Radionuclide Assessment of Nitroglycerin Influence on Abnormal Left Ventricular Segmental Contraction in Patients with Coronary Heart Disease

ANTONE F. SALEL, M.D., DANIEL S. BERMAN, M.D., GERALD L. DeNARDO, M.D., AND DEAN T. MASON, M.D.

SUMMARY Noninvasive gated cardiac blood pool imaging with technetium-99m autologous erythrocytes was employed to differentiate reversible versus irreversible abnormal ventricular segmental contraction by regional wall and pump responses to sublingual nitroglycerin in 25 patients with chronic coronary heart disease. In 12 patients without ECG infarctions compared to 13 with infarctions, radionuclide images demonstrated significantly greater percent decreases in end-systolic volumes (33.8 ± 6.7 SEM vs 18.7 ± 4.4; P < 0.05) without differences in percent reductions in end-diastolic volumes (13.7 ± 3.9 vs 11.6 ± 6.1; NS) and thereby significantly greater percent increases in ejection fractions (9.3 ± 1.6 vs 4.1 ± 2.0; P < 0.05). In the 22 patients with regional dyssynergy, improvement in disordered pattern and extent of localized dyssynergy following antanginal action of nitroglycerin was related to ECG absence of prior infarction. These observations demonstrate the clinical accuracy of atraumatic scintigraphy in the detection of reversible localized dyssynergy due to myocardial ischemia in coronary heart disease.

SINCE CHRONIC ATHEROSCLEROSIS affecting segmental branches of the coronary arterial system results in regional disorders of ventricular contraction,1,2 considerable investigation has been directed toward the differentiation of localized abnormalities of wall motion due to myocardial ischemia versus necrosis.3,4 However, the methods which have been developed for the identification of ventricular ischemia by demonstration of reversible left ventricular dyssynergy require cardiac catheterization with radiopaque angiography and thereby are limited in clinical application. Therefore, an important need remains for the noninvasive detection and assessment of abnormal ventricular segmental contraction caused by myocardial ischemia, as opposed to infarction, in the management and prognostic evaluation of patients with chronic coronary heart disease.

This study evaluates the ability of technetium-99m autologous red blood cell scintillation camera ventriculography with nitroglycerin to differentiate areas of ventricular dyssynergy due to myocardial ischemia from those consequent to necrosis in a large group of patients with chronic coronary heart disease proven by cardiac catheterization. This technique allows us to measure ventricular volumes at the same time that we are analyzing chamber wall motion.5,6

Methods and Materials

Twenty-five patients, 20 males and five females, ranging in age from 35 to 50 years, with chronic coronary artery disease demonstrated by cardiac catheterization and selective coronary arteriography, were selected for study. Significant coronary artery disease was defined as 75% or greater stenosis of one or more of the three major coronary vessels. Dyssynergy on radiopaque left ventriculography was defined as a localized abnormality of left ventricular contraction.

References

which was observed in 22/25 patients. Dyssynergy is used in this report as a general term signifying a localized disorder of wall motion: hypokinesis (diminished regional systolic shortening in which there was less inward excursion of the disturbed segment, < 20% decrease of end-diastolic minor diameter, than the remaining unaffected areas);3' 5, 12, 13 akinesis (absent systolic movement of the minor axis of a segment of the wall); and dyskinesis (paradoxic outward systolic expansion in which a portion of the end-systolic silhouette extended outside the end-diastolic perimeter). Thirteen patients had electrocardiographic evidence of old myocardial infarction manifested by pathologic Q waves corresponding in location to the site of dyssynergy observed on both the radionuclidic and contrast radiopaque left ventriculograms, while the remaining twelve had occasional anginal episodes but were without electrocardiographic documentation of infarction. All patients were in normal sinus rhythm.

For the radionuclidic portion of the study, all patients were in the basal, postabsorptive state and had not received nitroglycerin for at least twelve hours prior to the study. In addition, none of the patients were taking beta adrenergic blocking agents or antihypertensive agents; ten were chronically receiving digoxin and diuretics. The patients were placed supine in the 30° right anterior oblique (RAO) position beneath the scintillation camera detector (Searle Radiographics Pho/Gamma HP) equipped with a 16,000 hole high-resolution, low energy collimator as described in detail previously (fig. 1).11 The heart was located in the field of view of the detector by transmission scanning while observing the position of the cardiac image on a persistence oscilloscope. The phonocardiographic microphone was placed at the second left parasternal intercostal space. The end-systolic gating interval (panel A, fig. 1) was determined prior to imaging and consisted of the 60 msec interval immediately preceding the first high frequency component of the second heart sound signifying aortic valve closure and thereby termination of left ventricular ejection. The phonocardiographic gating marker was programmed to synchronize activation of the scintillation camera oscilloscope for this 60 msec period prior to aortic closure.

For the end-diastolic left ventricular image (panel B, fig. 1), a 60 msec unblanking interval occurring immediately before mitral valve closure was chosen. This 60 msec end-diastolic period was programmed to begin at the peak of the inscription of the electrocardiographic R wave. Thus, the selected end-diastolic imaging interval always occurred immediately after QRS onset and was independent of the R-R interval.

Fifteen to twenty mCi of 99mTc autologous red blood cells contained in a volume of less than 1.5 cc was injected as a bolus through a small plastic catheter previously placed in an antecubital vein. During the minute after injection the scintigraphic data were collected in un gated form on videotape for subsequent validation of the location of the aortic and mitral annuli. For analysis of the ventricular volume scintigrams, the gating intervals were set for end systole and end diastole as delineated above, and 500,000 count images were obtained on Polaroid film from the summation of 500 to 1,000 cardiac cycles which required approximately ten minutes. Linear calibration was accomplished by placing a ruler with parallel strips of lead 1 cm wide and spaced 1 cm apart on the collimator face and obtaining a 500,000 count image by placing a sheet source containing 99mTcO4 behind the lead grid.

Ventricular volumes were obtained by tracing the endocardial silhouette of the left ventricle on Polaroid film during end systole and end diastole. All tracings of left ventricular perimeters were confirmed by at least two independent investigators. In addition, calibration of the cardiac chambers was accomplished by utilization of the lead ruler images. Further, a mid-field oscilloscopic marker allowed precise superimposition of end-diastolic and end-systolic radionuclidic images for comparative analysis of both volumes and regional dyssynergy responses to nitroglycerin. The areas (A) of the traced ventricular volumes were measured by planimetry. The long axis (L) of the inner surface of the left ventricle was measured from the mid-aortic valve plane to the apex. End-systolic (ESV) and end-diastolic (EDV) left ventricular volumes were calculated utilizing the area length formula, \( V = 0.849A^2/L \), based on the standard equation of Sandler and Dodge.14 The scintig raphic ejection fraction was calculated by dividing stroke volume (end-diastolic volume minus end-systolic volume) by the end-diastolic volume.

In addition, the superimposed RAO images of end systole and end diastole were assessed for regional abnormalities of the contraction pattern.5 10 This evaluation included determination of the sites and nature of segmental wall disorders5 as well as quantification of the localized types of dyssynergy before and in response to nitroglycerin. The nature of dyssynergy was designated as hypokinesis, akinesis or dyskinesis as defined above.5 Quantitative analysis of regional wall abnormalities was achieved by measuring the extent of segmental ventricular motion from the superimposed radionuclidic tracings of end diastole and end systole in the following manner: the degree of left ventricular segmental shortening was determined as the percent of systolic shortening along each of four reference axes, the major length axis measured from the midpoint of the aortic valve plane to the left ventricular apex and three minor axes equidistant along and perpendicular to the major axis.16

During the control period, heart rate, blood pressure and the gated radionuclidic angiograms were obtained with the patients in the supine right anterior oblique position. A fresh 0.4 mg nitroglycerin (NTG) tablet was then ad-
ministered sublingually. Following a five minute interval, at the end of which heart rate increased and/or systolic blood pressure fell by at least 10% of control values, the gated images of end-diastolic and end-systolic ventricular volumes were redetermined. The absolute changes in radionuclide end-systolic and end-diastolic volumes before and following NTG were normalized in each patient by the pre-NTG ESV and EDV, respectively.

All patients had recently undergone complete diagnostic left heart catheterization. Radiopaque left ventricular bi-plane cineangiography was performed in the 30° RAO and 60° left anterior oblique projections on 35 mm film taken at 64 frames/sec using the Philips nine-inch cesium iodide image intensifier system. The ventricle was opacified with 50 cc of Hypaque-M 75% (Winthrop) containing sodium and meglumine diatrizoates injected at 250 pounds per square inch through an angiography catheter. Tracings of left ventricular end-diastolic and end-systolic endocardial sillhouettes were obtained in the RAO position for the qualitative and quantitative evaluation of localized regions of dys-synergy and for the determination of ventricular volumes by the area-length method. The first cardiac cycle in which the left ventricular cavity was completely opacified and which followed any premature contractions by at least two beats was used for analysis of the end-systolic and end-diastolic images.

Results

Pump Response to Nitroglycerin

The results of radionuclidic gated angio-cardiographic left ventricular volumes and ejection fractions are given in figures 2 and 3, respectively. The changes in end-diastolic volumes (fig. 2A) and end-systolic volumes (fig. 2B), and in ejection fractions (fig. 3) were determined from the differences between the control and 5 minute post-NTG radionuclidic images. In this investigation, each patient served as his own control. To allow accurate comparison between patients with ventricular volumes of varying size, all ventricular volume measurements were normalized to pre-NTG values with results expressed in terms of percent change from control.

Alterations in scintigraphic ventricular volumes induced by NTG were compared between the patients with (+MI) and without (-MI) electrocardiographic evidence of previous myocardial infarction. Although the EDV was significantly reduced by NTG (P < 0.01) in both groups, the percent decrease in end-diastolic volume in the post-MI patients, 11.6 ± 6.1 (SEM), was not statistically different from that in the non-MI patients (13.7 ± 3.9) (fig. 2A). On the other hand, a considerably different response was observed between the post-MI and non-MI patients in end-systolic volume after NTG (fig. 2B). Thus, while ESV was significantly lowered (P < 0.01) in both groups, in the group with previous myocardial infarction, the percent decrease in ESV of 18.7 ± 4.4 was significantly less (P < 0.05) than that of 33.8 ± 6.7 in the patients without infarction.

Ejection fraction following nitroglycerin increased substantially (P < 0.01) in both groups, but there was a significantly greater percent increase (P < 0.05) in the patients without previous infarction compared to those with prior infarctions: 9.3 ± 1.6 and 4.1 ± 2.0, respectively (fig. 3). There was no change in total peripheral vascular...
Regional Dyssynergy Response to Nitroglycerin

As with the assessment of ventricular volumes, the response of the pattern and extent of regional dyssynergy was examined by comparing the changes in the control and five minute post-NTG radioisotopic images (table 1). Of 22 dyssynergic regions, 13 (59%) improved after nitroglycerin. Five of the ten areas of hypokinesis showed increased systolic excursion with NTG, three demonstrated incomplete resolution of dyssynergy while two became normal. Only one of four patients with hypokinesis and ECG infarction revealed improved wall motion with NTG (fig. 4). In contrast, four of six patients with hypokinesis without ECG infarction showed improved extent of systolic motion with the nitrate. Furthermore, both patients who regained normal extent of contraction with NTG were without ECG evidence of prior necrosis (fig. 5).

Seven of the ten areas of localized akinesis showed partial improvement of wall motion abnormality during systole with NTG while the other three demonstrated no improvement following the agent (table 1). Five of the eight patients with regional akinesis and previous infarction by ECG...
TABLE 1. Response of Regional Dyssnergy to Nitroglycerin

<table>
<thead>
<tr>
<th>Location (N)</th>
<th>Pattern (N)</th>
<th>Extent (% abn. hemiasis shortening)</th>
<th>Pattern (N)</th>
<th>Extent (% abn. hemiasis shortening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With myocardial infarction (N = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ant. 9</td>
<td>Hypokinesis 4</td>
<td>6.8 ± 2.2</td>
<td>Hypokinesis 4</td>
<td>7.0 ± 2.3</td>
</tr>
<tr>
<td>Inf. 1</td>
<td>Akinesis 8</td>
<td>0.2 ± 0.1</td>
<td>Hypokinesis 5</td>
<td>4.9 ± 2.1*</td>
</tr>
<tr>
<td>Al. 3</td>
<td>Dyskinesis 1</td>
<td>-6.2</td>
<td>Akinesis 3</td>
<td>0.1</td>
</tr>
<tr>
<td>Without myocardial infarction (N = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ant. 5</td>
<td>Hypokinesis 6</td>
<td>7.2 ± 3.0</td>
<td>Normal 2</td>
<td>18.1 ± 3.7**</td>
</tr>
<tr>
<td>Inf. 1</td>
<td>Akinesis 2</td>
<td>0.2 ± 0.1</td>
<td>Hypokinesis 4</td>
<td>9.4 ± 1.4**</td>
</tr>
<tr>
<td>Al. 3</td>
<td>Dyskinesis 1</td>
<td>-5.6</td>
<td>Hypokinesis 1</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Abbreviations: N = number of patients; ant = anterior dyssnergy; inf = inferior dyssnergy; Al = anterior-inferior dyssnergy; % abn. hemiasis = percent abnormal hemiasis shortening; average values ± SEM are given. *P < 0.05, **P < 0.01, control compared to nitroglycerin extent shortening.

developed hypokinesis with NTG and the remaining three showed no response. On the other hand, both of the patients with akinesis but without prior ECG infarction developed at least some inward wall excursion during contraction and thereby akinesis was converted to hypokinesis by the nitrate.

Two patients exhibited localized ventricular dyskinesis before pharmacologic intervention (table 1). In the patient with previous infarction by ECG, the site of dyskinesis no longer demonstrated paradoxical outward motion during systole after NTG; thus the area of dykinesis became akinetic during contraction. In contrast, in the patient without prior ECG infarction substantial improvement in inward wall motion was induced by NTG so that the dyskinetic area became hypokinetic (table 1).

Comparison of Control Radionuclidic and Radiopaque Ventriculography

Contrast left ventriculography at the time of diagnostic cardiac catheterization was carried out 2–5 days prior to noninvasive radioisotopic angiography. There was a close correlation between the control radionuclidic and radiopaque ventricular volumes and ejection fractions (r = 0.93). In addition, the pre-NTG location, pattern and extent of regional wall motion abnormalities by radioisotopic and

Figure 5. Right anterior oblique views of left ventricular radiopaque images (A and E) and radionuclidic images (B,C,D,F,G,H) of EDV (left column), ESV (middle column) and traced endocardial perimeters (right column) before NTG (A and E, B and F), after NTG (C and G), and following aortocoronary bypass graft (D and H) in a coronary patient with angina pectoris without electrocardiographic myocardial infarction.
radiopaque angiography, assessed independently, were observed to be the same in the RAO views.

Discussion

The principal finding in this investigation was that noninvasive gated cardiac blood pool radionuclidic angiography combined with pharmacologic intervention is useful in evaluating the viability of abnormally contracting ventricular segments in clinical coronary disease. Thus, the responses of such regions of disordered wall motion and alterations in cardiac pump performance to sublingual nitroglycerin afford an atraumatic means for the differentiation of ischemic versus infarcted areas of dyssynergy. The present technique of gated blood pool scintigraphy also allows assessment of regional dyssynergy (figs. 4–6) as well as determination of ventricular volumes (figs. 2 and 3), whereas many of the previously described scintigraphic methods fail to provide information regarding patterns of segmental contraction.

While it is recognized that radiopaque ventriculography provides higher resolution of chamber perimeter than the scintigraphic approach, the radionuclidic method possesses the advantage of requiring only a single intravenous injection of a gamma emitting isotope which neither disturbs cardiocirculatory variables nor provokes cardiac arrhythmias. Indeed, the present report shows systematically for the first time that this radioisotopic technique is capable of providing accurate information concerning alterations in ventricular volumes, pump performance, and regional contraction patterns in the study of clinical pharmacology and therapeutics (figs. 2–6). Previous reports which have examined the responsiveness of ventricular segmental abnormalities to nitroglycerin were carried out by cardiac catheterization with radiopaque angiographic dye, the contrast material itself causing transient cardiocirculatory changes.

Echocardiography is another noninvasive method for estimating the effects of pharmacologic interventions on cardiac performance. While other workers have shown that sublingual nitroglycerin decreases left ventricular dimensions by echogram, the ultrasound methods are restricted to the examination of only limited sectors of the minor dimension of the heart. In addition, echocardiography is even less suited for the analysis of regional areas of dyssynergy since the technique allows study of only the septal and posterior walls of the left ventricle. A further disadvantage of ultrasound in the evaluation of dyssynergy is that the major areas of abnormal wall motion causing the greatest depression of cardiac pump performance usually occur in the anterior myocardial segments of the left ventricle. In contrast to echocardiography, the gated radionuclide blood pool angiocardiographic technique provides accurate quantitative information about the characteristics of anterior wall segmental motion (figs. 4–6).

This study demonstrates that abnormally contracting ischemic segments of the left ventricle are detectable by nitratre-improvement of dyssynergy utilizing noninvasive radioisotopic angiography (table 1). Further, the present investigation shows the usefulness of radionuclidic angiography in safely providing important information which may

**Figure 6.** Right anterior oblique views of left ventricular radiopaque images (A and D) and radionuclidic images (B,C,E,F) of EDV (left), ESV (middle) and traced perimeters (right) before (A and D, B and E) and after NTG (C and F) in a coronary patient with extensive acute anterior myocardial infarction with cardiogenic shock.
aid in the application of medical or surgical therapy in chronic coronary heart disease, particularly in high risk patients with severely depressed pump performance (figs. 4 and 6). Thus, in the coronary patient with chronic refractory congestive heart failure illustrated in figure 4, radioisotopic angiography established the presence of generalized hypokinesis which was not substantially improved by nitroglycerin. In this patient with diffuse coronary atherosclerosis demonstrated by previous arteriography, the possibility of ventricular segmental resection was excluded because of generalized dyssynergy.

In contrast, in the patient illustrated in figure 5, NTG produced considerable improvement in anterior-apical hypokinesis and a normal contractile pattern followed the agent (fig. 5; panels C and G). On the basis of this favorable response, it was predicted that coronary bypass graft surgery would be beneficial. The success of this revascularization procedure was documented postoperatively by the normal radioisotope angiographic contraction pattern (fig. 5, D and H). This example is consistent with the results of other workers who have shown by invasive methods the value of demonstrating reversible areas of dyssynergy which signify myocardial ischemia rather than necrosis in coronary disease, thereby allowing prediction of successful application of aortocoronary bypass surgery.

Helfant et al. postulated that improvement in ventricular function and segmental dyssynergy by nitroglycerin signifies viable regional ischemia; our observations in patients with and without previous ECG evidence of transmural infarction are consonant with that theory. Thus, in patients without infarction, NTG produced significantly greater reductions (P < 0.05) in end-systolic volume than in the patients with previous infarction (fig. 2), thereby resulting in substantial increases in ejection fraction in the former group compared to the latter (fig. 3). These findings are consistent with the effects of NTG on segmental dyssynergy in the infarction versus noninfarction patients (table 1). Thus, improvement in the pattern and extent of abnormal regional ventricular contraction following the antianginal action of nitroglycerin correlated with the electrocardiographic absence of prior myocardial infarction. Improvement in localized dyssynergy was related to the absence of prior infarction, and not to the specific nature or location of dyssynergy per se. Further, the location, types and degree of regional dyssynergy were equally distributed among the patients with and without old infarctions. It should be noted, however, that certain individuals with previous infarctions improved and, therefore, at least a component of reversible ischemia was often associated with prior infarction.

The enhancement of pump function following NTG in our patients without infarction but with frequent episodes of angina pectoris appeared to be the result of a reduction in ischemia-induced abnormal segmental motion with consequent improvement of both regional dyssynergy and ventricular performance. It should be pointed out that the differences in pump function observed in the infarction versus the noninfarction patients were not produced by disparate actions of NTG on the peripheral circulation. Thus, total peripheral vascular resistance was not affected by the agent in either group, while systemic venodilation occurred equally in both groups of patients as manifested by the similar reductions in left ventricular end-diastolic volumes following nitrate administration (fig. 2). Therefore, with regard to overall pump output in patients with active angina without necrosis, nitroglycerin-induced improvement of ischemic depression of contractility is capable of overcoming the predominant peripheral circulatory effects of NTG of reducing cardiac preload more than lowering ventricular afterload.

In addition, the gated blood pool scintigraphic method can be extended to the clinical evaluation of unstable cardiac patients. Such an example of the value of radioisotopic angiograms in emergency clinical care is shown by the additional patient with anterior wall myocardial infarction complicated by cardiogenic shock and recurrent, intractable ventricular tachyarrhythmias (fig. 6). Because the abnormal apical contraction pattern improved while the ejection fraction was considerably enhanced with NTG, it was concluded that substantial ischemic viable myocardium remained. Since ventricular function was shown to be improved by NTG, it was reasoned that this patient refractory to medical therapy was a potentially suitable candidate for surgical revascularization.

Thus, proper management of the critically ill coronary patient was accomplished because the reversible element of myocardial ischemia was initially identified quantitatively by atraumatic scintigraphy. From the above observations, it is concluded that the technique of gated blood pool radioisotopic angiography combined with pharmacologic intervention provides not only a noninvasive means for the clinical evaluation of ventricular function and detection of reversible ischemic areas of abnormal segmental motion in the treatment of chronic coronary heart disease, but also allows the safe and accurate assessment of myocardial performance in patients with unstable clinical situations.

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References

Effects of Procainamide on the Dispersion of Recovery of Excitability during Coronary Occlusion

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SUMMARY In 14 mongrel dogs, refractory periods were determined in nonischemic and acutely ischemic zones of myocardium during control conditions, 15 minutes after coronary ligation, and 10 and 20 minutes after a procainamide infusion. Following coronary ligation, refractory periods in the nonischemic area remained unchanged (100.8% of control) while in the ischemic area they decreased to 88.6% of control (<0.02) causing a dispersion of refractoriness of 12.2%. After the administration of procainamide, refractory periods lengthened in the nonischemic as well as in the ischemic areas, but the changes were such that the temporal dispersion caused by the coronary ligation was reduced from 12.2% to 5.5% (P < 0.01) after 10 minutes, and to 5.0% (P < 0.02) after 20 minutes of drug infusion. It is concluded that procainamide exerts different overall effects on the nonischemic and acutely ischemic canine myocardium. It is postulated that this action may play a role in the suppression of re-entrant arrhythmias.

Methods

Fourteen mongrel dogs weighing 17 to 26 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, intubated and mechanically respirated with a Harvard respirator. The left femoral vein was catherized for administration of drugs and to obtain blood samples for determination of procainamide levels, and the aortic pressure monitored via a catheter introduced in the left femoral artery, using a Statham P23Db transducer. After induction of complete heart block by injecting 0.2 ml of formaldehyde in the septum in the area of the bundle of His, heart rate was kept constant at a basic cycle length (S1-S1) of 500 msec by right ventricular pacing using a S-88 Grass stimulator. Four pairs of fine stainless-steel, Teflon-coated plunge electrodes (0.003 inch diameter) were inserted into the left ventricular myocardium, two pairs in an area subserved by the left anterior descending coronary artery that subsequently was made ischemic and the other two pairs in an area with intact coronary blood flow. Premature stimuli (S2) were introduced in each left ventricular zone through a pair of stimulating electrodes and a pair of sensing electrodes was placed at a distance of 5–8 mm.

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