Reflexes Unique to Myocardial Ischemia and Infarction

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Although arrhythmias caused by myocardial ischemia are a well recognized cause of sudden death, the potential influence of cardiogenic reflexes originating in areas of ischemia has received less attention. In this study, 12 patients with well documented single vessel coronary artery spasm, with a total of 2,240 episodes of transient transmural ischemia, are described. Continuous electrocardiographic and hemodynamic recordings were analyzed to determine possible relations between the anatomic area of ischemia and patterns of change in blood pressure and heart rate. Of seven patients with ischemia of the posterior or inferior left ventricular wall, six had associated bradycardia and hypotension, an apparent Bezold-Jarisch response. Only one of five patients with anterior ischemia had a similar response.

A hypertensive, tachycardiac response resembling the James reflex was seen in two of the patients with anterior ischemia, with an increase in blood pressure of 36/22 ± 12/6 mm Hg and an increase in heart rate of 8 ± 3 beats/min. This increase began before the onset of chest pain and was seen even in asymptomatic episodes. These reflexly mediated hemodynamic responses may modulate the direct effects of myocardial ischemia and could play a role in sudden cardiac death.

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Although myocardial ischemia is the most common precursor of sudden death, the precise mechanisms by which it leads to sudden death are unknown. It is clear that ischemia induces great alterations in the mechanical function of the heart and the chemical composition of its tissues. Stimulation of certain afferent fibers from the heart elicits profound systemic hemodynamic effects. Such stimulation of afferent nerve traffic may occur with either mechanoreceptor activation or chemoreceptor activation. It is likely that during myocardial ischemia, both types of cardiac receptors are activated.

Much effort is justifiably invested in the study of local mechanisms of arrhythmic generation in the setting of ischemia. It is also important to consider the possible complicating and interacting variable of reflexogenic alterations in sympathetic and parasympathetic control of the heart in situations where cardiac afferents are being activated. The potential role of disordered or uncoordinated sympathetic and parasympathetic input into the heart has been emphasized (1,2).

There have been a number of excellent general reviews (3–7) of the various kinds of reflexes that originate in the thoracic cardiovascular structures. In this discussion, we will concentrate on two reflexes that seem to have great potential to alter systemic hemodynamics in the setting of disordered coronary blood flow, namely the Bezold-Jarisch reflex (8–10) and the cardiogenic hypertensive chemoreflex of James (11).

Bezold-Jarisch Reflex

The Bezold-Jarisch reflex is elicited by stimulation of cardiac receptors with unmyelinated vagal afferents (C fibers) that terminate principally in the nucleus tractus solitarii of the brainstem (12–14). Although classically referred to as a chemoreflex because it was initially studied using veratrum alkaloids (8), it now appears that mechanical stimulation is the final common pathway of most such chemical agents through intermediary effects on contractility or other mechanical properties of the heart (15). In addition, some drugs (like digitalis) appear to sensitize these receptors to mechanical stimulation (16).

Whether elicited by chemical stimuli such as the veratrum alkaloids or by enhanced mechanical stimulation, the systemic effect is hypotension and bradycardia. Hypotension...
is due to both parasympathetic activation and sympathetic withdrawal and occurs, although in an attenuated form, even when heart rate is maintained by pacing. There is a reduction in arteriolar resistance as well as an enhancement of venous capacitance so that both preload and afterload are reduced (17). A third component of the Bezold-Jarisch reflex is nausea or vomiting, or both (18).

Many early studies of the hemodynamic effect of myocardial ischemia in animals documented the importance of a Bezold-Jarisch–like reflex (19), and these observations have been extended by more recent studies (20–24). There is general agreement in most animal studies that this reflex is most reliably elicited when the ischemia involves the posteroinferior wall of the left ventricle (24–26). This is demonstrated by the contrasting hemodynamic effect of the injection of veratridine into the canine circumflex coronary artery (which supplies the posteroinferior aspect of the left ventricle) as compared with the attenuated response after injection into the left anterior descending coronary artery (25).

**Bezold-Jarisch reflex in acute myocardial ischemia.** There have been a number of suggestions that a similar Bezold-Jarisch reflex occurs during myocardial ischemia in human subjects. When patients are examined within 30 minutes of the onset of chest pain, a large proportion manifest hypotension and bradycardia (27). This is especially likely to be true in patients with inferior myocardial infarction (Fig. 1) (28). Hypotension and bradycardia have been described less frequently in angina pectoris, but Perez-Gomez et al. (29) documented a decrease in heart rate from a mean of 77 to 65 beats/min during episodes of variant angina in patients whose ischemia involved the inferior left ventricular wall.

In a group of patients with frequent transmural myocardial ischemia due to coronary spasm, it is possible to carry out electrocardiographic and hemodynamic monitoring for a sufficient period of time to observe multiple episodes of unprovoked myocardial ischemia in a prospective fashion (30). In 12 patients with well characterized localization of myocardial ischemia patterns, it was possible to observe 2,240 episodes of spontaneous coronary artery spasm. An example of a Bezold-Jarisch–like hemodynamic response to severe inferior myocardial ischemia due to coronary spasm is shown in Figure 2. It can be seen that late in the episode, closely related to the resolution of ST segment elevation, marked bradycardia and hypotension supervened rapidly. Sometimes, as in our experience, it was unclear if the reflex was related to the cumulative effect of ischemia giving rise to a reflex response that resulted in parasympathetic vasodilation (31–33) of the coronary artery which, in turn, led to resolution of the episode, or if reperfusion itself caused elicitation of the reflex. In this patient with variant angina, we had observed the repeated association of bradycardia, hypotension and nausea with resolution of attacks. However, when a subsequent myocardial infarction occurred, no evidence of the Bezold-Jarisch reflex was noted (34). A prolonged episode of angina in this patient is shown in Figure 3. When substantial decreases in blood pressure and heart rate occurred, it was common for nausea to occur. We observed vomiting with spontaneous coronary
Figure 3. The tracing shows electrocardiographic (ECG) lead II in the top panel, radial artery pressure (RAP) in the middle panel and heart rate (HR) in the lower panel. This episode of chest pain lasted almost 25 minutes. The ST elevation was not preceded by an increase in either heart rate or blood pressure. On the left side, the T wave and ST segment can be seen as they begin to increase. They remained elevated throughout the 17 minutes excised from the tracing and then rapidly reverted to normal (arrowhead) coincident with nitroglycerin therapy (arrow), but the effect of the ST segment actually can be seen to begin within 12 seconds of the administration of sublingual nitroglycerin. The irregularity of the electrocardiogram at the far right side of the tracing was due to patient movement after the sensation of intense nausea. TNG = nitroglycerin. (Reprinted from Robertson RM, Robertson D [34] with permission.)

artery spasm in only one of our subjects, but this has often been known to accompany myocardial infarction, especially in the inferior distribution (18,35–37).

Of the seven patients with vasotonic angina who had myocardial ischemia of the posteroinferior left ventricular wall, six manifested both bradycardia and hypotension in the middle to late period of their spontaneous attacks of coronary artery spasm. In contrast, only one of five subjects with anterior ischemia had either hypotension or bradycardia.

Other causes of the reflex. It is noteworthy that the Bezold-Jarisch reflex may be brought into play in a variety of other clinical situations such as thrombolytic therapy in a myocardial infarction by streptokinase leading to myocardial reperfusion (38), coronary angiography (39), aortic stenosis syncope (40) and vasovagal syncope (18,41). A number of drugs appear to elicit the Bezold-Jarisch reflex directly or indirectly, or sensitize the relevant left ventricular receptors to other stimuli. This has been seen with digitalis (42,43), nitroglycerin (44) and the drug cryptenamine, a veratrum alkaloid, which is still available as an antihypertensive agent in the United States.

Cardiogenic Hypertensive Chemoreflex of James

In 1975, James et al. (45–47) characterized a cardiogenic hypertensive chemoreflex in animals that could be elicited by the injection of 100 μg of serotonin into the left atrium or the proximal left coronary artery. The vasoconstriction in response to this maneuver can be extraordinarily intense, with blood pressure elevations of greater than 100 mm Hg observed within seconds. The heart rate effect of the reflex is somewhat variable, but there was usually no change or only a slight increase in rate. Hyperpnea is generally seen in conscious animals (48,49). If serotonin is injected into the distal two-thirds of the left coronary artery, a Bezold-Jarisch response occurs instead of the expected hypertension. The responses are blocked by the serotonin antagonist, cyproheptadine (50).

The chemoreceptor area for the James reflex is a small area of tissue supplied by a vessel arising near the origin of the proximal left circumflex or the left anterior descending coronary artery (49). Afferent fibers travel in the vagus whereas the efferent limb extends through both the vagal and cardiac sympathetic nerves (51).

Mechanisms of sudden serotonin release. Because significant quantities of serotonin are present in platelets, it was postulated that this reflex might be activated in situations where platelets aggregated in the left main coronary artery, with the resulting powerful hemodynamic result having the potential to dislodge the nascent thrombus from this critical site, a so-called aortic cough (52). It is possible that other platelet or plasma constituents may contribute to such reflexes (53,54), but they have previously been characterized mainly by their elicitation of the Bezold-Jarisch reflex. Sympathetic hypertensive reflex reactions have also been observed when 100 ng/kg bradykinin was injected into the left coronary artery of conscious dogs (55). This was associated with an increase in heart rate, left ventricular pressure, left ventricular first derivative of pressure (dP/dt) and coronary blood flow (55).
Conclusions

Reflex responses resembling those described by von Bezold and Hirt (8) are frequently observed in the course of

tered it in a subgroup of patients. Typical pressor responses are shown in Figures 4 and 5. There was a mean increase in blood pressure of 36/22 ± 12/6 mm Hg and an increase in heart rate of 8 ± 3 beats/min. In the cases of anterior ischemia, the systemic reflex response generally started earlier than in the case with the Bezold-Jarisch–like response. In most cases it clearly preceded the onset of chest pain, so that the initial pressor effect cannot be said to be a response to discomfort. However, the peak pressor response typically occurred after the onset of pain, so that the maximal pressor response could be the outcome of both direct cardiogenic reflexes and the autonomic response to pain. Both of the pressor responders in our series of vasotonic angina patients had anterior ischemia. There was a remarkable uniformity of hemodynamic response within a given patient such that crossover from one hemodynamic response to the opposite response was not observed in this study (although we have observed it in a previous study in a patient who had episodic involvement of both right and left coronary arteries by spasm on alternate occasions). Furthermore, in two patients, no dramatic hemodynamic response ever seemed to occur during ST elevation. These nonresponders did not appear to differ from other study subjects in terms of severity of pain, magnitude of ST elevation or duration of ST elevation. We do not know why they exhibited no response, but it is noteworthy that, like the responders, they showed little intraindividual variability in their hemodynamic pattern from one attack to another.

Pressor responses in myocardial ischemia and infarction. An increase in blood pressure is commonly seen with myocardial infarction (27) and angina pectoris (56). When we examined patients with vasotonic angina for evidence of this type of hemodynamic response, we encountered it in a subgroup of patients. Typical pressor responses are shown in Figures 4 and 5. There was a mean increase in blood pressure of 36/22 ± 12/6 mm Hg and an increase in heart rate of 8 ± 3 beats/min. In the cases of anterior ischemia, the systemic reflex response generally started earlier than in the case with the Bezold-Jarisch–like response. In most cases it clearly preceded the onset of chest pain, so that the initial pressor effect cannot be said to be a response to discomfort. However, the peak pressor response typically occurred after the onset of pain, so that the maximal pressor response could be the outcome of both direct cardiogenic reflexes and the autonomic response to pain. Both of the pressor responders in our series of vasotonic angina patients had anterior ischemia. There was a remarkable uniformity of hemodynamic response within a given patient such that crossover from one hemodynamic response to the opposite response was not observed in this study (although we have observed it in a previous study in a patient who had episodic involvement of both right and left coronary arteries by spasm on alternate occasions). Furthermore, in two patients, no dramatic hemodynamic response ever seemed to occur during ST elevation. These nonresponders did not appear to differ from other study subjects in terms of severity of pain, magnitude of ST elevation or duration of ST elevation. We do not know why they exhibited no response, but it is noteworthy that, like the responders, they showed little intraindividual variability in their hemodynamic pattern from one attack to another.

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Figure 4. Typical response to anterior myocardial ischemia in a patient with vasotonic angina pectoris. The upper panel shows arterial blood pressure (AP), the middle panel shows the compact electrocardiogram (EKG) and the lower panel shows beat to beat heart rate (HR). It should be noted that blood pressure elevation occurs before the onset of pain.

Figure 5. Hemodynamic response to ischemia in vasotonic angina. The greatest pressor response occurred after onset of pain, but some blood pressure elevation occurred earlier. Panels as in Figure 4.
myocardial ischemia when the inferior myocardial wall is involved. Furthermore, involvement of the anterior wall is sometimes also associated with systemic hemodynamic events, in this case a pressor response that usually entails little change or only a slight increase in heart rate. The etiology of this latter response is unknown, but it is clearly not solely dependent on chest discomfort, although this may sometimes contribute to the maximal effect. Hemodynamically, it bears a resemblance to the cardiogenic hypertensive (James) reflex that has been described in several species.

The Bezold-Jarisch reflex has been considered to contribute to the hypotension and bradycardia of myocardial infarction; the syncope and perhaps sudden death of aortic stenosis; vasovagal syncope; the bradycardia of digitalis, nitrates and perhaps other drugs and to the nausea and vomiting sometimes associated with severe physical exertion. It has been proposed that its role is to prepare the circulation to receive an increased cardiac output and to lessen the work load of delivering that cardiac output. It is obvious that hypotension and bradycardia should lessen myocardial work and, therefore, the reflex may be beneficial in myocardial infarction and certain other situations in which myocardial work is very great.

The relation of these responses to arrhythmias can not be adequately assessed in the small number of studies that have been carried out thus far. True coronary artery spasm of the type seen in patients with vasotonic angina is probably relatively rare. The role of cardiogenic reflexes in the typical group of patients at the time of myocardial infarction may or may not be similar. Nevertheless, a role for such reflexes in some cases of sudden death appears likely.

References

38. Wei JY, Markis JE, Malagold M, Braunwald E. Cardiovascular reflexes stimulated by reperfusion of ischemic myocardium in acute myocardial infarction (in press).