Effects of Coronary Arteriography on Myocardial Blood Flow

By FRANK E. KLOSTER, M.D., W. GLENN FRIESEN, M.D., GERALD S. GREEN, M.D., AND MELVIN P. JUDKINS, M.D.

SUMMARY
Myocardial blood flow responses to selective coronary arteriography were studied in 22 patients. Left coronary flow was estimated by the radioactive inert-gas (133Xenon) washout technic using precordial detection. Duplicate control studies were obtained before radiocontrast injection and test studies were performed at 1 min and 3, 5, or 7 min after angiography. Eleven patients received a single 7-ml injection of methylglucamine diatrizoate and 11 were given a series of injections (average total 40 ml), with the test blood flow studies after the final injection.

Myocardial flow increased in every patient 1 min after contrast injection (average control flow 66.3 ml/min/100 g; test flow 78.8, +18.9%, \( P < 0.001 \)). Blood flow increased further in seven of 10 studied at 3 min (average 95.7 ml/min/100 g, +35.7%, \( P < 0.001 \)) and remained elevated at 5 and 7 min. Systemic pressure was unchanged from the control level, so coronary vascular resistance decreased in proportion to the increase in flow. Blood flow responses in patients with coronary artery disease were no different from normal subjects. Sham injections of normal saline produced no increase in coronary flow.

Selective coronary arteriography results in a prompt increase in myocardial blood flow which persists for several minutes. The probable mechanism is coronary vasodilatation produced by the markedly hypertonic contrast material, an effect demonstrated previously in other vascular beds.

Additional Indexing Words: Radiographic contrast material, Radioactive inert gas, Coronary angiography, Coronary artery disease, 133Xenon washout technic

Despite the wide use of selective arteriography for evaluation of coronary occlusive disease, the effects of radiographic contrast material on the coronary circulation have not been extensively studied in humans.

Reports demonstrating the marked hemodynamic and vascular effects of hypertonic contrast material on the systemic circulation suggest that important changes might occur with coronary arterial injection.1-5 Studies in open-chest dogs and in intact animals have demonstrated that increases in coronary blood flow do occur following intracoronary injection of contrast material.2, 6-11 The development of the radioactive inert-gas washout method for determination of myocardial blood flow has made studies of the coronary circulation readily available clinically.12 This technic is being used increasingly to evaluate responses to pharmacologic interventions and the effects of electrically induced tachycardia.
and exercise in normal individuals and patients with coronary heart disease. Radiographic contrast material is usually required for coronary catheter positioning in these studies and coronary angiography is frequently performed during the same procedure. Knowledge of the coronary hemodynamic effects of contrast material is important in evaluating the findings, as well as for a more complete understanding of responses to selective coronary angiography. The purpose of this study was to determine the effects of selective coronary arterial injection of radiographic contrast material on myocardial blood flow in patients with normal and diseased coronary arteries.

**Methods**

Myocardial blood flow through the left coronary artery was studied in 22 patients during diagnostic coronary arteriography. Twelve of the 22 had greater than 50% narrowing of the left main, anterior descending, and/or circumflex artery, and 10 had essentially normal vessels. Studies were performed using the Judkins technic for selective coronary injection. Methylglucamine diatrizoate (Renografin-76) was the contrast material used in all cases.

Myocardial blood flow was determined by the radioactive xenon ($^{133}$Xe) washout technic using a precordial scintillation detector as described by Ross et al. Patients were studied in the left anterior oblique position with the spectrometer probe positioned externally over the left ventricle using fluoroscopy. A 1-ml injection of normal saline solution containing 75 mCi of $^{133}$Xe was given selectively as a bolus into the left coronary artery for each blood flow determination and the catheter was flushed with 3 ml of normal saline solution. The resulting myocardial clearance curve of $^{133}$Xe was recorded using a 2-in scintillation detector with a 20° flat-field collimator and a spectrometer system with a time constant of 1 sec; and was inscribed on a direct-writing recorder. The radioactivity clearance curve was replotted semilogarithmically and myocardial blood flow was calculated by the standard method.

Control myocardial blood flow was determined in duplicate in all patients prior to contrast-material injection. In the first 11 individuals a rapid sequence of 5–7 injections of contrast was then made while routine coronary angiograms were filmed. The injections averaged 7 ml each and the total volume of all injections averaged 40 ml. In the final 11 patients a single 7-ml injection of contrast material was given. Myocardial blood flow determinations were repeated 1 min and 3, 5, or 7 min after the final injection of the series, or after the single injection.

In three individuals the mechanical effects of injection of a volume of fluid were assessed by giving a bolus of 7 ml of normal saline solution. Myocardial blood flow was determined in duplicate before saline injection and was repeated 1 and 3 min afterward. The same three patients were then given 7-ml injections of contrast material and blood flow studies were again repeated after 1 and 3 min.

Systemic arterial pressure, pulse rate, and the electrocardiogram were recorded continuously throughout the control and test studies. The results of all studies were analyzed statistically using the paired $t$ test.

**Results**

The results of duplicate determinations of myocardial blood flow through the left coronary artery in 41 patients are presented in figure 1. There was a small difference between the mean values for the two studies (64.9 vs...
69.6 ml/min/100 g) and an excellent correlation ($r = 0.94$). The average difference between the first and second study was $8.5 \pm 1.1$ ml/min/100 g (mean ± SEM).

Myocardial blood flow responses to radiocontrast material are shown in table 1. There was no difference between the results of patients having multiple contrast injections and those having single injections. The average increase in myocardial flow 1 min after injection was $10.6 \pm 2.4$ ml/min/100 g (mean ± SEM) in the multiple-injection group compared to $14.2 \pm 2.0$ in the single group ($P = \text{ns}$). After 3 min the mean values were $22.8 \pm 5.2$ vs $24.9 \pm 3.3$ ml/min/100 g ($P = \text{ns}$). Therefore, data from patients having single and multiple contrast injections are combined in the subsequent analysis of results.

Myocardial blood flow 1 min after contrast injection was higher than the control value in every patient. The average for the entire group rose from a control flow of 66.3 ml/min/100 g to 78.8, an 18.9% increase ($P < 0.001$). Blood flow increased further in seven of 10 studied after 3 min. The average flow at this time, 95.7 ml/min/100 g was 35.7% above the control level ($P < 0.001$). Myocardial flow remained elevated above the 1-min value in six of eight studied at 5 min and in

### Table 1

<table>
<thead>
<tr>
<th>Pt</th>
<th>Contrast injections (total no.)</th>
<th>Control flow (avg ml/min/100g)</th>
<th>Blood flow after contrast injection (ml/min/100g)</th>
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| No. | 22 | 22 | 10 | 8 | 3 |
| Mean flow | 66.3 | 78.8 | 95.7 | 80.3 | 84.0 |
| % change** | — | +18.9 | +35.7 | +32.1 | +29.6 |
| Significance | — | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ | — |

* Narrowing > 80% or complete occlusion of the left main, anterior descending, and/or circumflex coronary artery.
† With 50–80% narrowing of the left main, anterior descending, and/or circumflex coronary artery.
‡ Total of the control studies + postangiographic determinations.
§ Control values before contrast injection are the average of two studies.
** Based on the control values of the individuals observed at that time.
two of three patients after 7 min. Only one individual (patient 4) had a blood flow lower than the control level at any time after contrast injection.

The findings in the three patients who had sham injections of normal saline solution are shown in figure 2. There was essentially no change in myocardial blood flow at 1 and 3 min following saline injection. The same individuals were then given 7-ml injections of contrast material. Blood flow increased at 1 and 3 min following contrast injection to the same extent in these patients as was seen in the entire group.

Myocardial blood flow responses in patients with obstructive disease of the left coronary artery system are compared to those with normal vessels in figure 3. The average control flow was lower in patients with coronary obstructive disease ($61.1 \pm 2.1$ ml/min/100 g, mean $\pm$ SEM) than in those with normal arteries ($72.7 \pm 5.4$ ml/min/100 g) but the difference was not significant ($0.1 > P > 0.05$). Myocardial flow increased equally in the two groups after contrast injection with no significant difference at 1 or 3 min ($0.1 > P > 0.05$ and $P > 0.1$).

Systemic arterial pressure and pulse rate were unchanged between the control and test measurements. Characteristically there was either no alteration or a transient decrease in pulse rate and blood pressure immediately following contrast injection which persisted only a few seconds and had disappeared by the time of the 1-min flow study. Since coronary blood flow increased with no change in coronary perfusion pressure, coronary vascular resistance, the quotient of pressure over flow, must have decreased in proportion to the increase in flow.

Discussion

These studies demonstrate a consistent and substantial increase in myocardial blood flow following selective coronary angiography in patients with and without coronary heart disease. Earlier studies using flowmeters or rotameters in open-chest dogs found similar
increases in coronary blood flow after contrast-material injection, with elevations up to 150% over control levels. These technics monitoring beat-by-beat blood flow demonstrated an initial decrease in flow lasting a few seconds and corresponding to the time contrast material was in the artery. This was followed by a period of increased flow lasting 1–4 min. Carson, Weber, and Wilson first measured myocardial blood flow in intact animals before and after selective coronary angiography using the 133Xe washout method. They demonstrated an increase in blood flow of the same magnitude as in our group of patients, but of shorter duration, similar to the previous studies in dogs. The early decrease in blood flow found with flowmeters was not detected by either their study or ours, since the inert-gas technic provides average flow over a period of 20–60 sec rather than instantaneous flow.

The basis for the increase in blood flow appears to be the marked hyperosmolarity of radiocontrast materials. The osmolarity of methylglucamine diatrizoate (1648 mosm/liter) is five and one half times that of blood serum, and other contrast materials are of equal or greater hypertonicity. Previous studies have shown an increased cardiac output, decreased systemic pressure, and decreased systemic vascular resistance following systemic injection of a variety of contrast agents. Injections of other hypertonic materials, such as mannitol or hypertonic saline, have evoked similar responses. Mechanisms proposed for these responses have been expansion of the blood volume due to transfer of water from the tissue to the vascular space, a decrease in vascular tone mediated neurologically in part, and a further decrease in vascular resistance due to a direct effect of the hypertonic material on arterioles.

Similar mechanisms are probably operative in the coronary vascular bed following selective injection of contrast material. Increased coronary flow and decreased coronary vascular resistance have been demonstrated with a variety of angiographic contrast materials and differing technics of flow measurement. Friesinger et al. and Carson, Weber, and Wilson have shown similar hemodynamic responses in dogs following coronary injection of hypertonic materials other than radiocontrast agents. Lehan et al. found a massive transfer of water from tissue to capillaries immediately after contrast injection, indicated by a 35–50% fall in coronary hematocrit. This was followed by coronary vasodilatation and increased flow, a sequence similar to that in the systemic circulation. The rapid onset of increased flow, the consistent relationship to hypertonicity of the material injected, and the profound local fluid shifts have all pointed to a direct effect of contrast material on the vascular wall. Whether this is due to a reduction in vascular smooth muscle tone, or loss of fluid in the vessel wall with increased lumen size, has not been determined.

Reactive hyperemia might be anticipated following contrast injection due to temporary interruption of myocardial oxygenation and perhaps accentuated by the high viscosity and slow passage of contrast through the coronary circulation. However, Griggs et al. found that the rise in coronary flow following contrast injection in dogs was greater than that attributable to reactive hyperemia. Further, they found the large increase in coronary flow was paralleled by a rise in coronary sinus blood oxygen, with no change in myocardial oxygen consumption. This would seem to exclude reactive hyperemia as a major determinant of the increase in flow. Their studies of coronary sinus blood oxygen saturation in five patients having selective coronary arteriography suggested the same was true in humans.

A reflex decrease in vascular resistance which can be prevented by ganglionic blockade has been demonstrated following systemic angiography. However, Marshall and Shepherd found that increases in femoral artery flow following hypertonic injections in dogs were unchanged after denervation of the leg. Whether coronary injection of contrast material might activate a coronary chemoreflex or central circulatory reflexes, or would act more as an isolated vascular bed similar to the leg, is not known. Pharmacologic interventions to

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determine the possible role of autonomic influences on myocardial blood flow were not feasible in our patients. However, from the above data it appears that vasodilatation due to a direct action of contrast material on the vascular wall is the primary mechanism for the changes in coronary vascular resistance and blood flow.

Previous studies using the \(^{133}\)Xe technic and other methods have shown that myocardial blood flow is normal at rest in patients with coronary artery disease.\(^{12, 15-17, 23-25}\) Further investigations using a variety of stresses designed to increase coronary flow, including exercise, isoproterenol and epinephrine infusion, and pacing-induced tachycardia, have usually demonstrated no difference between the responses of normal individuals and those with coronary stenosis.\(^{15-17, 24, 25}\) Knöebel et al. did find a correlation between the severity of coronary artery disease and the response of myocardial blood flow to increased myocardial oxygen demand induced by right atrial pacing or isoproterenol infusion.\(^{26}\) Measuring myocardial blood flow by the rubidium clearance technic, they demonstrated that patients with more severe coronary disease were unable to increase myocardial flow to the same extent as normal volunteers or patients with less severe coronary disease using either form of stress. In our studies the increase in myocardial flow in response to a completely different challenge from those above was the same in patients with coronary narrowing as in normal subjects, and was unrelated to the degree of narrowing. Indeed, it seemed remarkable that even individuals with extensive severe obstructive disease (patients 9, 11, 16, 17, 21, and 22) were capable of appreciable increases in coronary flow after contrast injection. This suggests, as Rowe has proposed, that even in diseased coronary vessels the site of vascular resistance still lies peripherally in the arterioles rather than in the areas narrowed by atherosclerosis.\(^{22}\) Such vessels might still have a considerable capacity for increased flow, as indicated in the above studies. Rowe has expressed the need for a method for determining maximal coronary blood flow to more critically evaluate the significance of obstructing coronary artery disease.\(^{22}\)

Two implications of these findings are apparent. The first concerns the potential protective effect of increased blood flow on myocardial oxygenation during coronary angiography. Radiographic contrast material is very viscous, markedly hypertonic, nonoxygenated, and not a desirable medium for perfusing the coronary arteries. The anticipated adverse effects of the contrast material may well be counterbalanced by the increase in myocardial blood flow and tissue perfusion resulting promptly after contrast injection and persisting for several minutes.

Second, any interpretation of changes in myocardial blood flow resulting from pharmacologic or other interventions must consider the possible influence of contrast material on the results. Contrast material is commonly used when positioning the catheter in the coronary artery and in verifying the position subsequently. It is apparent that this alone may alter coronary blood flow appreciably and that the effect may persist for at least 7 min.

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