Acute Effect of Intravenous Dipyridamole on Regional Coronary Hemodynamics and Metabolism

ROBERT L. FELDMAN, M.D., WILMER W. NICHOLS, PH.D., CARL J. PEPINE, M.D., AND C. RICHARD CONTI, M.D.

SUMMARY The acute coronary hemodynamic and metabolic effects of intravenous dipyridamole were studied in 13 patients. Total left ventricular (LV) oxygen delivery and lactate extraction were assessed from the coronary sinus and great cardiac vein. Perfusion of LV regions was classified as potentially "normal" or "abnormal," based on coronary angiographic findings.

Intravenous dipyridamole bolus (20 mg) increased LV oxygen delivery in both normal and abnormal regions, with increases ranging from 10 to 100%. After injection of dipyridamole, total coronary flow increased 51% (p < 0.05). Fifteen minutes after injection, total coronary flow increased 75% (p < 0.05). Mean regional LV oxygen delivery and lactate extraction were not significantly decreased in either normal or abnormal regions. Lack of lactate production occurred more often after dipyridamole injections.

These results suggest that during dipyridamole-induced hyperemia, regional coronary flow and metabolic responses depend upon the status of the arteries supplying the LV region. Regional differences in flow and metabolism occur independent of major changes in heart rate and aortic and LV pressures.

EXPERIMENTS in anesthetized dogs with a normal coronary circulation showed that i.v. dipyridamole has a more pronounced effect on the coronary circulation than on the circulation of other organs. Both coronary venous oxygen and coronary blood flow were increased, but whether the increase in coronary blood flow is potentially useful has not been clearly defined.

Results from studies of canine models of acute and chronic ischemic heart disease have conflicted concerning effects of dipyridamole on regional ventricular (LV) blood flow. When one left coronary branch was acutely occluded or narrowed, flow supplied by the normal coronary branch uniformly increased. However, flow and oxygen delivery responses varied in regions supplied by a narrowed branch. Becker observed that dipyridamole increased flow to the region perfused by an occluded branch when other branches were normal, but decreased flow if other branches were narrowed. Several investigators found that when one branch was occluded, dipyridamole decreased the predicted size of myocardial infarction associated with increased ischemic region flow. In contrast, Marshall and Parratt used an acute model similar to Becker's, with one totally occluded branch and the others normal, and observed that dipyridamole decreased flow to the region perfused by the occluded branch. Nakamura et al. and Flameng et al. used a different model, which had decreased flow to the inferior region, and found that dipyridamole caused nonhomogeneous transmural flow distribution and, in some experiments, redistributed flow away from the inferior region. Further, in models of chronic coronary occlusion, dipyridamole alone or dipyridamole plus rapid pacing caused nonhomogeneous flow distribution and in some experiments decreased flow in the region supplied by collaterals. This reported variability of dipyridamole's effect on ischemic myocardium did not relate to drug-induced changes in heart rate, coronary perfusion pressure or LV filling pressure.

Results of clinical trials using either oral or i.v.
Dipyridamole have also conflicted. Uncontrolled trials often suggested potentially beneficial responses in certain patients with chronic angina pectoris or acute myocardial infarction.\textsuperscript{12-13} Preliminary results also showed that dipyridamole may be useful for patients with smooth muscle spasm resulting in either asthma or gall bladder and renal colic.\textsuperscript{14} In a controlled trial in patients with ischemic heart disease, however, dipyridamole induced no consistently detectable beneficial response relative to findings thought secondary to myocardial ischemia.\textsuperscript{15}

Recently, investigators have suggested that dipyridamole-induced coronary vasodilatation may be useful in assessing the physiologic significance of coronary artery narrowings.\textsuperscript{16-18} Noninvasive myocardial imaging techniques showed that dipyridamole-induced coronary vasodilatation separated most LV regions supplied by angiographically normal coronary arteries from regions supplied by narrowed arteries. However, in patients these noninvasive imaging techniques show only relative changes in tracer uptake and have other limitations.\textsuperscript{19-20} Thus, the precise action of dipyridamole on the coronary circulation in patients with coronary disease needs to be more completely defined. Accordingly, we designed this study to further define regional coronary hemodynamic and metabolic responses to dipyridamole in patients with normal and narrowed coronary arteries.

**Methods**

**Patients**

The subjects were 13 men (mean age 50 years, range 35–65 years) undergoing cardiac catheterization to further define the cause of chest pain. Committees for protection of human subjects approved the study and each patient gave informed consent. ECG evidence (≥ 1.0 mm of ST-segment depression) for transient myocardial ischemia was evoked by stress testing in 11 patients. In the other two, the ECG response to stress was normal. Eleven patients were taking propranolol (320 ± 43 mg/day, mean ± SEM).

**Cardiac Catheterization**

Patients were in a fasting, postabsorptive state, without premedication, when we performed catheterization. Nitroglycerin was withheld for at least 8 hours before study. A \#8F Sones catheter was advanced through the right brachial artery to the left ventricle, and pressure recordings were made as the catheter was withdrawn to the aorta. Coronary angiography was performed as described elsewhere.\textsuperscript{21-23} After aortic pressure, heart rate and any ECG changes related to coronary angiography returned to baseline values (±10%), the Sones catheter was replaced by a catheter containing two equisensitive pressure micro-manometers (Millar). This catheter was positioned with one manometer in the left ventricle and the other in the ascending aorta. A \#18 Teflon catheter was inserted percutaneously into the left brachial artery to sample arterial blood, and in patient 10 this catheter was used to estimate aortic pressure (Statham P23Db transducer). Mean aortic pressure was obtained by electronic filtration. A \#8F multithermistor catheter was advanced from a right antecubital vein and positioned in the coronary sinus (CS). Our design and use of this special catheter to measure regional LV flow has been described in detail.\textsuperscript{24-25} Briefly, the distal external thermistor was advanced to the great cardiac vein (GCV). The proximal external thermistor was positioned in the sinus between the ostium and termination of middle cardiac veins. A \#5F NIH catheter was positioned near the CS thermistor of the regional flow catheter for blood sampling. During each measurement period after a flow recording was made, this sampling catheter was advanced under fluoroscopic control to the GCV thermistor for GCV sampling and then withdrawn to the CS thermistor for CS sampling. In each patient brief regional flow runs done before and after placing this catheter into the CS showed that this catheter did not alter temperature signals.

Arterial and regional coronary venous blood samples were obtained during each measurement period and analyzed in duplicate for lactate and oxygen content. Briefly, 2.5-ml blood samples from the brachial artery, GCV and CS were simultaneously obtained 15–30 seconds after each flow measurement. Blood samples were injected into preweighed tubes containing 2.5 ml of iced perchloric acid. Samples were weighed, corrected for total volume and assayed in duplicate by a fluoremetric enzymatic technique.\textsuperscript{26} Another set of samples was collected in 3-ml heparinized glass syringes. Samples were capped, placed in ice, and analyzed immediately in duplicate or triplicate for pH, PO\textsubscript{2} and PCO\textsubscript{2} (Model \#213, Instrumentation Laboratories). Standard limb and V\textsubscript{5} ECG leads were recorded during each measurement period. Leads showing the greatest ST-segment shifts during the previous stress-induced chest pain were continuously monitored. Signals were recorded on an oscilloscopic photographic recorder (Electronics for Medicine, DR12).

**Control Period**

After all catheters were positioned, ECG and aortic and LV pressures were monitored continuously. When monitoring showed that these variables were stable (±5%), recordings of temperature in the CS and GCV (CS flow [CSF] and GCV flow [GCVF] signals, respectively) were made at 10 and 25 mm/sec with pressure and ECG signals. Blood samples were obtained.

**Dipyridamole Period**

While aforementioned signals were being recorded at 10 mm/sec, 20 mg of dipyridamole* was injected into the right atrium over 10 seconds. Recording continued for 60–90 seconds after the injection was complete.

*Supplied by Dr. Wolf Michaelis, Boehringer Ingelheim, Ltd., as Persantine.
completed. Then aortic and LV pressures and the ECG were continuously recorded at 2.5 mm/sec until 20 minutes after dipyridamole injection. Recordings (10 and 25 mm/sec) were made of ECG, aortic and LV pressures and CSF and GCVF signals at 5, 10, 15 and 20 minutes after dipyridamole administration. Blood was drawn at 5, 10 and 20 minutes for dipyridamole concentration* (Bio Science Laboratories),27 lactate concentration and oxygen content. Before each measurement, positions of the catheters were verified by comparison with a videotrack image obtained immediately before dipyridamole administration. Renografin-76, 2–3 ml, was also frequently injected into the CS through the multithermistor or the NIH catheter to confirm thermistor and sampling sites relative to coronary vein branch positions.

At the conclusion of these studies, the Sones catheter was reinserted and left ventriculography was performed in the right anterior oblique projection. The ejection fraction in these patients averaged 55 ± 8%, and no patient had mitral insufficiency. No patient had elevated right atrial pressure or ventricular rhythm, which have been associated with right atrial–CS admixture in animal studies.28 No patient showed respiration-related fluctuations in the CS temperature signal recorded at high gain, which occur with right atrial–CS admixture.29 To further check for the possibility of right atrial contamination of CSF and GCVF measurements, in five patients, at the end of the procedure after brachial artery repair, the NIH catheter was withdrawn from the CS and positioned in the lower right atrium near the CS os. Normal saline (24°C) was infused (50 ml/min) during five respiratory cycles while CS and GCVF thermistor temperature signals were recorded. The absence of a decrease in CS temperature confirmed that atrial–CS admixture was not present.

Measurements and Calculations

During each period, phasic and mean aortic pressure, LV end-diastolic pressure, heart rate and ST-segment shifts were measured from at least 10 consecutive beats and averaged. CSF and GCVF were calculated as described elsewhere.22–25 Multiple flow calculations were made at 10–15-second intervals and results averaged from respective temperature deflections. Total LV blood flow was taken as CSF.26–29 Flow from the anterior LV region, supplied predominantly by the left anterior descending coronary artery, was taken as GCVF.24, 80 By subtracting GCVF from CSF, an index of flow from other LV regions was obtained. Flow from other regions should be predominantly supplied by circumflex and right coronary arteries with a variable contribution from anterior descending branches.80 This region was arbitrarily referred to as inferior. To estimate total change in regional coronary flow we constructed coronary flow time (0 [control], 1, 5, 10, 15 and 20 minutes after dipyridamole) plots during dipyridamole-induced hyperemia for each region. Total area, inscribed by these flow-time plots between control and 20 minutes, was obtained by planimetric integration. The amount of flow that would have occurred under basal conditions (control flow × 20 minutes) was subtracted from this total area. The remaining portion was taken to represent dipyridamole-induced hyperemia.28 Redistribution of flow away from a region (e.g., "coronary steal") was arbitrarily defined as ≥ 25% decrease in regional flow compared with control flow. This value was used because it represents 2½ times the usual maximal variation in flow recorded in our laboratory when pressure and heart rate are stable.

Inferior region oxygen and lactate concentrations were calculated as: CS concentration = GCV concentration (GCVF/CSF) + inferior concentration ([CSF – GCVF]/CSF). Oxygen content was calculated by multiplying oxygen saturation, hemoglobin concentration and 1.34. Regional oxygen delivery (ml/min) was determined by multiplying the difference between arterial and regional coronary venous oxygen content by regional flow. Regional lactate extraction (%) was calculated as: arterial lactate – regional coronary venous lactate/arterial lactate × 100%. A value ≥ 0% was considered normal.84

Coronary Angiographic Analysis

The degree of coronary artery diameter reduction was evaluated by techniques described elsewhere.21, 22 When the major artery supplying a LV region had a diameter narrowed ≥ 50%, perfusion of the region was considered potentially abnormal. When no narrowing ≥ 50% was present in the major artery supplying a region, perfusion of the region was considered potentially normal. Experiments in dogs have shown that long and multiple coronary narrowings can alter coronary hemodynamics similar to short or single higher degree diameter narrowings.85–87 Therefore, patients were not included if they had long (e.g., > 5 mm) or multiple 30–40% narrowings in one vessel. Angiographic classification was made by one of us not participating in that particular case study and without knowledge of pressure, flow or metabolic responses in that case.

Statistical Analysis

The mean ± SEM were determined for each variable during each period. An analysis of variance was performed for the factors group (e.g., normal region vs abnormal region), time (0, [control], 1, 5, 10, 15 and 20 minutes after dipyridamole) and a group by time interaction. If significant, the analysis of variance was followed by comparison of least-squares means. An unpaired t test was used for group (normal vs abnormal) total dipyridamole-induced hyperemic responses in anterior and inferior regions. Group lactate extraction data were compared using the Fisher exact probability test. A p value < 0.05 was considered statistically significant.

*Free and total dipyridamole concentrations were determined by an enzymatic-fluorometric technique. Samples from all 13 patients were frozen and analyzed at the same time to avoid variation.
Results

Possible Right Atrial Admixture and Potential Changes in Intravascular Volume

No effect on either the CS or GCV thermistor deflection was noted during injection of indicator into the low right atrium. To measure regional venous flow repeatedly, it was necessary to infuse approximately 325 ml of saline over the 25-30-minute study period. Approximately 125 ml of blood were removed during this period for blood samples.

Dipyridamole Blood Concentration

Free dipyridamole blood concentration (fig. 1) was 2.1 ± 0.2, 1.2 ± 0.1 and 1.2 ± 0.2 µg/ml at 5, 10 and 20 minutes, respectively, after dipyridamole. Total dipyridamole blood concentration (fig. 1) was 2.3 ± 0.3, 1.5 ± 0.1 and 1.4 ± 0.2 µg/ml at 5, 10 and 20 minutes, respectively, after dipyridamole. The 5-minute values for both free and total drug were higher (p < 0.05) than the 10- or 20-minute value. The 10- and 20-minute values were not significantly different.

Coronary Angiographic Findings

Table 1 summarizes coronary angiographic findings. Patients 1 and 2 had normal angiograms, and patient 3 had no coronary narrowing ≥ 50%. Thus, of the anterior and inferior regions, six regions were considered normal. Patients 4–13 had ≥ 50% narrowing in at least one major artery. Of these 20 possible LV regions, eight were considered normal and 12 abnormal. Thus, a total of 14 normal and 12 abnormal regions were examined. Seven of the normal regions were anterior and seven were inferior. Of the 12 abnormal regions, six were anterior and six inferior.

### Table 1. Coronary Angiographic Results

<table>
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<tr>
<th>Pt</th>
<th>LAD</th>
<th>CX</th>
<th>RCA</th>
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<tr>
<td>13</td>
<td>0</td>
<td>80</td>
<td>90</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

*Small circumflex artery.

Abbreviations: LAD = left anterior descending artery; CX = circumflex artery; RCA = right coronary artery.

Clinical and Electrocardiographic Findings

Three patients reported chest pain after dipyridamole: patient 13 at 1 minute, patient 3 at 7 minutes and patient 6 at 15 minutes. In patient 13 the pain was considered very mild, disappeared spontaneously within 5 minutes and no intervention was taken. In the other two patients, chest pain was considered moderate to severe. Aminophylline (25 mg/min; total dose, 200 mg), which specifically blocks the vasodilator action of dipyridamole,** was administered at 10 minutes to patient 3, who thus terminated the study early, and to patient 6 at 20 minutes, after completion of the study. These three patients had no consistent change in aortic systolic and LV end-diastolic pressures; these pressure changes averaged 4 mm Hg and 1 mm Hg, respectively. The increase in heart rate averaged 11 beats/min during chest pain. Neither these three patients nor the 10 patients who did not report chest pain had significant ST-segment shifts. No other problems or adverse effects occurred related to either the procedures or dipyridamole administration.

Systemic and Left Ventricular Hemodynamic Findings

The mean heart rate (66 ± 3 beats/min) increased minimally after dipyridamole and remained increased throughout the 20-minute study period (71 ± 3, 72 ± 3, 71 ± 3, 73 ± 3 and 70 ± 3 beats/min at 1, 5, 10, 15 and 20 minutes, respectively (all p < 0.05). Systolic aortic pressure (131 ± 4 mm Hg) decreased after dipyridamole to 126 ± 5, 127 ± 5 and 126 ± 5 mm Hg at 1, 5 and 10 minutes, respectively (all p < 0.05). Systolic pressure increased, approximating control values at 15 and 20 minutes (128 ± 6 and 130 ± 6 mm Hg, respectively; p = NS). Mean aortic
pressure (99 ± 3 mm Hg) decreased after dipyridamole to 96 ± 4, 97 ± 4 and 98 ± 4 mm Hg at 1, 5 and 10 minutes, respectively (all p < 0.05), but returned to control values at 15 and 20 minutes (99 ± 4 and 100 ± 4 mm Hg, respectively). The mean LV end-diastolic pressure (16 ± 1 mm Hg) decreased after dipyridamole and remained decreased for 20 minutes (15 ± 1, 15 ± 1, 14 ± 1, 14 ± 1 and 14 ± 1 mm Hg at 1, 5, 10, 15 and 20 minutes, respectively [all p < 0.05]).

Coronary Hemodynamic Findings

Total LV blood flow (103 ± 7 ml/min), reflected in CSF, increased between 12 and 60 seconds (34 ± 4 seconds) after injection of dipyridamole (fig. 2). A CSF increase to 90% of the peak response was observed in seven patients by 1 minute, in four additional patients by 5 minutes and in the remaining two by 10 minutes. Coronary sinus flow increased 51% at 1 minute, and the increase persisted at 5 (53%), 10 (52%) and 15 minutes (39%) (all p < 0.05 vs control; fig. 3). Coronary sinus flow measurements 1–15 minutes after dipyridamole were all similar (p = NS). Twenty minutes after dipyridamole, CSF (115 ± 6 ml/min) decreased and was not significantly different from control values. Total coronary resistance was 1.00 ± 0.07 mm Hg/ml/min during the control period and decreased to 0.63 ± 0.05 mm Hg/ml/min 1 minute after dipyridamole (p < 0.05). Total resistance remained decreased to 0.67 ± 0.05, 0.66 ± 0.05 and 0.70 ± 0.05 mm Hg/ml/min at 5, 10 and 15 minutes, respectively, after dipyridamole (all p < 0.05). Values for total coronary resistance were similar 1–15 minutes after dipyridamole (p = NS). At 20 minutes after dipyridamole, total resistance was not significantly different from control (0.89 ± 0.06 mm Hg/ml/min; p = NS).

During the control period, coronary flows (fig. 3) in both normal and abnormal regions were similar (51 ± 6 and 52 ± 5 ml/min, respectively; p = NS). One minute after dipyridamole, flow increased in normal regions (75%). This flow increase persisted at 5 (80%), 10 (88%) and 15 (71%) minutes (all p < 0.05). Normal region values at 1, 5, 10 and 15 minutes after dipyridamole were similar (p = NS). By 20 minutes, flow decreased to 60 ± 7 ml/min, a value similar to control (p = NS). By contrast, flow to abnormal regions was not significantly increased at any time after dipyridamole. From 1–15 minutes after dipyridamole, normal and abnormal region flow measurements differed (p < 0.05).

Individual patient responses, however, varied widely (table 2, fig. 4). Coronary flow responses considered with respect to anterior and inferior LV regions, as well as normal and abnormal angiographically defined regions, are summarized in table 2. Flow in the anterior LV region was increased 1–15 minutes after dipyridamole, whether the region was considered normal or abnormal (both p < 0.05). In

![Figure 2](image_url)

**Figure 2.** Example (patient 12) of the prompt increase in coronary flow after dipyridamole administration (arrow). Coronary sinus flow (CSF) (126 ml/min) and great cardiac vein flow (GCVF) (76 ml/min) increased at approximately 12 seconds after dipyridamole. By 40 seconds CSF (190 ml/min) and GCVF (107 ml/min) had increased markedly. Accompanying these large coronary flow changes, there was only a small decrease in systolic pressure and no change in left ventricular end-diastolic pressure or heart rate.

![Figure 3](image_url)

**Figure 3.** Total and regional coronary venous flow during the control period and serially 1, 5, 10, 15 and 20 minutes after dipyridamole. Total coronary flow increased largely because of the increase in normal region flow.
### Table 2. Summary of Regional Coronary Flow Responses to Dipyridamole

<table>
<thead>
<tr>
<th></th>
<th>Anterior left ventricle</th>
<th>Inferior left ventricle</th>
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<tbody>
<tr>
<td></td>
<td>&quot;Normal&quot; regions</td>
<td>&quot;Abnormal&quot; regions</td>
</tr>
<tr>
<td></td>
<td>Pt</td>
<td>1   2   3   4   8   9   13</td>
</tr>
<tr>
<td>Control</td>
<td>32</td>
<td>66</td>
</tr>
<tr>
<td>Minutes after dip</td>
<td>1</td>
<td>38</td>
</tr>
<tr>
<td>dipyridamole (ml/min)</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>10</td>
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<td>—</td>
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<tr>
<td></td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Total hyperemic flow (ml)</td>
<td>400</td>
<td>880</td>
</tr>
</tbody>
</table>

|                      |                      |                      |
| Total hyperemic flow (ml) | 600 | 220 | 1400 | 800 | 340 | 240 | 600 ± 185 | 280 | 200 | 180 | -440 | -160 | -440 | -63 ± 134 |

Dash indicates data not available.

*Study terminated because of patient's chest pain.
contrast, flow in the inferior LV region was increased only in regions considered normal.

Total dipyridamole-induced hyperemia could not be calculated in patient 3 because of incomplete data sampling. In patients 1, 7 and 8 the missing flow value was assumed to represent the average of values obtained just before and after the missing data. Total hyperemic flow to normal regions was greater than that to abnormal regions comparing either anterior (793 ± 103 vs 407 ± 92 ml, respectively; \( p < 0.05 \)) or inferior (600 ± 185 vs -63 ± 134 ml, respectively; \( p < 0.05 \)) LV regions.

Regional coronary resistances during the control period were similar in both normal and abnormal regions (2.28 ± 0.24 and 2.14 ± 0.20 mm Hg/ml/min, respectively; \( p = NS \)). After dipyridamole, however, resistance decreased in normal regions to 1.27 ± 0.21, 1.26 ± 0.15, 1.18 ± 0.12 and 1.30 ± 0.17 mm Hg/ml/min at 1, 5, 10 and 15 minutes (all \( p < 0.05 \)) and returned toward control by 20 minutes (2.02 ± 0.31 mm Hg/ml/min, \( p = NS \)). Normal region values 1-15 minutes after dipyridamole were similar (\( p = NS \)). By contrast, resistance in abnormal regions was unchanged after dipyridamole to 1.78 ± 0.24, 1.75 ± 0.24, 1.73 ± 0.27, 1.84 ± 0.22 and 2.10 ± 0.27 mm Hg/ml/min at 1, 5, 10, 15 and 20 minutes, respectively (all \( p = NS \)). From 1-15 minutes after dipyridamole, normal and abnormal region resistance differed (\( p < 0.05 \)).

Myocardial Metabolic Findings

After dipyridamole, coronary sinus \( \text{PO}_2 \) (23 ± 2 mm Hg) increased to 31 ± 2, 29 ± 2 and 28 ± 2 mm Hg at 5, 10 and 20 minutes, respectively (all \( p < 0.05 \)). Total myocardial oxygen uptake (fig. 5) was 10.8 ± 0.8 ml/min during the control period and was not significantly changed after dipyridamole. Lactate production, using CS lactate values, was observed in patient 4 during the control period. Five minutes after administration of dipyridamole, lactate production persisted in patient 4 and also occurred in patient 10. At 10 minutes patients 9, 10 and 13 and at 20 minutes patients 8, 9 and 10 produced lactate. Thus, lactate production was observed in four patients after dipyridamole, compared with only one patient before (\( p = NS \)).

Regional coronary venous \( \text{PO}_2 \) usually increased after dipyridamole in both normal and abnormal regions, from 22 ± 1 and 24 ± 1 mm Hg during control to 30 ± 2 and 32 ± 3 mm Hg at 5 minutes, 30 ± 2 and 27 ± 1 mm Hg at 10 minutes, and 28 ± 2 and 28 ± 2 mm Hg at 20 minutes after dipyridamole, respectively (all \( p < 0.05 \)). Regional venous \( \text{PO}_2 \) values were similar in normal and abnormal regions at all times (\( p = NS \)). During the control period, myocardial oxygen uptake was similar in both normal and abnormal regions (5.7 ± 0.7 and 5.0 ± 0.5 ml/min, respectively; \( p = NS \)). After dipyridamole, however, oxygen uptake in normal regions increased slightly and in abnormal regions decreased slightly, but these changes were not significant (fig. 5). Values for oxygen uptake in both normal and abnormal regions were not significantly different at any time after dipyridamole.

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**FIGURE 4.** Individual data and mean regional coronary flow responses (means placed on the horizontal and vertical axis) comparing control flow values and values obtained 5 minutes after dipyridamole. Although mean values for the normal and abnormal regions differed 5 minutes after dipyridamole (\( p < 0.05 \)), the changes in individual flow values were variable.

**FIGURE 5.** Total and regional myocardial oxygen uptake during the control period and at 5, 10 and 20 minutes after dipyridamole. No significant change in total or regional oxygen uptake occurred.
Myocardial lactate production (table 3) did not occur in normal regions but did occur in three abnormal regions (in patients 4, 6 and 9) during the control period \((p = NS)\). After dipyridamole, lactate production was not observed in normal regions at 5 and 10 minutes but was observed at 20 minutes in patient 8 \((p = NS)\). After dipyridamole, lactate production was observed in five abnormal regions at 5, 10 and 20 minutes (patients 4, 9 and 13 and in both regions in patient 10 at 5 minutes; patients 5, 9, 10, 12 and 13 at 10 minutes; and patients 4, 8 and 9 and in both regions in patient 10 at 20 minutes) \((all p = NS)\). Lactate production, however, was found more often 5 and 10 minutes after dipyridamole in abnormal regions compared with normal regions \((both p < 0.05)\).

**Evidence for Dipyridamole-induced Redistribution of Coronary Flow**

Compared with coronary flow during the control period, inferior regional flow in patients 7, 9, 10 and 13 decreased \(\geq 25\%\) during at least one dipyridamole period. In patient 7 this apparent coronary flow reduction involved an angiographically normal region, occurred only at 20 minutes (table 2) and was not associated with lactate production (table 3). In contrast, the evidence for a physiologically significant redistribution of coronary flow was stronger in patients 9, 10 and 13, who had angiographically abnormal inferior regions. A decrease in regional coronary flow \(\geq 25\%\) occurred at 1, 5, 10 and 15 minutes in patient 9, at 10 and 15 minutes in patient 10, and at 1, 5, 10 and 15 minutes in patient 13 (table 2). At 20 minutes, flow values returned toward control levels in these three patients. There three patients also had lactate production in inferior regions (table 3) coincident with these flow measurements. During these periods when regional coronary flow and sometimes abnormal lactate metabolism suggested physiologically important redistribution of coronary flow, heart rate usually increased slightly and mean aortic pressure changed variably (table 4). These changes in heart rate and mean aortic pressure were similar to observations in

### Table 3. Regional Lactate Metabolism: Percentage of Lactate Extraction

<table>
<thead>
<tr>
<th></th>
<th>Anterior left ventricle</th>
<th>Inferior left ventricle</th>
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<tr>
<td></td>
<td>&quot;Normal&quot; regions</td>
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<td>Control</td>
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<tr>
<td>Minutes after</td>
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<td>dipyridamole</td>
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<td>Dash indicates data not available.</td>
<td>*Study terminated because of patient's chest pain.</td>
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the other patients whose flow measurements did not suggest a dipyridamole-induced redistribution of coronary flow.

**Discussion**

Results of this study show that dipyridamole alters blood flow to certain LV regions. In these patients, before dipyridamole, blood flow and oxygen and lactate metabolism were similar in LV regions supplied by coronary arteries that appeared to be normal or abnormal by coronary angiography. Total LV blood flow, reflected in CSF, began to increase 34 seconds (mean) after the i.v. bolus of dipyridamole. After 1 minute, regional coronary flow and resistance values were different when regions supplied by normal and abnormal coronary arteries were identified. This difference in regional coronary flow and resistance responses persisted for 15 minutes. Differences in regional lactate metabolism were detected at 5 and 10 minutes. Total and regional myocardial oxygen uptake did not change. Coronary hemodynamic and metabolic changes observed after dipyridamole were no longer apparent by 20 minutes. These coronary hemodynamic and metabolic changes were accompanied by only very minimal increases in heart rate and decreases in aortic and LV pressures.

Intravenous dipyridamole-induced coronary vaso-dilatation was used in patients by Albro et al.\(^\text{18}\) to evaluate the functional significance of coronary narrowings. Myocardial imaging with thallium-201 showed similar regional uptake after both maximal treadmill exercise and dipyridamole administration. They observed much greater increases in heart rate (38%) and decreases in mean blood pressure (6%) than we observed. Differences in blood pressure were probably secondary to enhanced peripheral blood pooling due to changes from supine to standing positions in the study by Albro et al.\(^\text{18}\) The greater decrease in pressure would be expected to evoke baroreceptor-mediated increases in heart rate. Our patients, however, remained supine, and most were receiving propranolol. These factors would be expected to attenuate possible reflexly mediated changes in heart rate. Drug administration also differed in the two studies. Albro and co-workers\(^\text{18}\) infused i.v. dipyridamole at 0.142 mg/kg/min for 4 minutes, or a total dose of 0.568 mg/kg. We administered a fixed dose of 20 mg by rapid i.v. bolus or approximately 0.29 mg/kg.

Chest pain occurred in three of our 13 patients, but none had ST-segment shifts considered ischemic in origin. The absence of ST-segment shifts was surprising, considering that 11 of our patients (including two of the three with pain after dipyridamole) had ischemic ST responses during stress testing. Albro et al.\(^\text{18}\) also noted that angina was less frequent, less severe and less frequently accompanied by ST-segment shifts after dipyridamole than after exercise testing. Other workers\(^\text{98, 40}\) however, using larger doses of i.v. dipyridamole (i.e., 80–100 mg over approximately 20 minutes\(^\text{98}\) or 0.6 mg/kg over 5 minutes\(^\text{40}\) noted adverse effects including chest pain accompanied by reversible ST elevation or ventricular tachycardia and several cases of myocardial infarction. Although no permanent or serious adverse effects were observed in our study and others,\(^\text{18, 40}\) caution seems appropriate when administering this agent in large doses to patients with suspected coronary artery disease.

In patients described here, dipyridamole appeared to have a proportionately greater effect on coronary flow than on some hemodynamic determinants of myocardial oxygen consumption. The minimal increase in heart rate was probably offset by reduced LV systolic pressure, because neither total nor regional myocardial oxygen uptake changed in the entire group. In this regard, dipyridamole may be useful in studying the relationship between coronary flow and ventricular function in man. Some animal experiments, using isolated heart models, showed evidence for increased function during periods of increased coronary flow.\(^\text{41, 42}\) We are currently conducting a more detailed investigation into the effects of dipyridamole-induced increased coronary flow on LV hemodynamic function in man.

After dipyridamole was administered, regional lactate metabolism was altered in several patients. In regions supplied by abnormal coronary arteries, lactate production occurred during the control period in three patients and after dipyridamole in seven patients. In angiographically normal regions, lactate was not produced during the control period and after dipyridamole, it occurred only once. There was an association between lactate production and chest pain only in patient 13. These data suggest that in some angiographically abnormal regions, dipyridamole was detrimental to lactate metabolism. Lactate production is probably an early ischemic event, and lack of changes in LV end-diastolic pressure or significant ST-segment shifts and development of chest pain were not necessarily expected.\(^\text{44, 45}\)

Animal experiments have shown that in certain situations, some coronary vasodilators,\(^\text{44–46}\) including dipyridamole,\(^\text{5, 7, 11}\) cause redistribution of flow away from one region toward another. The region in which flow was reduced had been supplied by a coronary artery with a high degree of narrowing. This potentially deleterious “steal” phenomenon, to our knowledge, has not previously been documented in humans, but could be inferred from adverse effects after large parenteral doses of dipyridamole.\(^\text{59, 40}\) In patients 9, 10 and 13 we found reasonable evidence that flow was redistributed away from an LV region (fig. 6). In these patients, inferior regional flow decreased after dipyridamole and returned toward control values by 20 minutes after dipyridamole. In two of these patients, coronary arteries supplying the anterior region were angiographically normal. In the third patient the anterior descending was narrowed 50% (table 1), but the degree of narrowing in arteries supplying the inferior region was greater. In addition, in each of these three patients, the degree of narrowing in arteries supplying respective inferior regions was ≥ 80% and at least one artery was narrowed.
≥ 90%. There appeared to be an association between symptoms and decreased regional coronary flow only in patient 13. However, lactate production after dipyridamole was observed in each of these three regions in these patients. This metabolic evidence for ischemia was temporally associated with dipyridamole-induced redistribution of flow away from the inferior region. This observation supports the concept that dipyridamole-induced redistribution of flow could be physiologically important. Similarly, after dipyridamole, a large decrease in inferior regional myocardial oxygen uptake was observed in these patients. The functional consequences of this metabolic change are unknown. Major changes in aortic and LV end-diastolic pressures, heart rate and ECG did not accompany dipyridamole-induced flow and metabolic changes. High-degree narrowing, as seen in patients 9, 10 and 13, however, did not cause dipyridamole-induced redistribution of regional coronary flow in other patients. Some patients may have developed redistribution of transmural (i.e., endocardial/epicardial) flow without change in total regional flow.

One potential limitation of this study was that the degree of change in coronary hemodynamic and metabolic data varied between regions defined by angiography as potentially normally or abnormally perfused. Thus, the technique separated group responses but not regional responses in individual patients or regions. In this regard, criteria used to divide the LV into potentially normally and abnormally perfused regions were based on quantitative coronary angiography. An independent technique to assess the angiographic results was not available. We chose ≥ 50% as the abnormal degree of diameter narrowing of coronary arteries because animal studies have shown that peak coronary flow responses during reactive hyperemia decrease with ∼50% narrowing.35,37 However, even in animal models, when the narrowing was short (∼1 mm), the flow limitation was only 10–15% when vessel diameter was narrowed 50 ± 10% and flow responses varied considerably.38

![Figure 6](https://example.com/figure6.png)

**Figure 6.** Example (patient 10) of the redistribution of regional coronary flow that can occur after dipyridamole. (A) Right and left coronary angiograms show multiple coronary narrowings (arrows). (B) Regional coronary flow responses. Anterior regional flow increased and inferior regional flow decreased after dipyridamole, accompanied by worsening of both anterior and inferior regional lactate metabolism. After dipyridamole, left ventricular systolic (average 11 mm Hg) and mean aortic (3 mm Hg) pressures decreased, left ventricular end-diastolic pressure was unchanged and heart rate increased by 5 beats/min. CSF = coronary sinus flow; GCVF = great cardiac vein flow.
Therefore, the variability in flow values found in this study was not surprising and could be explained by varied interpatient responsiveness and degrees of coronary narrowing and the potential for angiographic measurements to be imprecise.

Another potential limitation is that we divided the LV into only two regions, so our results could reflect only average changes occurring within relatively large myocardial areas. Heterogeneity within certain anterior or inferior LV regions relative to flow or metabolic findings would probably be responsible for some of the variability in data when trying to separate potentially normal and abnormal regions. Division of the LV into anterior and inferior regions with GCV and CS sampling deserves further comment. We recognize that the definition of the inferior region is questionable. Depending on the exact position of the coronary venous catheter in the CS, the CS thermistor and CS sampling may miss a portion of the posterior descending contribution. In addition, portions of the anterior region circulation may be sensed only by the proximal (CS) thermistor. The net gain in intravenous volume secondary to repeated blood flow measurements may have partially attenuated some hemodynamic changes related to dipyridamole, perhaps limiting the decrease in blood pressure due to dipyridamole-induced peripheral vasodilatation. Effects of concurrent propranolol, taken by 11 of our 13 patients, may have also altered responses to dipyridamole by both the coronary and systemic circulations. Dipyridamole could also have affected coronary venous drainage.

In conclusion, intravenously administered dipyridamole causes prompt coronary vasodilatation in man and results in increased flow, predominantly to regions supplied by coronary arteries without angiographically significant narrowing. Coincident with these changes in regional flow, myocardial metabolism is also altered. Regional lactate metabolism responses to dipyridamole differed in LV regions supplied by coronary arteries with and without significant narrowings. Total and regional myocardial oxygen uptake values were unchanged. These results further define the effect of dipyridamole on the human coronary circulation.

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