronary occlusion in conscious dogs.

Despite this controversy, it is obvious that ischemia affects both systolic and diastolic function. Different studies, however, defined dysfunction according to their specific techniques, which may have caused apparently disparate and conflicting results as to the sequence of events in the ischemic cascade. Within the context of our technique, we defined the different phases of ischemia-induced systolic and diastolic dysfunction based on specific changes observed in regional ejection and filling patterns. Using these definitions, we found that patterns of response to coronary flow restriction varied widely between animals. In particular, diastolic dysfunction did not precede systolic changes in every ischemic episode. Instead, these manifestations of acute ischemia appeared in either order with nearly equal frequency (Fig. 6).

However, we found that temporal abnormalities in either systolic or diastolic regional LV function preceded the changes in magnitude of wall motion in most cases. Indeed, these temporal changes were extremely difficult to visualize in the dynamic two-dimensional gray-scale images and were subtle in the color-coded images (see Figs. 1 and 2, rows 1 and 3). However, the analysis of color-coded images revealed ischemia-induced differences that could be both readily visualized and quantified (see Figs. 1 and 2, rows 2 and 4). Intracoronary contrast injections corroborated that the location of the changes in the timing and/or magnitude of wall motion coincided with the perfusion defects created by coronary occlusions (Fig. 3).

One could expect some of the early ischemic temporal changes to go undetected in complete occlusions because of our relatively low data acquisition rate (every 10–20 s). Nevertheless, regardless of the extent of occlusion, the ratio of tardokinesis to hypokinesis as a first or only ischemic response was similar within each coronary perfusion territory (Fig. 6). Interestingly, clear differences existed between perfusion territories, such that temporal changes were more frequent in LAD than in LCX occlusions (Fig. 6). This could
be explained by differences in the size of both territories, their positions relative to the imaging transducer, and the segmentation scheme used (Fig. 3). In other words, the effects of ischemia may be diluted in the distal, relatively small LCX territory that spreads over both inferior and posterior segments (Fig. 5).

The physiological mechanisms underlying the changes in temporal sequence of systolic contraction as well as LV filling due to ischemia have long been the subject of extensive research (1, 5, 10, 11, 13, 15, 22, 27, 28). Ischemia is known to cause local decrease in efficiency of both contraction and active relaxation, which in the myocardium manifests as either delayed regional systolic or diastolic endocardial motion (i.e., tardokinesis) or a decrease in contractile properties, resulting in hypokinesis. This delayed motion in the ischemic segments is represented by the “wedge” of late colors in the stacked histograms (Fig. 4) and quantified by the significant changes in ejection and filling parameters (Figs. 4 and 5).

One might expect tardokinesis to continue into the hypokinetic phase, in other words, the delay in endocardial motion to continue while the magnitude of motion decreases. Data obtained in this protocol did not, however, consistently confirm this hypothesis (Fig. 4). On the other hand, we previously noticed that in patients with resting wall motion abnormalities, the residual wall motion occurred early in systole, which we attributed to passive tethering rather than active contraction (16). It is thus not unreasonable that in the transition between these two phases, the timing of wall motion may appear normal while hypokinesis is apparent.

Despite the variability in patterns of ischemic response we have observed, the results of this protocol suggest that regional temporal wall motion abnormalities could be used in the clinical setting as early markers of ischemia. However, the accuracy of these possible markers in humans remains to be determined in future clinical studies.

Protocol 2 was designed to study the changes in wall motion induced by a combination of subcritical coronary occlusions and dobutamine stress. This model is relevant because it mimics the clinical circumstances of echocardiographic stress testing, since most patients who show ischemic response to stress have subcritical coronary stenosis and no detectable changes in their wall motion patterns at rest. As we previously showed in human subjects (12), color kinesis images enhance the visual impact of stress-induced changes in wall motion, and the segmental analysis provides quantitative information on these changes (Fig. 7).

The subcritical flow restrictions with dobutamine stress resulted in similar alterations in either timing or magnitude of wall motion or both in the ischemic segments in all animals studied. The high prevalence of temporal changes as the first or only marker of ischemia suggests that they may have significant diagnostic utility. In the clinical setting, the ability to detect these changes online at lower doses of dobutamine could possibly result in alternative protocols of pharmacological stress testing. Importantly, the ability to detect early ischemic changes noninvasively has the potential to improve the diagnostic sensitivity of dobutamine stress testing.

Limitations. The species selected for this study was swine because of the close similarities between human and porcine coronary physiology (29, 30). Although one of the known limitations of swine catheterization studies is the propensity for development of ventricular arrhythmias that frequently cause mortality (25), the prophylactic use of antiarrhythmic agents in our experiments significantly reduced the incidence of persistent ventricular arrhythmias.

Theoretically, in an open-chest animal model, we could expect better control of the degree of coronary occlusion and better quality of images, when obtained directly from the epicardial surface. However, our pilot studies showed that with the pattern of cardiac translation in an open-chest pig, high-quality epicardial images were difficult to obtain. In fact, right parasternal transthoracic images were of superior quality, and cardiac translation was less of a problem in a closed-chest preparation. In a closed-chest animal, coronary balloon occlusions could be easily achieved by varying balloon inflation pressure, which allowed us to study repeated occlusion and reperfusion sequences. The ability to quickly release the occlusion in response to severe ventricular arrhythmias contributed to the high survival rates throughout the entire experiment.

The use of repeated occlusions in the same animal might have affected our results by causing cumulative irreversible damage induced by ischemia and reperfusion (18, 4). To minimize these effects, the animals used in protocol 2 were limited to those that showed normal wall motion after recovery from previous ischemic insults. Despite the possibility of undetected myocardial damage, the effects of pharmacological stress on the temporal indexes of wall motion were consistently observed in each animal. In addition, repeated occlusions in the same animal might have biased our results via possible effects of ischemic preconditioning (20). To circumvent this limitation, we analyzed a subset of data obtained in each animal during the first partial occlusion only. The responses to these occlusions varied, and the small number of occlusions did not allow us to make definitive conclusions. However, in-depth study of preconditioning and reperfusion damage was not the focus of this study, and optimizing the protocol for this goal would have interfered with our objectives.

To accurately determine the sequence of events triggered by coronary occlusions, the ideal technique would be to color encode endocardial motion throughout the entire cardiac cycle. However, because of software constraints, systolic and diastolic images were obtained consecutively rather than simultaneously. Nevertheless, by alternating systolic and diastolic image acquisition, we observed measurable differences in the temporal indexes of both systolic and diastolic performance, which in most cases clearly preceded hypokinesis.
Also, it would be useful to verify our findings by using another independent, established technique. Theoretically, M-mode echocardiography could be used for this purpose, since it has the important advantage of high temporal resolution, necessary for accurate evaluation of timing of events. However, the ischemia-induced changes we observed developed very quickly, sometimes too quickly to be detected within the limitations of the current technology. To verify these findings, we would need to perform simultaneous M-mode imaging, which would be technically impossible.

Another qualifying aspect of our study was the variable degree of coronary occlusions, which was not quantitatively assessed by direct invasive measurements of coronary flow. Instead, flow restriction was calibrated according to balloon pressure by visual assessment of distal flow. The variable degree of partial occlusions in protocol 1 may partially account for the variability in individual responses. Whereas in protocol 2 the occlusions had to be significant enough to induce ischemia at rest, the occlusions in protocol 2 needed to have no effect at rest yet cause ischemic changes under stress. Although qualitative, the visual calibration of coronary flow restrictions against balloon pressure allowed us to observe consistent patterns of response to acute ischemia in both protocols.

We have previously detailed the limitations of color kinesis and those of segmental analysis, which was developed to quantify endocardial motion from color-encoded images (6, 16, 19, 32). The main limitation of this technique is most likely the ability of acoustic quantification technology to accurately track the endocardial motion throughout the cardiac cycle, which is directly related to image quality. An additional limitation of this technique is the potential cardiac translation. In our experiments, it was minimized by using a closed-chest preparation.

In summary, this experimental study was designed to study ischemia-induced variations in temporal indexes of regional LV systolic and diastolic endocardial motion derived from color-encoded echocardiographic images. This goal was achieved by acquiring and analyzing data in a group of pigs undergoing coronary occlusions of variable degree at rest and with pharmacological stress. The results of these studies demonstrated that in both settings, ischemia results in non-invasively detectible and quantifiable changes in several temporal indexes of wall motion, which in most ischemic episodes were the first markers of ischemia. Although ischemia-induced temporal changes in regional wall motion have been described in the past, this information has not become part of the routine clinical practice because of the invasive nature of the techniques formerly required for their detection. As our study shows, today’s echocardiographic techniques provide the basis for noninvasive objective assessment of the temporal aspects of regional wall motion abnormalities. This ability to extract clinically relevant information from ultrasound images leading to objective detection of early ischemia promises to improve the sensitivity of echocardiographic diagnosis of coronary artery disease.

We are thankful to David Prater, Joel Friedman, and Tony Valve of Agilent Technologies for enthusiastic help and support. V. Mor-Avi is a recipient of the Clinical Investigator Award and a grant-in-aid from the American Heart Association.

REFERENCES


15. Labovitz AJ, Lewen MK, Kern M, Vandormael M, Deligonal U, and Kennedy HL. Evaluation of left ventricular systolic...


