Cardiovascular Reflexes Stimulated by Reperfusion of Ischemic Myocardium in Acute Myocardial Infarction

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SUMMARY Acute myocardial infarction (AMI), especially of the inferior left ventricular wall, where most cardiac receptors with vagal afferents that are stimulated during coronary occlusion are located, is commonly associated with reflex hypotension and sinus bradycardia. To determine whether reperfusion of an acutely ischemic area can activate cardiac reflexes, changes in the heart rate, arterial pressure and rhythm were correlated with the time course and location of intracoronary thrombolytic therapy in 41 patients with AMI. Of the 27 patients with successful reperfusion, 17 developed significant transient bradycardia and hypotension and one became tachycardic and hypertensive at the time of recanalization. Spontaneous reversion of the bradycardia and hypotension occurred definitely in six patients and possibly in more (nine reverted after atropine and two after fluids). A positive correlation existed between the changes in heart rate and blood pressure, in contrast to the usual inverse relationship when baroreceptors are stimulated. Two of the three patients in whom reperfusion was transient also developed hypotension and bradycardia. In contrast, all 11 patients with persistent occlusion demonstrated no reflex cardiovascular changes during intracoronary thrombolytic therapy. Thus, successful reperfusion in AMI stimulates cardioinhibitory and vasodepressor (Bezold-Jarisch) reflexes. These findings raise the possibility that the transient hypotension and bradycardia observed during AMI, particularly inferior MI, may sometimes reflect the occurrence of spontaneous reperfusion of the acutely ischemic myocardium.

ACUTE myocardial infarction (AMI), especially of the inferior left ventricular wall, is often associated with transient hypotension and sinus bradycardia. Experimental evidence suggests that this cardiac reflex may result from activation of inhibitory cardiac receptors with vagal afferents located predominantly in the inferoposterior wall of the left ventricle. Acute occlusion of the coronary artery and restoration of flow after prolonged occlusion have been associated with abrupt increases in discharge of left ventricular receptors in the cat. Whether reperfusion of ischemic myocardium also influences cardiac reflexes is not established. In the past, this question has not lent itself easily to investigation in humans, largely because reperfusion after acute coronary occlusion has not been widely studied until recently. However, the use of thrombolytic agents in conscious patients in the early hours of AMI permits an evaluation of the reflex effects associated with coronary reperfusion.

The present study was undertaken to assess the effect of reestablishment of coronary flow to ischemic myocardium on blood pressure and heart rate in humans. Because coronary spasm and perhaps its reversal as well as intracoronary contrast injection have elicited the hypotensive-bradycardic response, we hypothesized that reperfusion of acutely ischemic myocardium might activate cardiac reflexes. We sought to correlate the cardiovascular response with the site of myocardial reperfusion. Patients with AMI who also underwent intracoronary infusion of thrombolytic agents but in whom reperfusion was unsuccessful served as controls.

Methods

In 41 consecutive patients with AMI documented by history, elevation of serum CK-MB, acute electrocardiographic (ECG) changes, and arteriographic evidence of occlusion of the coronary artery supplying the...
corresponding area, a thrombolytic agent was infused into an occluded coronary artery according to a protocol described previously. Briefly, the criteria used for patient selection were as follows: (1) The patient presented within 3 hours after the onset of prolonged chest pain that was not relieved by sublingual nitroglycerin and had persistent pain at the time of presentation; (2) there was acute electrocardiographic ST-segment elevation of 2 mm or more that was unresponsive to sublingual nitroglycerin and persisted for more than 1 hour; (3) the patient had no contraindication to anticoagulation; and (4) informed consent was obtained. Although the serum CK-MB was not available at the time a decision was made to initiate the protocol, it became positive during the first several hours in every patient.

The protocol included left ventriculography and coronary arteriography. After an initial intracoronary bolus of nitroglycerin (200 µg) failed to open the occluded vessel, a thrombolytic agent (streptokinase in 36 patients and urokinase in five) was administered as a 20,000-IU bolus followed by an infusion of 4000 IU/min into the occluded coronary artery until patency was achieved or until approximately 300,000 IU had been infused. When the artery reopened, the infusion rate was decreased to 2000 IU/min for 30 minutes. The total dose of thrombolysate was 200,000–360,000 IU. Arteriography was performed at frequent intervals to assess patency. The intraarterial pressure, heart rate, rhythm, and symptoms were continuously recorded and were correlated with the location of the acute arterial occlusion and the time course of thrombolysis.

The time course and magnitude of changes in heart rate and arterial pressure were correlated with the outcome and site of coronary reperfusion. In patients in whom reperfusion was successful, the heart rate and arterial pressure at the time of reperfusion (i.e., when the coronary arteriogram first revealed passage of contrast material past the obstruction) were compared with stable preinfusion levels. In those with persistent occlusion, the maximal changes in arterial pressure and heart rate during the infusion (if any) or at the end of the infusion, whichever was greater, were compared to the preinfusion levels. The t test, analysis of variance and analysis of covariance were performed where indicated. The level of significance was set at p < 0.05.

Results

The 41 patients were 34–70 years old (mean 59 years); 36 were men and five were women. Six patients had a prior myocardial infarction. This was not related to the response to reperfusion. The area of acute infarction, as documented by ST-segment elevation on the ECG and regional dyskinesis on the radiographic ventriculogram, was located in the anterior left ventricular wall in 16 patients and the inferior/posterior wall in 25. The acutely occluded vessel was the right coronary artery in 21 patients, the left anterior descending coronary artery in 14 and the left circumflex coronary artery in four. Two patients had occlusion of both left anterior descending and left circumflex arteries.

Of the 41 patients receiving intracoronary thrombolytic therapy, 27 were successfully reperfused and 14 were not. Three patients in whom the coronary artery opened but reoccluded several minutes later were included in the nonreperfused group. The mean age and sex distribution of the two groups were similar. In the reperfused group, the infarct was anterior in nine and inferior in 18; in the nonreperfused group, the infarct was anterior in seven and inferior in seven. Before thrombolysis, the mean basal arterial pressure and heart rate of the patients in whom reperfusion was successful were similar to these in patients in whom it was not (131/81 mm Hg and 81 beats/min vs 126/76 mm Hg and 81 beats/min).

The relationship of changes in heart rate to changes in systolic and diastolic pressures are shown in figure 1. The patients with coronary opening and the three with only transient opening tended to have a greater change in heart rate and blood pressure than patients whose artery failed to open, who tended to show little change and clustered around the origin. (Some points

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** (A) Systolic (delta SBP) and (B) diastolic (delta DBP) pressure responses plotted against heart rate response (delta HR) in each patient subjected to thrombolytic therapy. O = patients with opening; T = patients with transient opening; F = patients who failed to recanalize.
represent the superposition of identical responses from more than one patient.) As a consequence of these changes, the systolic (−26 ± 6 mm Hg) and diastolic (−15 ± 4 mm Hg) pressures as well as the heart rate (−12 ± 2 beats/min) in the reperfused group fell significantly more and to significantly lower levels (p < 0.05) than those in the nonreperfused group (−8 ± 5 mm Hg, −1 ± 2 mm Hg, and −3 ± 2 beats/min, respectively). These changes usually lasted only several minutes. Of 17 patients with significant bradycardia and hypotension, nine responded after atropine administration (0.4–1.0 mg i.v.) and two responded after fluids alone; in six patients these hemodynamic changes reversed spontaneously. It is possible that the patients receiving atropine or fluids also reverted spontaneously.

To characterize further the cardiovascular responses associated with reperfusion, the changes in arterial pressure and heart rate in the 27 successfully reperfused patients were compared according to the region of myocardium supplied by the reperfused coronary artery. Because every reperfused left ventricular inferior wall (18 patients) was supplied by the right coronary artery and every reperfused anterior wall (nine patients) was supplied by the left coronary artery (left anterior descending in eight, left circumflex in one), this approach was equivalent to an analysis by coronary artery. The time to reperfusion, measured from onset of pain to coronary opening, was not different in the left and right coronary artery groups. The time to reperfusion ranged from 180–460 minutes, but there was no relationship between the time from onset of symptoms to reperfusion and the magnitude of the systolic or diastolic pressure or heart rate response. Figure 2 shows the individual systolic and diastolic arterial pressure responses vs the site of coronary reperfusion (i.e., right or left coronary artery). The mean decline in arterial pressure in the right coronary artery group was significantly greater than that in the left coronary artery group (−36 ± 6/−21 ± 4 vs −7 ± 8/−4 ± 5 mm Hg, p < 0.02). The heart rate changes of −21 ± 4 beats/min and 6 ± 5 beats/min (fig. 3) were also different (p < 0.001). The absolute level of systolic and diastolic pressures and heart rate, initially similar in the right and left coronary artery groups, became significantly different (p < 0.02) after establishment of flow (table 1). A hypertensive, tachycardic response was elicited by reperfusion in the one patient with a left circumflex occlusion.

To define further the relationship of heart rate and arterial pressure responses and the site of coronary reperfusion, we performed linear regression analysis for each coronary artery group. A direct correlation

![Graph](http://circ.ahajournals.org/)

**Figure 2.** Systolic (delta SBP) and diastolic (delta DBP) blood pressure responses in 27 successfully reperfused patients. The responses are divided according to the vessel acutely occluded and recanalized, i.e., the right or left coronary artery (RCA or LCA).

![Graph](http://circ.ahajournals.org/)

**Figure 3.** The change in heart rate (delta HR) at recanalization in 27 successfully reperfused patients. The responses are divided according to the site of reperfusion, i.e., right or left coronary artery (RCA or LCA). A significant bradycardic response is demonstrated in the RCA group (−21 beats/min vs +7 beats/min).
between changes in heart rate and systolic or diastolic arterial pressure, in contrast to the inverse correlation between these variables in the usual arterial baroreflex, was present in both groups (fig. 4). Although the slopes of the heart rate–arterial pressure relationships were similar for the right and left coronary artery groups, the intercepts on the heart rate axis were different (p < 0.01, analysis of covariance). This relationship held regardless of whether the patient with the left circumflex occlusion was included.

Discussion

The results of this study demonstrate that reperfusion in AMI may be associated with stimulation of cardioinhibitory and vasodepressor, or Bezold-Jarisch, reflexes. These reflexes are more prominent in patients with occlusion of the right coronary artery and inferior wall infarction. That the reflexes occurred with reperfusion and not as a result of the myocardial ischemia or infarction is substantiated by the fact that the acute changes in arterial pressure and heart rate coincided with or preceded the reestablishment of flow in the reperfused group and that there were no significant changes in heart rate or arterial pressure throughout the infusion of the thrombolytic agent in patients in whom reperfusion did not occur. Interestingly, there was a marked hypotensive-bradycardic response associated with the transient coronary opening in two of the three patients who were transiently reperfused. Hypotension and bradycardia often occurred before any documentation of coronary opening by arteriography, and in several instances these hemodynamic changes actually signaled that the occluded coronary artery was beginning to open; this was immediately confirmed by arteriography. Finally, the fact that the hemodynamic event correlated in time with the opening of the occluded vessel and not with the duration of ischemia suggests that the reflex responses observed were not just a function of the duration of the occlusion, but are causally related to reperfusion.

In 1867, von Bezold and Hirt described a hypotensive and bradycardic reflex that was elicited by i.v. injection of veratum alkaloids.16 Jarvisch later established that the sensory receptors for this response are in the heart and travel to the central nervous system through vagal afferents.3 This reflex has continued to be of interest to laboratory investigators, but its functional significance remains unclear.17 Reflex bradycardia with hypotension has been observed to occur dur-

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Relationship of changes in heart rate (delta HR) to changes in (A) systolic (delta SBP) and (B) diastolic (delta DBP) pressures at recanalization in 27 successfully reperfused patients. A positive correlation between heart rate and blood pressure exists for both right (R) and left (L) coronary artery groups. The slopes are similar, but the axis intercepts are different for both systolic (y = -6.36 + 0.41x for R, y = 8.36 + 0.35x for L, p < 0.01) and diastolic (y = -7.82 + 0.63x for R, y = 8.37 + 0.68x for L; p < 0.01) pressure changes in the two coronary artery groups.
ing the early phase of acute myocardial infarctions in humans, after coronary occlusion in anesthetized or awake animals, after intracoronary injections of contrast material, and in association with episodes of coronary spasm.

It is likely that this reflex plays a role in the response to certain pathologic states. During acute myocardial ischemia or infarction, reflex systemic vasoconstriction and bradycardia would decrease myocardial oxygen demand by lowering the afterload and heart rate. It may also simultaneously enhance myocardial perfusion through collaterals by increasing the duration of diastole, and perhaps by causing coronary dilatation as well. The reflex probably occurs as a result of stimulation of mechanoreceptors located in the ventricular myocardium. Other possible, but less likely, origins of the reflex include the receptors around the occluded vessel in and adjacent to the infarcted tissue, chemical receptors in the ventricular myocardium or vessel wall that are sensitive to local hypoxia, hypercapnia, accumulated metabolites, or electrolytes and, perhaps, serotonin and other mediators released as a result of the reperfusion, or a combination of several of these events.

Previous investigators have attributed the hypertensive and bradycardic response to the acute occlusion and the resultant ischemia. However, several experimental protocols used temporary rather than permanent occlusions, followed by release. Although occlusion may activate the cardiac vagal afferents, reperfusion may also have this result. Therefore, the reflex response observed in these studies may actually reflect, in addition to the ischemic response, a response to reperfusion of the acutely ischemic myocardium. The reperfusion response may be less prominent in the animal studies with short-lived occlusions, for Thoren showed that the increased receptor discharge after reperfusion was more pronounced after prolonged occlusion.

In humans, the density of cardiac receptors that mediate cardioinhibitory and vasodepressor responses are greater in the distribution of the inferior myocardium, which is more often supplied by the right than the left coronary artery. This finding correlates with the more intense response we noted after reperfusion of the right compared with the left coronary artery. The cardioinhibitory vagal afferents modulate the arterial baroreflex. Therefore, one might expect that the slope of the relationship of arterial pressure and heart rate response would be steeper with right coronary perfusion. Our findings show that the interaction of the two opposing reflexes resulted in a similar slope, but a significantly different intercept, in the reperfused right coronary group. Because reperfusion of the inferior wall probably results in stimulation of more cardioinhibitory receptors, these findings suggest that the modulation by cardiac vagal afferents of arterial baroreflexes is quantitatively related, and that this modulation results in an altered set point of the baroreflex.

Awareness of the probable reflex nature of an abrupt reduction of heart rate and arterial pressure during the early hours of an AMI, especially of the inferior wall, should be helpful in patient management. It may obviate the unnecessary and potentially hazardous administration of vasoconstrictors. In six of the 17 patients with significant bradycardia and hypotension in the present study, these changes reversed spontaneously; nine patients responded to atropine alone and two responded to volume expansion. In addition, the abrupt fall in arterial pressure and heart rate coincident with reperfusion suggests that these findings in patients with an acute infarct may signal the spontaneous reopening of the occluded vessel. This notion is supported by the observation that the fraction of patients with AMI who have thrombosis of the coronary artery supplying the infarcted myocardium declines as a function of time from the onset of symptoms. If the reperfusion (spontaneous or induced) caused reflex changes it must have activated viable receptors; this suggests that the myocardium near these receptors may be viable as well. If so, then the occurrence of these reflex changes during an acute infarct may be used as an indicator of reperfusion and therefore salvage of ischemic myocardium. Further studies should clarify this possibility.

In conclusion, this study shows that reperfusion after intracoronary thrombolysis in patients with AMI may be associated with stimulation of a cardioinhibitory and vasodepressor reflex. This reflex is elicited when reperfusion is successful and is more prominent in patients in whom the inferior wall of the left ventricle is reperfused through the right coronary artery. These observations also suggest that the elicitation of this reflex in patients with AMI not treated by thrombolytic agents may signal the onset of spontaneous relief of the obstruction and reperfusion of ischemic myocardium. Perhaps the time has come for the Bezold-Jarisch reflex, which has been largely a laboratory curiosity, to assume clinical significance.

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