Failure of Dipyridamole (Persantin) in Reducing the Infarct Size Following Experimental Coronary Occlusion

Tan Watanabe, M.D., Fujio Shintani, M.D., Longtai Fu, M.D., Kazuo Kato, M.D., and Shintaro Koyama, M.D.

Summary
This study examined the systemic and coronary hemodynamic effects of dipyridamole on experimental myocardial infarcts. Electrograms were recorded from the left ventricular surface 15 min. after ligation of the left anterior descending coronary artery. Average ST segment elevation and number of sites with ST segment elevation greater than 2 mV., indices of the magnitude and extent of acute myocardial ischemic injury, were increased in 9 dogs following intravenous infusion of dipyridamole (0.01–0.05 mg./Kg./mm.) from 4.6 ± 0.3 (Mean value ± SEM) during control simple occlusion to 6.8 ± 0.9 mV. (p<0.025), and 6.2 ± 0.6 to 8.1 ± 1.2 (p<0.05), respectively. This was accompanied by significant decreases in mean blood pressure from 105 ± 5 to 79 ± 6 mm.Hg (p<0.025) and in mean value of coronary perfusion pressure index (Mean blood pressure × Heart rate × Diastolic duration in aortic pressure) from 4,100 ± 180 to 3,130 ± 210 mm.Hg sec./min. (p<0.01), respectively. Coronary blood flow measured by a flow probe applied around the root of the circumflex coronary artery was markedly increased from the mean value of 115 ± 6 during control occlusion to 284 ± 45 (arbitrary unit, p<0.01).

Thus, we concluded that dipyridamole does have deleterious effects on acute myocardial ischemic injury by reducing coronary perfusion pressure which importantly influence the blood supply to the ischemic zone of myocardium, in spite of augmented total coronary blood flow.

Additional Indexing Words:
Coronary blood flow Coronary perfusion pressure Epicardial mapping Coronary steal

It is clear that the balance between local myocardial oxygen demand and supply is an important determinant of the extent of ischemic injury or damage following an acute coronary artery occlusion.1)–4) Since the experimental studies have shown that intravenous administration of dipyridamole (Persantin) resulted in a marked and sustained increase in coronary blood flow,5)–9) this drug has been widely used as a potent coronary vasodilator in...
the treatment for the patients with ischemic heart disease. Clinical evaluation of this drug, however, has been somewhat controversial. A number of evidences attested a favorable therapeutic experience with dipyridamole, while some well-controlled studies have shown no significant difference between this agent and placebo in the management of angina pectoris or acute myocardial infarction. Although clinical observations have shown that even in the subjects with myocardial infarction the total coronary blood flow increased and coronary arteriovenous oxygen difference decreased after dipyridamole administration, a serious question remained to be answered. Does total coronary blood flow, measured at its root or coronary sinus with the use of several different techniques represent and/or parallel the blood supply to the anoxic myocardium in the presence of coronary obstruction? The investigation which is the subject of the present study was designed to elucidate the effects of this drug on the severity and extent of acute ischemic myocardial injury following coronary artery occlusion, with simultaneous measurement of unoccluded left circumflex coronary blood flow along with systemic variables.

Materials and Methods

Studies were carried out in 9 mongrel dogs weighing about 10 Kg and anesthetized with an intravenous administration of 25 mg./Kg. of sodium pentobarbital. Respiratory ventilation was maintained with a Harvard respirator, and the heart was exposed through a left thoracotomy and suspended in a pericardial cradle. One of main branches of the left anterior descending coronary artery was dissected free for repeated occlusions, and also the left circumflex artery was freed at its root for the purpose of coronary blood flow measurement.

Aortic and left ventricular pressures were measured through metal cannulae introduced via the left carotid artery and left ventricular apical dimple, respectively, and connected to Statham P23Db transducers. Cardiac output was determined by a Gilford IR 103 cuvette densitometer after injection of 1 mg. of indocyanine green into the right atrium. A flow transducer was placed around the left circumflex artery, and blood flow velocity was recorded with a gated sine wave electromagnetic flowmeter (Statham M-4001). Mean circumflex flow was electronically obtained. All the variables, including the epicardial electrogram, were recorded simultaneously on a multichannel oscillographic recorder (Brush Clevite M-260).

The severity and extent of left ventricular myocardial ischemic injury following anterior descending artery occlusion were assessed by epicardial mapping technique described in detail elsewhere. In short, unipolar leads (central terminal) were registered from 12 to 20 sites on the left ventricular surface, using a cotton wick electrode soaked in normal saline. Sites were selected so as to be located within the area supplied by the occluded branch, in areas adjacent to this zone, as well as remote portions which were adequately perfused by unaffected arteries. The sites at which myocardial ischemic injury were considered to exist were those where the ST segment elevation exceeded 2 mV, when recorded 15 min. after anterior
descending artery occlusion. In each experiment, ST elevations in mV. from such sites were added and divided by the total number of sites, and this value, E-ST, served as an index of the severity of ischemic injury in any given experiment. Also, the number of sites with ST segment elevation higher than 2 mV. (N-ST) served as an index of the extent of the injury following the descending branch occlusion. Epicardial mappings were obtained before and 15 min. after each occlusion. A control simple occlusion was at first carried out. After release of the occlusion and return of the each hemodynamic parameter along with epicardial electrograms to pre-occlusion state, a constant rate infusion of dipyridamole (0.01—0.05 mg./Kg./min.) was started 5 to 10 min. prior to second occlusion and maintained until final mapping was completed. The paired t-test technique was employed to determine the significance of the effects of the drug on the severity of myocardial ischemic injury.

Fig. 1. Representative set of recordings obtained 15 min. after anterior descending artery occlusion before and during dipyridamole infusion. From top to bottom: LVP=Left ventricular pressure, LVEDP=LV end-diastolic pressure, dP/dt=first derivative of LVP, AP=aortic pressure, CBF=coronary blood flow, measured by an electromagnetic flow probe applied at the root of circumflex coronary artery, ECG=epicardial electrogram, recorded by an electrode fixed on the central zone of ischemic injury, HR=heart rate, and CO=cardiac output.
injury, along with on the hemodynamic alterations.

Results

A representative set of variables recorded 15 min. after descending branch occlusion before and during dipyridamole infusion is shown in Fig. 1. Comparing with the values during control simple occlusion in the experimental animal, heart rate was reduced from 131 to 115/min. when recorded 15 min. after the occlusion during dipyridamole infusion. At the same time, left ventricular end-diastolic pressure fell from 2.0 to 0.5 mm.Hg, the maximal rate of left ventricular isovolumic pressure rise (max dP/dt) and Vpms, calculated from max dP/dt/kP (k=28), did not change substantially, aortic pressure (max./min. (mean)) fell from 125/105 (112) to 100/70 (81) mm.Hg, and cardiac output reduced from 0.68 during control simple occlusion to 0.61 L./min. 15 min. after the occlusion during dipyridamole infusion. There was a marked increment in circumflex coronary blood flow. Expressed as a percentage of the value measured just prior to initial occlusion, it increased from 111 to 511%. Remarkable ST segment elevation was, however, recognized on the epicardial electrogram, recorded from the electrode placed on the center zone of the ischemic myocardium. It was augmented from 3 during control occlusion to 11 mV. during the occlusion with dipyridamole.

Data from all the 9 experiments are summarized with their mean value and standard error of the mean in Table I. As depicted in Fig. 2-A, a significant increase was noticed in the severity of acute myocardial ischemic injury

Table I. Effects of Intravenous Administration of Dipyridamole Obtained Fifteen Minutes after Anterior Descending Artery Occlusion

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-ST (mV.)</td>
<td>9</td>
<td>4.6±0.3</td>
<td>6.8±0.8*</td>
</tr>
<tr>
<td>N-ST</td>
<td>9</td>
<td>6.2±0.6</td>
<td>8.1±1.2**</td>
</tr>
<tr>
<td>HR (/min.)</td>
<td>9</td>
<td>145±8</td>
<td>127±5 N.S.</td>
</tr>
<tr>
<td>BF (mm.Hg)</td>
<td>9</td>
<td>105±5</td>
<td>79±6*</td>
</tr>
<tr>
<td>CO (L./min.)</td>
<td>7</td>
<td>1.07±0.09</td>
<td>0.96±0.13  N.S.</td>
</tr>
<tr>
<td>Vpms</td>
<td>5</td>
<td>1.64±0.16</td>
<td>1.60±0.11  N.S.</td>
</tr>
<tr>
<td>BP·HR (mm.Hg/min.)×10⁸</td>
<td>9</td>
<td>153±14</td>
<td>102±12 #</td>
</tr>
<tr>
<td>CBF (%)</td>
<td>8</td>
<td>115±6</td>
<td>284±45 #</td>
</tr>
<tr>
<td>CPPI (mm.Hg sec. /min.)</td>
<td>9</td>
<td>4,000±180</td>
<td>3,130±210 #</td>
</tr>
</tbody>
</table>

Footnote: E-ST: Average value of S-T segment elevation; N-ST: Number of site with S-T segment elevation; HR: Heart rate; BP: Mean blood pressure; CO: Cardiac output; Vpms: max dP/dt/kP (k=28); CBF: Left circumflex coronary blood flow, and CPPI: Coronary perfusion pressure index.

* p<0.025, ** p<0.05, N.S. p>0.05, # p<0.01.
Fig. 2. Average values of mean S-T segment elevation (E-ST) (Column A) and number of sites with S-T segment elevation (N-ST) (Column B) obtained 15 min. after anterior descending artery occlusion before and during dipyridamole infusion. White column = before dipyridamole infusion, Shadowed column = during dipyridamole infusion. Bars represent standard error of the mean. Symbols are hereafter the same.

Fig. 3. Average values of mean aortic pressure (BP) (Column A) and coronary perfusion pressure index (CPPI) (Column B) obtained 15 min. after anterior descending artery occlusion before and during dipyridamole infusion. CPPI was derived from the product of mean blood pressure, heart rate and duration of diastole in aortic pressure.
(E-ST) from the mean value of $4.6 \pm 0.3$ following control occlusion to $6.8 \pm 0.8$ mV. during successive occlusion with dipyridamole infusion ($p<0.025$). Also, as shown in Fig. 2-B, there was an increment in the extent of ischemic injury (N-ST) from $6.2 \pm 0.6$ to $8.1 \pm 1.2$ ($p<0.05$). These changes were followed by a significant decrease in mean blood pressure from $105 \pm 5$ to $79 \pm 6$ mm.Hg ($p<0.025$) (Fig. 3-A). As an index of coronary perfusion pressure, we calculated the product of mean blood pressure, heart rate and diastolic duration in aortic pressure tracing. This value fell significantly following the occlusion with dipyridamole infusion from $4,100 \pm 180$ during control occlusion to $3,130 \pm 210$ mm.Hg sec./min. ($p<0.01$) (Fig. 3-B).

Fig. 4 depicts a remarkable increment in mean value of circumflex coronary artery blood flow in 8 dogs, which was augmented from $115 \pm 6$ to $284 \pm 45\%$ following dipyridamole infusion ($p<0.01$). Heart rate fell slightly and insignificantly after dipyridamole, and cardiac output in 7 experiments and contractile state of the whole heart expressed by $dP/dt/kP$ in 5 experiments did not change substantially.

**Discussion**

It has been recently shown, by means of epicardial electrography, that
marked alterations in the severity and extent of ischemic injury can be produced by pharmacologic and hemodynamic interventions affecting myocardial oxygen demand and supply.\textsuperscript{1)}\textsuperscript{1},\textsuperscript{18)}\textsuperscript{1} These studies have also proven that elevation of epicardial ST segment predict subsequent myocardial ischemic injury or necrosis, as reflected by enzymatic activity and histologic changes in the myocardium following an acute coronary occlusion.\textsuperscript{22)} Since the procedure, per se, is non-invasive and reliable, modified “semi-direct” methods have been applied in the clinical settings.\textsuperscript{23)}\textsuperscript{24)} With the use of this epicardial electrographic technique, result of the present study is simple and evident: Dipyridamole augments the severity and extent of myocardial ischemic injury, when administered in the acute phase of coronary occlusion.

It is widely accepted that myocardial contractile state and left ventricular wall tension are the major determinants of oxygen requirement of the heart.\textsuperscript{25)}\textsuperscript{29)} In this study, no substantial change in the former was found when assessed by dP/dt/kP, and the latter expressed by the product of mean aortic pressure and heart rate, fell slightly during dipyridamole after coronary occlusion. There is, therefore, no reason for these factors to augment the ischemic injury through an increase in oxygen demand. On the other hand, it was accompanied by a significant fall in mean blood pressure and coronary perfusion pressure index after administration of dipyridamole. There are several evidences that the extent of ischemic injury increases when mean blood pressure is lowered in the normal heart subjected to an acute coronary ligation and vice versa.\textsuperscript{15)}\textsuperscript{20)} The result in this study seems to be in accordance with their observation. From the observations of other investigators, it is likely that the collateral networks into or adjacent to the ischemic area following coronary occlusion have been already maximally dilated by adenosine, formed from the breakdown of myocardial adenosine nucleotides by hypoxia itself.\textsuperscript{30)}\textsuperscript{31)} This is, therefore, the very portion where the viability of anoxic myocardium does depend on any increase in blood supply, which takes place only through maintenance or elevation of coronary perfusion pressure, i.e. mean blood pressure.

Although the magnitude of ischemic injury following anterior descending artery occlusion was aggravated by dipyridamole administration, total coronary blood flow at the root of circumflex artery increased, and total coronary resistance was reduced when calculated by a form of mean blood pressure/coronary blood flow. A mechanism might be quoted known by the catchy title of “coronary steal” for the explanation of this discrepancy.\textsuperscript{28)}\textsuperscript{34)} Dipyridamole is known to exert a greater effect on the “resistant” arterioles rather than on the larger “conductive” arteries.\textsuperscript{35)}\textsuperscript{36)} Reduced or even reversed flow would occur if the arteriolar bed in the ischemic area were already
maximally dilated following occlusion, and if the resistance of normally perfused arterioles were fallen by the drug. It was impossible to clarify this phenomenon by the present experimental preparation, since mean blood pressure was not kept constant but was fallen after dipyridamole. Lowered blood pressure might itself be responsible for the deterioration of ischemic injury. A great care should be paid on evaluating total coronary blood flow in the presence of uneven distribution of myocardial perfusion.

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**REFERENCES**