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Research Article

Radionuclide and contrast ventriculography were evaluated for their ability to estimate myocardial ischemia. In 14 closed-chest, sedated dogs, a small and larger region of ischemia were produced by inflating balloon occluders on the left anterior descending coronary artery. The systemic arterial pressure, atrial-paced heart rate, global ejection fraction by radionuclide and contrast ventriculography, regional wall-motion abnormalities (as the percentage of abnormally contracting segments), and regional myocardial blood flow (using the microsphere technique) were measured during an initial control period, two separate ischemic periods, and a final control period. The regional ischemic weights based on myocardial blood flow ranged from 0 to 38.5 g and were grouped as zero, small (range 0 to less than 10 g, mean 3.40 g), and large regions of ischemia (greater than 10 g, mean 24.8 g). Regional wall-motion abnormalities were sensitive qualitative indicators of ischemia. Receiver operating characteristic analysis showed that both ventriculographic methods were highly sensitive, specific, and accurate for detecting regional ischemia. Contrast ventriculography was slightly superior for detecting small regions less than 4 g, but the methods were equal for regions greater than 4 g. The arterial pressure and heart rate were unchanged during ischemia. For small regions of ischemia, the global ejection fraction did not fall using either the contrast or radionuclide technique, but it fell significantly when large regions were […]

Comparison of Radionuclide and Contrast Ventriculography for Detection and Quantitation of Regions of Myocardial Ischemia in Dogs

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ABSTRACT Radionuclide and contrast ventriculography were evaluated for their ability to estimate myocardial ischemia. In 14 closed-chest, sedated dogs, a small and larger region of ischemia were produced by inflating balloon occluders on the left anterior descending coronary artery. The systemic arterial pressure, atrial-paced heart rate, global ejection fraction by radionuclide and contrast ventriculography, regional wall-motion abnormalities (as the percentage of abnormally contracting segments), and regional myocardial blood flow (using the microsphere technique) were measured during an initial control period, two separate ischemic periods, and a final control period. The regional ischemic weights based on myocardial blood flow ranged from 0 to 38.5 g and were grouped as zero, small (range 0 to <10 g, mean 3.40 g), and large regions of ischemia (>10 g, mean 24.8 g). Regional wall-motion abnormalities were sensitive qualitative indicators of ischemia. Receiver operating characteristic analysis showed that both ventriculographic methods were highly sensitive, specific, and accurate for detecting regional ischemia. Contrast ventriculography was slightly superior for detecting small regions <4 g, but the methods were equal for regions >4 g.

The arterial pressure and heart rate were unchanged during ischemia. For small regions of ischemia, the global ejection fraction did not fall using either the contrast or radionuclide technique, but it fell significantly when large regions were produced. There was a quantitative relationship between the percentage of abnormally contracting segments and the grams of myocardial ischemia (for radionuclide ventriculography, $r = 0.65$, $P = 0.003$, and for contrast ventriculography, $r = 0.75$, $P < 0.001$), but for many small regions of ischemia, wall-motion changes were greater than anticipated, suggesting hypofunction of the continguous normal tissue.

This study demonstrated that both radionuclide and contrast ventriculography were quite sensitive and specific for detecting measured amounts of regional ischemia. The functional changes resulting from ischemia are quantitatively related to the extent of regional ischemia, small areas resulting in regional wall motion abnormalities, and large areas producing both reduced global ejection fraction and wall motion changes.

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INTRODUCTION

Both contrast and radionuclide ventriculography have been used to detect left ventricular dysfunction due to coronary atherosclerosis (1–23); however, the ability of either method to detect and quantitate known degrees of ischemia has not been studied adequately. To examine this question, we evaluated a canine model of induced, transient, anterior-wall myocardial ischemia,

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and calculated the mass of ischemic myocardium by means of changes in myocardial blood flow. We compared the results of the radionuclide method with contrast ventriculographic findings.

METHODS

Experimental preparation. At thoracotomy, two inflatable balloon occluders were placed around the left anterior descending coronary artery. The first was placed just beyond the first septal perforating branch, and the second was placed around the junction of the proximal and distal halves of the vessel (Fig. 1). They were exteriorized to a subcutaneous location, along with two right atrial pacing wires (Flexon, American Cyanamid Co., Pearl River, N. Y.) and a left atrial cannula for injecting radioactive microspheres and radiographic contrast.

Study protocol. Approximately 7 d after surgery, the dogs underwent a study protocol consisting of a control period, a period of ischemia during a distal occlusion (small region of ischemia), a period of proximal occlusion (large region of ischemia), and a second control period prior to sacrifice of the dog. The dogs were sedated with morphine sulfate and diazepam and secured on a radiolucent sponge on a catheterization table in the 30° right anterior oblique (RAO)[1] position. Polyethylene cannulas were secured in the femoral artery and vein, and a constant heart rate was achieved via atrial pacing at a rate 10–20 beats/min greater than the spontaneous sinus mechanism. Small doses of atropine sulfate were given intravenously if atrioventricular nodal block occurred. An electrocardiographic rhythm strip, systemic arterial pressure, orthogonal 30° RAO and 60° left anterior oblique (LAO) radionuclide ventriculograms (RVG), similar biplane contrast ventriculograms (CVG), and myocardial blood flow measurements by the microsphere technique (24) were obtained during the four experimental periods. Each occlusion was produced by inflating an occluder with air and was relieved by deflating. During occlusion, 3 min was allowed for stabilization of the ischemic state, 5 min for each of two RVG and 5 min for obtaining the CVG prior to release of the occlusion. At least 20 min was allowed between occlusions and prior to the final control measurements.

The study was performed in two stages. An initial group of five dogs was studied with RVG during control and ischemic periods, then moved to the catheterization laboratory for CVG using the same occluder to produce a second period of ischemia (serial studies). A later group of nine dogs was studied in the catheterization laboratory with RVG followed immediately by CVG during the same coronary occlusion, according to the protocol listed above (paired studies).

RVG were collected after in vivo erythrocyte labeling (25). A dose of 15.4 mg stannous pyrophosphate (Mallinckrodt Inc., St. Louis, Mo.), containing 3.4 mg stannous chloride, was administered intravenously, followed after 20 min by 20–30 mCi intravenous sodium pertechnetate (New England Nuclear, Boston, Mass.). Images were collected using an Ohio Nuclear portable gamma camera (series 120, Ohio-Nuclear Inc., Solon, Ohio) equipped with a medium resolution, parallel-hole collimator, and were recorded as 5-min 11-frame studies at 30–40 ms/frame in a 64 × 64-image matrix, using a PDP-11/05 computer (Digital Equipment Corp., Marlboro, Mass.) equipped with variable hardware zoom. At each period in the protocol, 30° RAO followed by orthogonal 60° LAO RVG were collected for 5 min each. This produced $2.8 \times 10^5 \pm 8.6 \times 10^4$ counts (SD) in the average RAO end-diastolic frame ($n = 14$). Similar biplane CVG were performed immediately after the RVG by injecting 30 ml of a mixture of sodium and meglumine diatrizoate (Renograffin-76, E. R. Squibb and Son, Inc., Princeton, N. J.) in the left atrial cannula at 10 ml/s, recording at 60 frames/s.

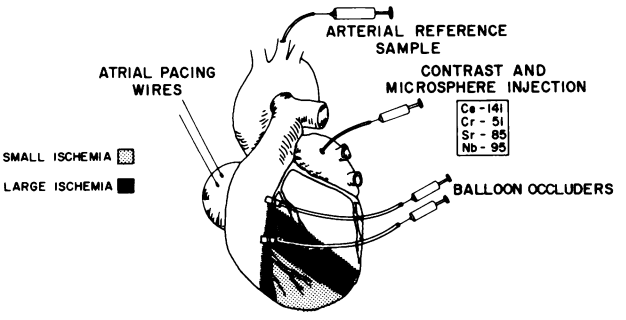

FIGURE 1 Surgical preparation. Inflatable balloon occludes were positioned on the proximal and mid-left anterior descending coronary artery to produce large and small areas of ischemia. A left atrial cannula was inserted for contrast and microsphere injection. Arterial blood was sampled from the carotid or the femoral artery.

Myocardial blood flow (MBF) was determined during each experimental period using injections of 15-μm microspheres labeled with ^{141}Ce, ^{51}Cr, ^{85}Sr, or ^{95}Nb (3M Company, St. Paul, Minn.) at $\sim 2 \times 10^6$ microspheres/injection. Femoral artery samples were collected to allow calculation of MBF in milliliters per minute per gram.

Dogs were sacrificed via barbiturate injection. Each heart was excised and divided into serial 4-mm transverse slices using a meat slicer. Each slice was examined for its gross morphology and divided into segments, which were subdivided into endocardial and epicardial sections.

MBF analysis. The myocardial sections and the arterial reference samples were counted in a multichannel analyzer (AutoGamma scintillation spectrometer, model 5986, Packard Instrument Co., Inc., Downers Grove, Ill.), and MBF was calculated in both absolute and relative terms by methods previously described (26). For each section at each time period, relative MBF was calculated by dividing its absolute MBF (milliliters per minute per gram) by the weighted mean-normal MBF at that time, determined from 10–20 normal posterior wall sections.

Definition and quantitation of ischemia. By inspection of the data, a set of three relative MBF criteria was established which defined the mass of hypoperfused (ischemic) myocardium best: (*a*) relative MBF > 0.6 during the initial control period; (*b*) a decrease of ≥25% in MBF during occlusion; (*c*) MBF <0.6 during occlusion. These criteria were similar to those used in a prior study from this laboratory (26).

CVG analysis. End-diastolic (ED) and end-systolic (ES) outlines were traced from the first well-opacified non-PVC or

[1] *Abbreviations used in this paper*: ACS, abnormally contracting segments; CVG, contrast ventriculogram; ED, end-diastole; EF, ejection fraction; ES, end-systole; FPF, false-positive fraction; GMI, grams of myocardial ischemia; LAO, left anterior oblique; MBF, myocardial blood flow; RAO, right anterior oblique; ROC, receiver operating characteristic; RVG, radionuclide ventriculogram.

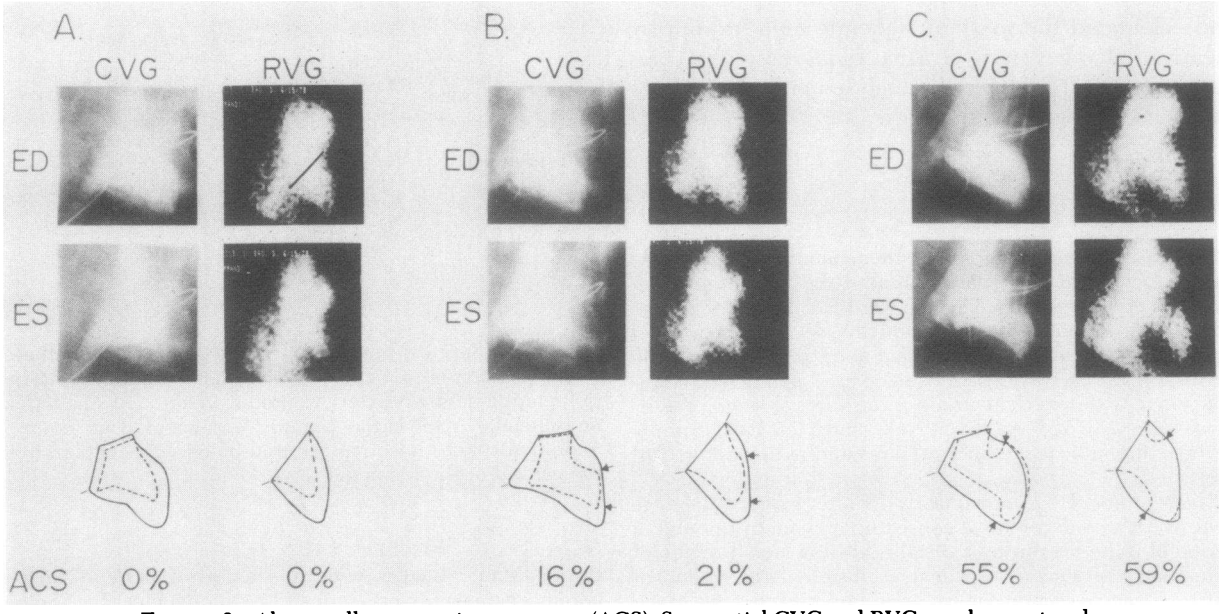

FIGURE 2 Abnormally contracting segments (ACS). Sequential CVG and RVG are shown at end-diastole (ED) and end-systole (ES) during control (A), first coronary occlusion (B), and second coronary occlusion (C) in a single dog. In A, a dark line at the base of the RVG defines the visible limits of the left ventricle. On the traced outlines, thin markers denote the limits of the contractile perimeter. Arrows denote the length of ACS projected on the ED perimeter. For each pair of studies, the percent ACS is comparable; however, the RVG underestimates the degree of abnormal wall motion. Thus, in B, hypokinesis on CVG is less pronounced than on RVG. In C, there is dyskinesis on CVG and akinesis on RVG.

post-PVC beat in the RAO and LAO views. The global ejection fraction (EF) was calculated using single-plane and biplane data by the area-length method (15).

Wall-motion defects, with or without an abnormal EF, were used for the qualitative diagnosis of ischemia. For quantitation of the wall motion abnormalities, ED and ES frames were traced, and the length of abnormally contracting segments (ACS) was calculated as a percentage of the ED outline (percent ACS) by a modification of the method of Feild et al. (18), as shown in Fig. 2. For this, an experienced observer marked the length of the ACS on the ED perimeter. The mitral and aortic valve planes were excluded from the measured perimeter. Areas of localized hypokinesis (asyneresis), akinesis, and dyskinesis were considered to represent ACS. Their diagnosis was based on established criteria (17). It was believed justified to group the abnormalities for analytical purposes because (*a*) each defect was likely to be ischemic by the design of the study, (*b*) comparison to the best-contracting ventricle in each set of studies helped identify new ACS, and (*c*) these wall-motion grades overlap frequently when RVG are compared with CVG (4, 5, 7). Fig. 2 demonstrates the percent ACS measurements during the initial control period and during two coronary occlusions in sequential studies in an animal with all three types of ischemic wall-motion abnormalities. There is a strong visual comparability between RVG and CVG. However, in this example, the RVG underestimated the grade of wall-motion abnormality, but not its extent. Thus, it was useful to calculate the percent ACS as a measure of the extent of abnormal wall motion.

RVG analysis. The global EF was calculated using a non-geometric radioactive count-based method. For this, a semi-automatic border detection algorithm and a variable region of interest technique (27) were employed. Because there is little right-left ventricular overlap in the supine dog, the EF was calculated from both RAO and LAO images. For visual analysis and measurement of the percent ACS, the four RAO or LAO RVG of each dog (two controls, two periods of ischemia) were displayed on a video screen as moving, closed-loop "playback buffers" with no identifying information. The percent ACS was calculated as for the contrast studies by tracing the left ventricular perimeter, excluding basal areas overlapped by other vascular structures (Fig. 2).

Receiver operating characteristic (ROC) analysis was used to determine sensitivity, specificity, and accuracy for detecting ischemic dysfunction on RVG and CVG according to the description of Metz (28). Such ROC curves compare diagnostic sensitivity to the false-positive fraction. For this, two independent observers employed a subjective visual grading scale of 1–4, where 1 = definitely not ischemic, 2 = probably not ischemic, 2.5 = equivocal, 3 = probably ischemic, and 4 = definitely ischemic. To produce ROC curves, the visual threshold for diagnosis of ischemia on ventriculography was varied from 1 (loose) to 4 (strict), and two threshold levels of myocardial ischemia were tested: >0.001 g and >4.0 g. The final control ventriculograms were excluded.

Data were entered into a computer data base management system (CLINFO, Division of Research Resources, National Institutes of Health, Bethesda, Md.) and were expressed as the mean and standard deviation. Analytic methods included formulas for sensitivity and specificity (28), linear regression analysis, and paired and unpaired *t* tests (29), adjusted for multiple comparisons (30).

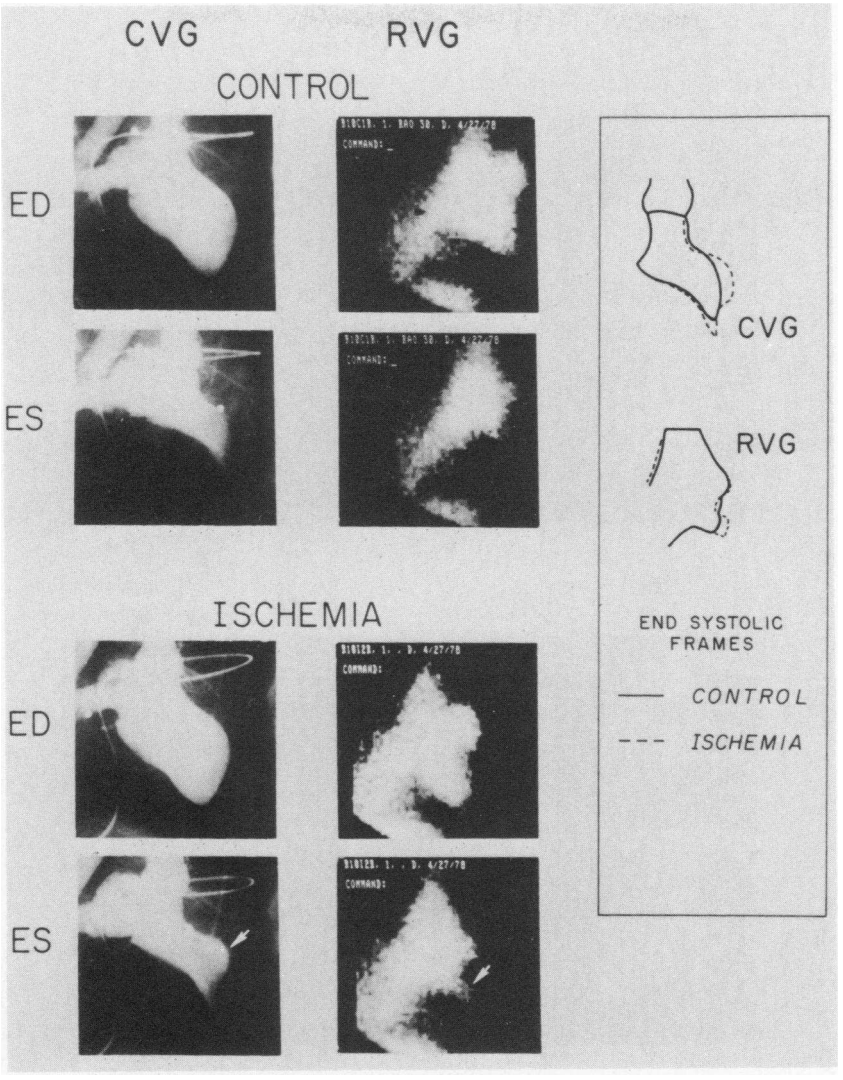

FIGURE 3 A small region of ischemia. The CVG and RVG are compared at ED and ES in control and ischemic periods. Paired ES frames demonstrate regional dysfunction during ischemia on both RVG and CVG. MBF defined only 2.0 g ischemia, despite the large wall motion defect. Superimposed ED and ES frames (not shown) demonstrated 18.5% abnormally contracting segments on CVG and 34.6% on RVG.

RESULTS

21 dogs were prepared. 14 had sufficient data for the RVG-CVG comparison. Of these, five had serial studies and nine had paired studies. The other seven dogs were excluded because of ventricular arrhythmias (three), occluder malfunction (three), or computer disc failure (one). There were no significant differences in the results in serial and paired studies. The results are presented as the combined data for all 14 dogs unless noted otherwise.

Quantitation of ischemia. The occlusions lasted 19.0±1.2 min. The dogs weighed 23.8±4.2 kg, and the left ventricles weighed 110.8±24.3 g. The ventricles were divided into a total of 1,310 sections, weighing 1.8±0.70 g (wet wt). Sections in the anterior descending distribution were cut smaller than average in order to obtain a more accurate estimate of ischemic tissue. The regions of ischemia ranged from 0 to 38.5 g, averaging 13.62±12.73 g. Of a total of 30 occlusions performed in the 14 dogs, 5 yielded no ischemia by flow criteria. There were nine small regions of ischemia <10 g, averaging 3.40 g (range 0.94–9.48 g). There were 16 > 10 g, averaging 24.80 g (range 12.07–38.5 g) (large regions

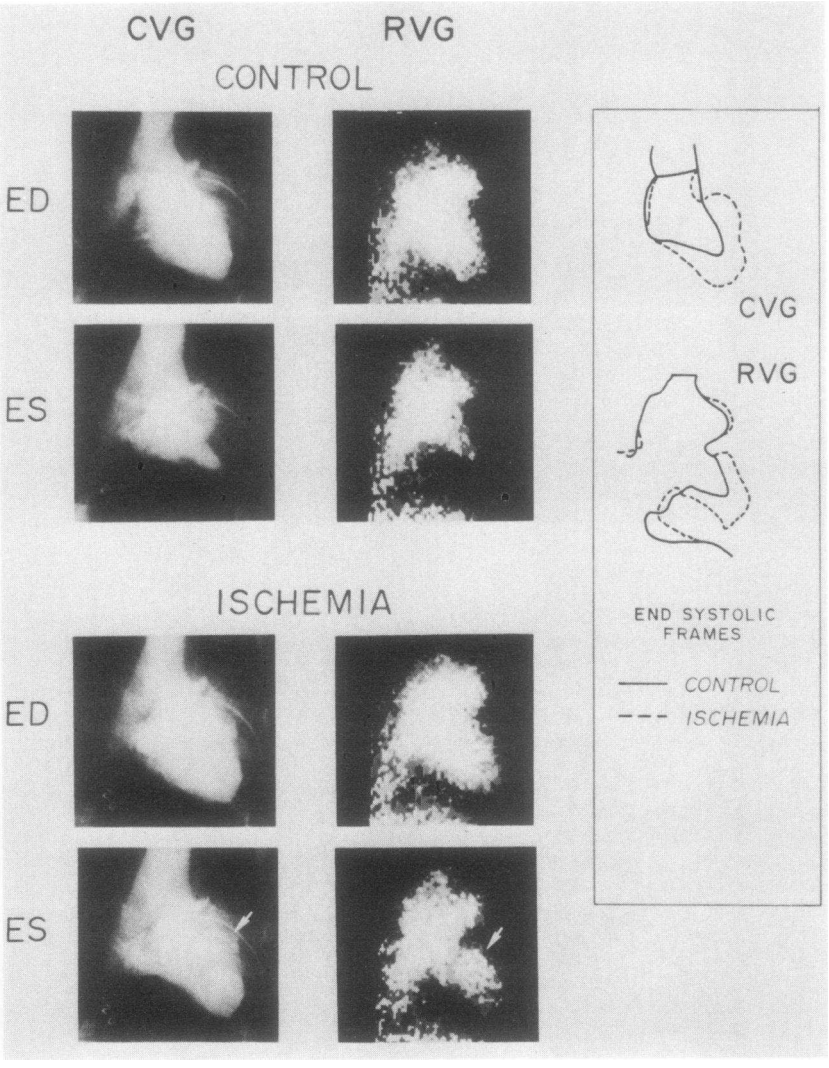

FIGURE 4 A large region of ischemia. There was 35.07 g of ischemic tissue, which caused 45.6% ACS on CVG and 44.4% on RVG.

of ischemia). Seven dogs had two occlusions using the same occluder. These seven ischemic weights ranged from 0.94 to 32.71 g, and the mean difference between the paired ischemias was 0.17 ± 1.58 g (P = NS).

Hemodynamic data. The dogs were stable during the experiment. The mean control systolic pressure (145 mm Hg), diastolic pressure (88 mm Hg), mean arterial pressure (108.7 mm Hg), and paced heart rate (121/min) were essentially unchanged from control during the two ischemic periods and the final control period. Also, there were no hemodynamic differences when divided by the weight of ischemic tissue into no, small, and large regions of ischemia, when compared with their respective controls.

Qualitative analysis of ischemia. Wall-motion abnormalities on the RVG were highly comparable to the findings on the paired CVG. Fig. 2 demonstrates this similarity and the tendency of the RVG to mirror the extent, but to partially underestimate the degree, of the CVG abnormalities. Figs. 3 and 4 show the visual comparability of CVG and RVG for both small and large regions of ischemia. In each case, the control ventriculograms had normal contractility. Ischemia was associated with small and large wall-motion defects, respectively, and the defects were seen on both RVG and CVG. There were 26 paired studies during control and ischemic periods. 16 RVG had wall motion abnormalities, and 14 of the 16 (88%) had wall-motion abnormalities within one grade of the CVG abnormality.

For the paired studies, Fig. 5 (top) demonstrates ROC

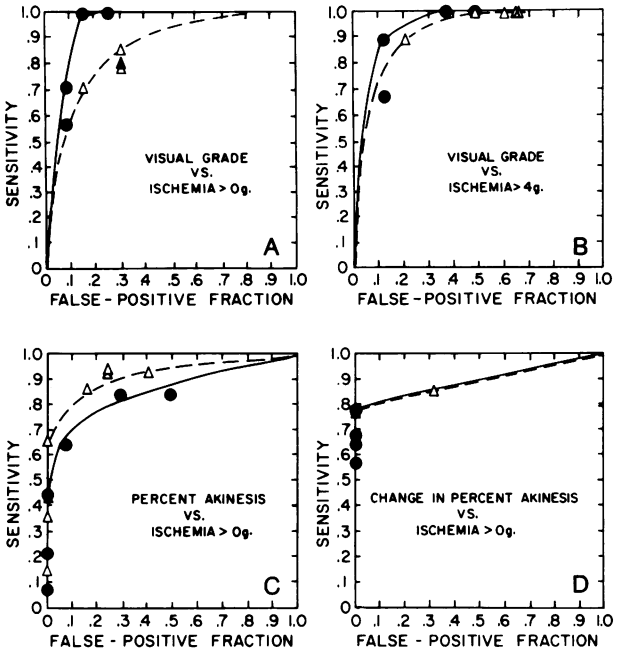

FIGURE 5 ROC analysis. Qualitative visual criteria for ischemia (top) showed high sensitivity and specificity (low FPF) for both CVG and RVG (A, B). The CVG and RVG were nearly equal tests at a threshold of 4 g of ischemia (B). Quantitative measurement of the percent ACS (bottom) showed comparable results (C), which improved further when small regions of reduced wall motion on control ventriculograms were taken into account (D). ●, CVG; △, RVG.

curves for the visual qualitative diagnosis of ischemia. Threshold levels of 0.001 (Fig. 5A) and 4 g (Fig. 5B) of ischemia are depicted. At the 0.001-g level (i.e., ≥0.94 g in this series), the greatest accuracy in RVG diagnosis (0.78) was achieved when only visual grade 4 was accepted as positive. At this operating point, the RVG sensitivity was 0.71, and the false-positive fraction (FPF) was 0.15. The FPF rose to 0.30 when grade 3 was also accepted as positive. For the CVG, the greatest accuracy (0.92) was achieved using grades 2.5–4. At that operating point, sensitivity was 1.0 and FPF was 0.15. At the level of ≥0.001 g, the CVG was slightly more sensitive, specific, and accurate than the RVG for detecting ischemia, since the standard deviation for each ROC point was 0.1, and the upper left CVG point was between 1 and 2 SD distant from the adjacent RVG point.

At the 4-g level, the ROC curves were nearly superimposable. The RVG had its greatest accuracy (0.81) using grade 4, and the CVG accuracy was best using grades 3 and 4 (0.85). The FPF was low for both RVG and CVG (0.22 and 0.13, respectively).

Quantitative analysis of ischemia. The myocardial blood flow to normal tissue was 1.30±0.21 and 1.14 ±0.20 ml/min per g during the two ischemic periods. Flow to the ischemic tissue averaged 0.44±0.19 and 0.42±0.22 ml/min per g during the occlusions.

Global left ventricular EF. There were 53 LAO RVG, 40 RAO RVG, and 41 biplane CVG. The number of studies was unequal due to the initial group of serial studies. For the paired data, the contrast RAO EF ranged from 0.32 to 0.81. There was no significant difference between the RAO and biplane data. Thus, only the RAO CVG results are presented. The correlation coefficient (r) for EF between paired CVG and RVG was 0.61 in the RAO position ($n = 34$, $P < 0.001$) (Fig. 6),

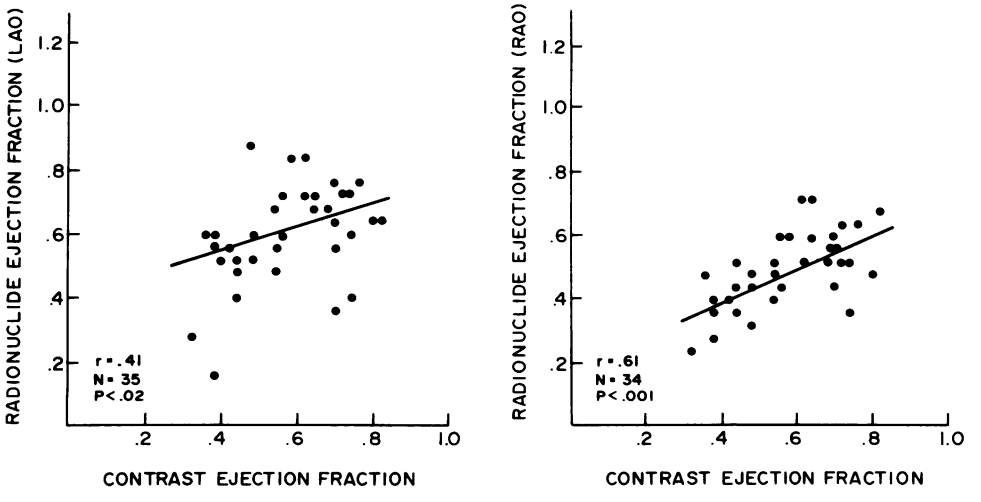

FIGURE 6 EF correlations. The RAO RVG had a closer relationship to the contrast EF than did the LAO studies. (See Discussion).

TABLE I

Correlation of Radionuclide and Contrast EF in Individual Dogs

Animal	Contrast EF*			r value*
	Minimum	Maximum	Range	
20	0.32	0.75	0.43	0.91
12	0.37	0.72	0.35	0.89
13	0.44	0.69	0.25	0.74
16	0.56	0.72	0.16	−0.52
17	0.44	0.57	0.13	0.99
10	0.62	0.75	0.13	0.92
15	0.70	0.81	0.11	0.12
14	0.43	0.54	0.11	−0.15
11	0.35	0.41	0.06	−0.98

* Correlation coefficient; paired studies; RAO projection.

but was only 0.41 when using the LAO RVG (n = 35, P = 0.015).

The correlation between RVG and CVG was also examined for each of the nine dogs with paired studies. The results are displayed in Table I, ranked by the difference (range) between maximum and minimum contrast EF for each dog. The ranges varied from a maximum of 0.43 to a minimum of 0.06. There were high r values in five of six dogs whose range of EF values was ≥0.13, and there were low r values for dogs with a smaller range of EF. Animal weight and LV weight showed no relationship to the EF correlation.

Changes in the RAO global EF and the percent ACS were compared with the extent of ischemia on both CVG and RVG for the entire series (Fig. 7). For the EF, there were no significant changes for regions of ischemia of 0 g or 0 to <10 g, but the EF dropped signifi-

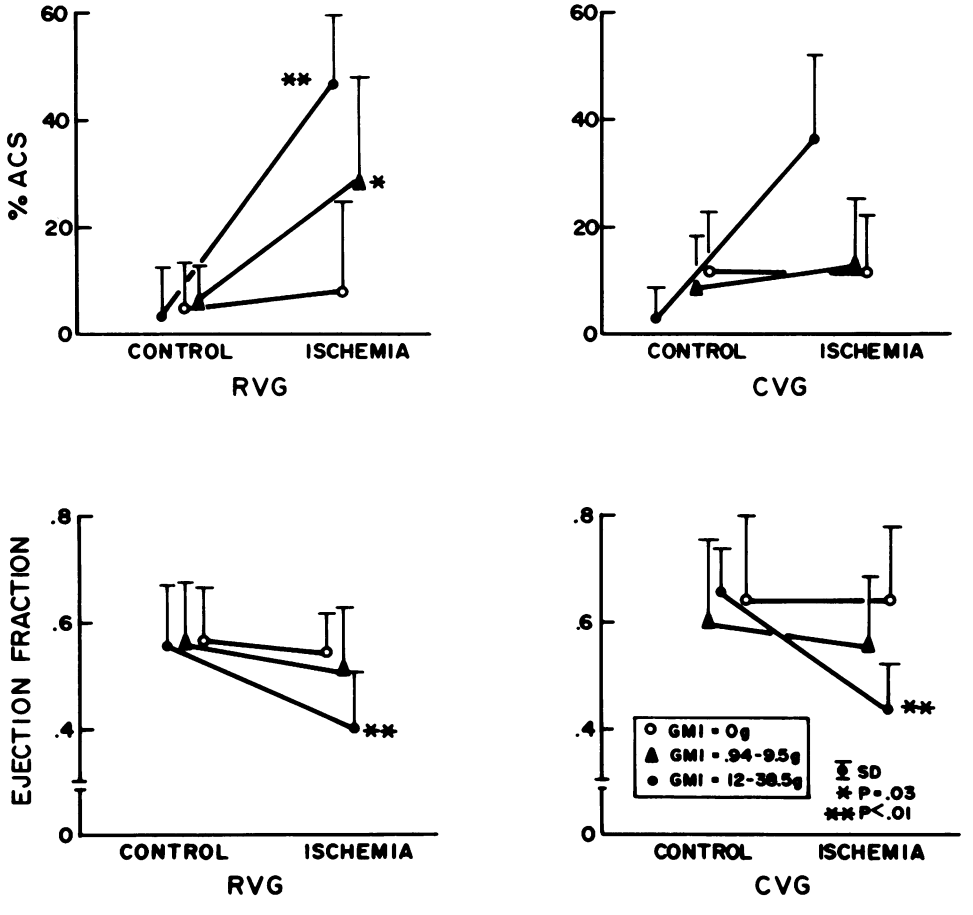

FIGURE 7 Changes in regional wall motion and EF compared with the grams of myocardial ischemia (GMI). Both RVG and CVG demonstrated significant changes in wall motion and EF for large regions of ischemia. The wall motion change for small regions of ischemia on RVG was also statistically significant. Ischemic regions on RVG formed a greater proportion of the visible perimeter than on CVG.

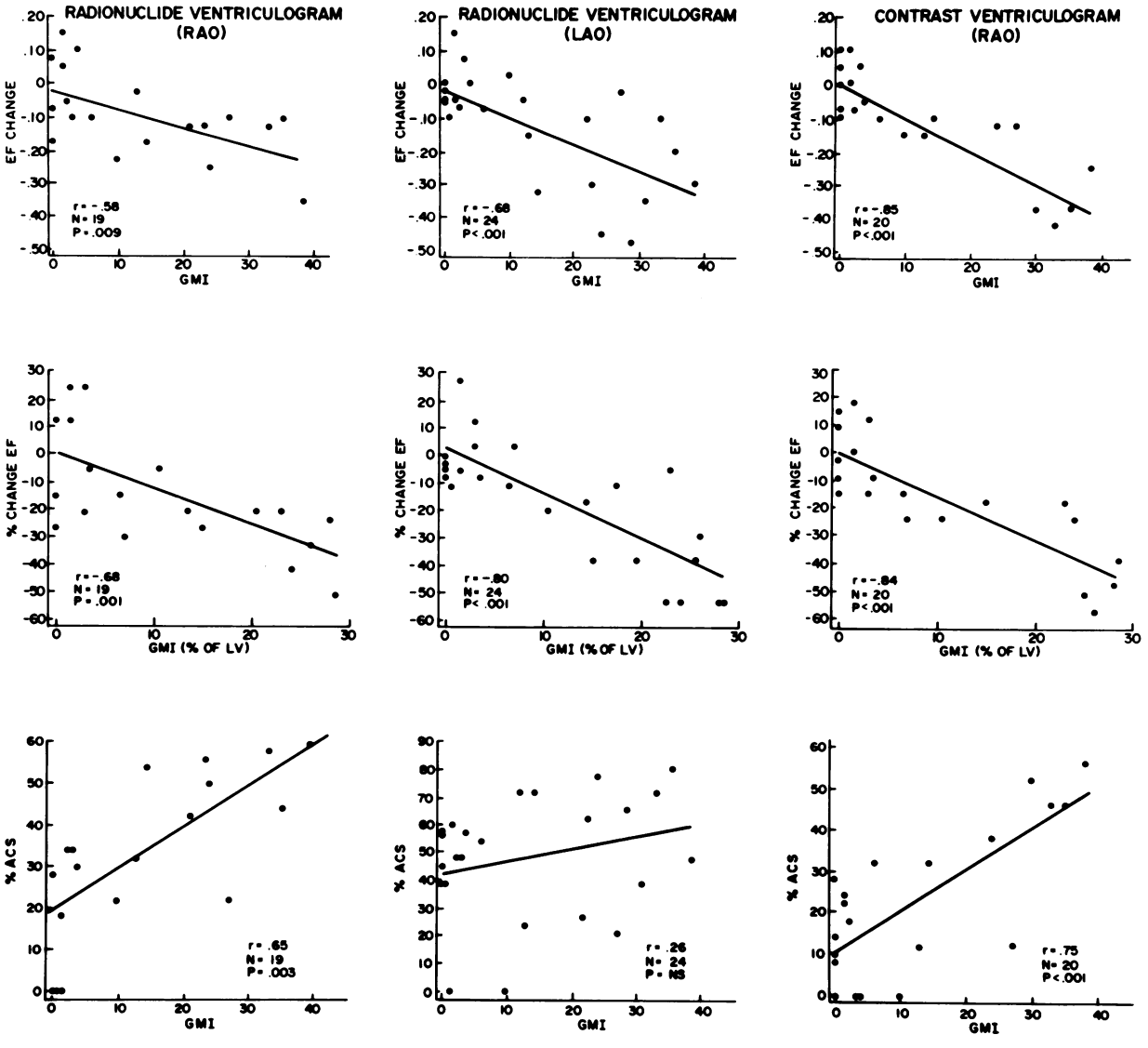

FIGURE 8 Correlation of EF and abnormally contracting segments with grams of myocardial ischemia (GMI). The relationships are quantitative; however, contrast ventriculography had a closer correlation with GMI than did the radionuclide studies. The RVG relationships improved when the change in EF was expressed as a percentage of the control value and the GMI was expressed as a percentage of left ventricular weight (middle row). Three RVG had no ACS with GMI of 0, 0, and 1.8 g (bottom left), but the percent ACS was considerable for the other small ischemias, possibly due to abnormal contraction of contiguous normal myocardium.

cantly for the large regions—from 0.66 to 0.44 for CVG and from 0.57 to 0.40 for RVG (both $P < 0.01$). For the percent ACS, both RVG and CVG had large amounts of abnormal wall motion when regions of ischemia were >10 g. Compared with control, the changes were highly significant using the paired t test (for RVG, $P < 0.001$, for CVG, $P < 0.009$); however, the CVG change was not significant after Duncan's correction (30), due to results in a single dog. For regions of ischemia 0 to <10 g, the CVG did not have significant changes in wall motion. However, there was a significant difference in the radionuclide percent ACS, even for these small regions, because the ACS occupied a greater percentage of the visible contractile perimeter, and thus, the same ischemia produced a larger change in percent ACS on RVG than on CVG.

Control tracings often had small anterolateral wall-motion "abnormalities," even though MBF was

normal. These averaged 5.1% on CVG and 7.2% on RVG. This type of wall motion is normal in the dog, since it was seen in two of three CVG performed on normal dogs with no prior surgery.

The percent ACS was evaluated as a quantitative measurement for diagnosing ischemia using ROC analysis of the paired studies. Fig. 5 (bottom) demonstrates that this measurement had a high degree of sensitivity and a low FPF on both RVG and CVG. When any control defects were subtracted (Fig. 5D), the change in percent ACS was 80% sensitive for ischemia without false positives, and the RVG and CVG curves were superimposable.

Several ventriculograms demonstrated considerable contractile abnormalities in spite of small amounts of measured flow reduction, as seen in Fig. 3. During that occlusion, the percent ACS was 18.5% on CVG and 34.6% on RVG, in spite of only 2 g of tissue hypoperfused.

Quantitative relationships between ischemic tissue weight, left ventricular dysfunction, and wall-motion abnormalities. The RAO and LAO radionuclide studies were compared with RAO CVG for quantitation of ischemia using linear regression analysis. Fig. 8 demonstrates the relationship between (*a*) the change in EF and grams of myocardial ischemia (GMI) (*b*) the percent change in EF and GMI as a percent of left ventricular weight; (*c*) the percent ACS and GMI. The number of observations was unequal due to the initial serial studies.

All three CVG measurements had higher r values than the RVG measurements. The RVG correlation coefficients were strengthened (middle row) by adjusting for the change in EF as a percentage of the control value and for the GMI as a percentage of left ventricular weight. Changes in RVG EF were related better to the GMI in the LAO than in the RAO view. The RVG percent ACS related better to the GMI in the RAO view ($r = 0.65$) than in the LAO view. Since the anterior wall was seen best in the RAO projection, this was predictable. For CVG, this correlation coefficient was 0.75.

Residual contractile abnormalities and ischemia. In the second control period, only 16 of 1,310 tissue sections met the criteria for GMI (1.2%). These few sections produced an average GMI of 1.2 ± 1.8 g. Although there were occasional persistent wall-motion defects despite nearly complete return of normal regional MBF, there was no consistent or significant change in EF or percent ACS compared with the first control period.

DISCUSSION

Numerous and varied clinical studies have utilized RVG to detect and estimate the severity of myocardial ischemia (1–14) with methods and concepts derived from study of CVG (15–23). However, the sensitivity, specificity, and accuracy of ventriculography for quantitating known amounts of left ventricular ischemia have not been carefully studied. To clarify these questions, we examined serial changes in regional MBF to estimate myocardial ischemia, and compared the weight of poorly perfused myocardium with changes in global and regional left ventricular function in the sedated dog. Contrast ventriculography was used as the standard for comparison. The results confirm that both RVG and CVG are sensitive to ischemia and reflect quantitatively the amount of ischemic myocardium.

Qualitative changes. Anterior descending coronary artery occlusions were chosen to provide an optimal location for detection. The occlusions produced anterolateral regions of hypokinesis, akinesis, or dyskinesis, which were easily seen on both RVG and CVG. These ischemic abnormalities were consistent with the systolic segmental dysfunction recorded during coronary occlusion in dogs using mercury-in-Silastic strain gauges (31), ultrasonic transducers (32–34), and frame-by-frame analysis of CVG (35).

ROC analysis (29) was used to evaluate and compare the RVG and CVG for their sensitivity and specificity in detecting left ventricular ischemia using visual analysis and measurement of the percent ACS. The ROC curves compared the true-positive fraction (sensitivity) and the FPF (1 − true-negative fraction), the latter equivalent to 1 − "specificity". The CVG curve was marginally superior to the RVG (by 1 to ≤2 SD) when all amounts of ischemia were considered as "disease-positive" (Fig. 5A). The CVG advantage was probably due to better resolution than the RVG. However, when the arbitrary criterion of 4 g of ischemia (4% of left ventricular weight) was chosen as the threshold for positivity, the curves were nearly identical (Fig. 5B). When the percent ACS was used for diagnosing ischemia, the ROC curves were nearly equivalent (Fig. 5C), and were actually superimposable when the control wall-motion defects were taken into account (Fig. 5D). Further mathematical study of these curves requires a larger number of cases for valid comparisons.

In this study, sensitivity and specificity were determined in a carefully controlled experimental environment. Although, the results should not be generalized to clinical situations where other disease processes may coexist, the concept is applicable, such as in patients with known, localized coronary atherosclerotic lesions.

Quantitative factors. Accurate estimates of ischemia and the EF were required in this study. Since there was no visible evidence of myocardial damage after the transient occlusions, MBF criteria were used to define "ischemia." Meaningful criteria should account for the large normal variability in MBF (26, 36–38) and should

define the degree of flow reduction necessary for physiologic evidence of ischemia or histopathologic change (26, 38–40). Our criteria were based on the presence of flow reduction sufficient to cause ischemia in a prior study of dogs with permanent coronary occlusion (26). In that study, the MBF criteria accurately defined the sections with confluent necrosis 48–72 h after occlusion. However, sections with "patchy" necrosis were not well-defined, because they had only small flow reductions (81% of normal), which were within the normal range. Marcus et al. (40) also used a blood flow algorithm to define ischemic sections of the left ventricle 5 min after coronary occlusion. Both Marcus' criteria and ours were insensitive to small flow reductions which were still within normal range of flow. Vatner et al. (34) have compared regional MBF and function during coronary occlusion. They found that even small degrees of flow reduction to 80% of normal produced small amounts of electrocardiographic ST-segment elevation and small wall-motion changes in ischemic "border zones," which had been selected during a prior test coronary occlusion. Their study did not account for the known intrinsic serial variability in MBF (36), but the flow results were statistically significant. Others have compared flow and the measured percentage of myocardial necrosis and have demonstrated minimal damage until MBF was reduced by at least 25–40% (38, 39). Although our estimates of GMI might underestimate the GMI slightly, Vatner et al. (34) also found that moderate or severe ischemia was needed to cause substantial wall-motion abnormalities of the degree we report here. Thus, the level of ischemia we detected seems well-matched to the wall-motion defects which we included in the percent ACS.

The radionuclide global EF correlated significantly with the CVG results, but the correlation coefficient (0.61) was lower than customarily seen in clinical studies using the same methods in our laboratory and in others (1, 41). Several factors may influence the strength of this relationship. Most important was the relatively narrow range of EF results (0.32–0.81), lacking the very low values seen in most clinical studies, and reducing the correlation coefficient. When EF below 0.30 are eliminated from our clinical series (27), the correlation coefficient with contrast ventriculography decreases from 0.93 (n = 18) to 0.67 (n = 13, P < 0.001), a value similar to the results in this study. Okada et al. (42) reported similar results in man.

When individual dogs were ranked by their range of EF values, the RVG-CVG correlations were best when the range of values was wide. Swain et al. (43) also found a close relationship between the radionuclide and ultrasonic transducer-derived EF in dogs when a broad range of EF was produced. Other factors in the RVG-CVG correlation include variable ^{99m}Tc attenuation and background among dogs, and overlapping blood pool structures.

Quantitative changes during ischemia. As seen in Fig. 7, for both CVG and RVG, the EF was unchanged by zero ischemia and insignificantly lowered by small amounts of ischemia (<10 g). However, the EF was reduced considerably by the large zones of ischemia (>10 g).

The percent ACS also had a quantitative relationship to the GMI. However, for any amount of ischemia, the RVG tended to have greater areas of akinesis than the CVG. This finding was due to exclusion of the normal inferobasal and anterobasal left ventricle on the RVG compared with the CVG, thus making the same dysfunctional area a greater fraction of the total perimeter. Other factors may be the relatively poorer resolution on RVG, which might cause an overestimation of the percent ACS and, possibly, the 5-min duration of RVG collection. Approximately 600 cycles were collected during this period, and respiratory variation could have accentuated abnormalities on RVG, compared with single nonshifted CVG frames.

Due to our correction for multiple comparisons, the difference in the percent ACS between control and ischemia was statistically insignificant on CVG. However, ROC analysis showed equal and good results of RVG and CVG for detecting regions of ischemia (Fig. 5).

The superimposed curves in Fig. 5D demonstrate the improvement that occurred by accounting for pre-existing control changes. This is similar to present clinical methods for diagnosing ischemic abnormalities on exercise RVG. Although one-vessel coronary occlusion in dogs differs from exercise-induced ischemia in man, the method for diagnosis of the amount of ischemic tissue may be analogous.

We are not aware of other published data comparing the extent of RVG abnormalities to known amounts of ischemia. However, thallium-201 scintigrams have been evaluated for their quantitative sensitivity to ischemia. Mueller et al. (44) graded thallium images of canine hearts and compared changes with MBF data. The smallest definitely detectable ischemia was 4.5 g with 45% reduction in MBF. In man, Neiss et al. (45) found a quantitative relationship between ^{201}Tl defects after infarction and the percent ACS on biplane contrast ventriculography. Such thallium defects were seen in 20 of 22 patients with areas of akinesis over 6% of the perimeter. Measured thallium defect size also correlated with the percent ACS they measured on CVG (r = 0.80). These relationships between thallium evidence of infarction, the presence of observable wall motion defects, and the extent of such defects are similar to the regional wall motion changes we report here.

There was moderate scatter of data comparing the EF

and percent ACS to the GMI (Fig. 8). The CVG had stronger r values than did RVG, perhaps due to improved resolution, but the relationships had moderate variance on CVG as well. There may be several factors causing this degree of variance. First, the ischemic area is three-dimensional, while the perimeter on either method of ventriculography is two-dimensional. Second, the estimates of percent ACS, EF, and ischemia might have been erroneous, but for reasons discussed above, we believe they are quite likely to be accurate. Third, there may be effects of ischemic dysfunction upon the adjacent normally perfused myocardium. Our data and others' support the possibility that there may be abnormalities in wall motion produced by contiguity to an ischemic segment. In this study, percent ACS increases with GMI, but may overestimate it. Fig. 3 demonstrates this type of large wall-motion abnormality associated with only 2 g of measured ischemia. Evidence from open-chest canine studies by Wyatt et al. (31) supports the premise that contractile abnormalities can occur by contiguity to an ischemic segment. Similar results were found by Kerber et al. (46, 47) using echocardiography in open-chest dogs. Vatner et al. (34) did not demonstrate such abnormalities in normal myocardium; however, our data and the results of Wyatt et al. and Kerber et al. support the hypothesis that regions of ischemia have a geometrical importance beyond their borders by preventing contraction of nearby normal myocardium. Although direct myocardial studies have shown these effects on selected adjacent regions, ventriculography has demonstrated the effect on the entire visible left ventricular perimeter, and shows that it is sometimes large. Further study of the question of contiguous dysfunction is indicated, since changes in ventricular function after medical or surgical intervention in ischemic heart disease may be related to this effect.

There were no significant residua of ischemia, as measured by blood pressure, EF, or the percent ACS on ventriculography. Normal flow and function were restored to nearly all tissue sections during the second control period, and our results are in agreement with Jennings et al. (48), who found that 20 min of ischemia was necessary to produce even minimal infarction after circumflex coronary occlusion in the dog. Using more sensitive ultrasonic segment length transducers, Heyndrickx et al. (33) have demonstrated abnormal wall motion for several hours after 5- or 15-min coronary occlusions. Kerber et al. (47) also showed persistent dysfunction after 45-min occlusions. Precise measurement frame-by-frame of the left ventricular contraction pattern on CVG might show residual abnormalities (35), but that analysis was not performed in the present study.

In this study, by use of objective blood flow criteria, the extent of experimental ischemia necessary for detection by contrast and radionuclide ventriculography has been established. Both radionuclide and contrast techniques were shown to be sensitive for detecting small amounts of ischemic tissue by both visual analysis and computer-assisted quantitative measurements. Regional wall motion is the more sensitive measurement for detecting ischemia on both radionuclide and contrast ventriculography. Correlation of ischemia with the EF and the percent ACS has moderate scatter on both RVG and CVG. Some of the wall-motion abnormalities may be disproportionately large compared with the extent of measured ischemia, and such results may be due to the effects of an ischemic region upon contiguous tissue.

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