Clinical and Experimental Pharmacology and Physiology (1996) **23**, 709–714

SYMPOSIUM
Experimental Biology 1995
Congestive Heart Failure

REFLEXES MEDIATED BY CARDIAC SYMPATHETIC AFFERENTS DURING MYOCARDIAL ISCHAEMIA: ROLE OF ADENOSINE

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SUMMARY

1. Myocardial ischaemia and infarction activate vagal and sympathetic sensory endings in the ischaemic myocardium, resulting in powerful reflex effects. The vagal afferents are either mechano- or chemosensitive, whereas sympathetic afferents may be mechano-, chemosensitive or both.

2. Activation of vagal afferents results in sympathoinhibitory, cardioinhibitory, vasodepressor responses. Cardiac sympathetic afferents activated during myocardial ischaemia mediate sympathoexcitatory, vasoconstrictor cardioaccelerator responses.

3. The focus of the present review is on the activation of sympathetic afferents by myocardial ischaemia and on the resulting reflex responses that they mediate.

4. These endings are more likely to be activated as the degree of ischaemia progresses from subendocardial towards transmural. They are evenly distributed between the anterior and inferoposterior wall. Although it has been suggested that these endings are activated by bradykinin, recent evidence indicates that they are activated by adenosine released from the ischaemic myocardium. Results from our laboratory indicate that this effect is due to the activation of adenosine A_1, but not adenosine A_2 receptors.

5. Activation of ventricular vagal and sympathetic afferent fibres during myocardial ischaemia in humans is responsible for the autonomic changes observed and, in the case of the sympathetic afferents, for the sensation of angina pectoris.

Key words: myocardial ischaemia, reflex responses, sympathetic afferents.

INTRODUCTION

Myocardial ischaemia and infarction result in both changes in regional and global left ventricular function and in the release of many chemicals, including adenosine, bradykinin, prostaglandins and lactic acid. Mechanosensitive sensory endings whose activity is determined by cardiac mechanics and chemosensitive sensory endings, which respond to chemical changes in their local environment, increase their discharge frequency in response to these mechanical and chemical changes occurring in the ischaemic myocardium. The afferent fibres that subserve the sensory endings in the ischaemic ventricular myocardium travel either in the vagal nerves (vagal afferents) or in the sympathetic nerves (sympathetic or visceral afferents). Most of afferent fibres that subserve these endings are non-myelinated, although a small portion are also myelinated fibres. In addition to endings that are either mechanosensitive or chemosensitive, others are polymodal (i.e. both chemo- and mechanosensitive). Activation of vagal and sympathetic afferent fibres results in powerful reflex responses that may contribute to the haemodynamic response to myocardial ischaemia and infarction and may play an important role in the pathogenesis of cardiac arrhythmias. Activation of cardiac receptors is also responsible for the sensation of angina pectoris in humans. While there is a significant amount of information regarding the behaviour of these cardiac sensory receptors in response to normal physiological stimuli, it will be the focus of this review to describe: (i) the behaviour of cardiac sympathetic sensory endings in response to myocardial ischaemia and infarction; (ii) the reflex responses that result from their activation; and (iii) the local mechanisms responsible for activation of these sympathetic afferents. Finally, we will review the evidence that such reflexes are activated in humans during myocardial ischaemia and infarction and will discuss the clinical implications of these reflexes. The behaviour of cardiac vagal afferents during myocardial ischaemia have been reviewed by Schultz and Ustinova in a companion manuscript.[1]

CARDIAC SYMPATHETIC AFFERENT BEHAVIOUR

The behaviour of cardiac sympathetic afferent fibres has been investigated much less extensively than that of the vagal affer-

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Presented at the Experimental Biology Symposium on Congestive Heart Failure, Atlanta, Georgia, April 1995.

Received 18 January 1996; accepted 18 January 1996.

ents. Brown[2] was one of the first to record impulses from cardiac sympathetic afferents and to activate their sensory endings within the heart using mechanical or chemical stimuli. He subsequently showed that occlusion of the coronary artery in the cat increased the afferent activity of multiunit preparations of sympathetic afferent fibres,[3] although the exact anatomical location of these endings was not determined. Malliani *et al.*[4] subsequently recorded from atrial and ventricular sensory endings with sympathetic afferent fibres and demonstrated them to be mechanosensitive in that they responded with a cardiac rhythm in response to alterations in mechanical events of the cardiac cycle. Lombardi *et al.*[5] demonstrated that many of these sympathetic afferent fibres increased their discharge not only in response to cardiac events, but also following their exposure to naturally occurring substances, such as bradykinin, thus establishing that many of these endings are polymodal. Uchida *et al.*[6] recorded from mechanosensitive afferent cardiac sympathetic nerve fibres in the dog and showed that coronary occlusion resulted in excitation of these ventricular afferent sympathetic nerve fibres.[7] This finding was subsequently confirmed.[8] Finally, Baker *et al.*[9] provided evidence of sympathetic afferent endings that are principally mechanosensitive and others that are chemosensitive. This was based on their responses to stimulation by bradykinin. Thus, there appears to be a spectrum of endings in the left ventricle with sympathetic afferent fibres that are either mainly mechanosensitive, polymodal or principally chemosensitive. As will be described later, activation of these sympathetic afferent fibres results in reflex sympathoexcitatory, cardioaccelerator and vasopressor responses.

REFLEXES DUE TO ACTIVATION OF SYMPATHETIC AFFERENTS

The investigation of reflexes mediated by sympathetic afferents during myocardial ischaemia has been much less extensive than for the vagal afferents. Activation of cardiac sympathetic afferent fibres by electrical stimulation or by stimulation of the sensory endings with bradykinin or other irritant substances generally results in sympathoexcitatory responses.[10] The occurrence of an excitatory cardiocardiac sympathosympathetic reflex (afferent and efferent limbs of reflex travel with sympathetic nerves) response to the stimulus of coronary occlusion was initially and most convincingly demonstrated in cats with spinal cord transection. The work of Malliani *et al.*[11] is particularly noteworthy in this regard. The issue of the physiological significance of the activation of cardiac sympathetic afferents by myocardial ischaemia and the resulting reflex responses was raised by Felder and Thames.[12] In their experiments in vagotomized dogs, neither left anterior descending nor circumflex coronary occlusion provoked a cardiocardiac sympathoexcitatory response as had been described in cats with spinal cord transection. In a subsequent study[13] it was shown that, following spinal cord transection, an excitatory cardiocardiac sympathetic reflex could be activated in which the cardiac sympathetic afferent fibres served as the afferent pathway and the cardiac sympathetic efferent fibres served as the efferent pathway. These observations were consistent with those made previously in spinal cats.

Weaver *et al.*[14] demonstrated that there was an important species difference between the responses of cats and dogs to coronary occlusion. They found that in cats (in contrast to dogs) simple coronary occlusion was an adequate stimulus for the activation of cardiac sympathetic afferent fibres and that this resulted in reflex increases in renal sympathetic nerve activity. These responses were most evident in cats with vagal denervation. In contrast, in cats with sympathetic deafferentation, cardioinhibitory, sympathoinhibitory, vasodepressor responses were observed during coronary occlusion. Thus, reflex responses mediated by vagal afferents could also be demonstrated. When both afferent pathways were intact, the net response was the result of the integration of these two sensory inputs, although the vagal afferent mechanisms appeared to be somewhat predominant. Figure 1 contrasts the effects of coronary occlusion on sympathetic nerve activity in vagotomized barodenervated dogs and cats. The lack of an excitatory response in dogs during myocardial ischaemia is surprising as the activation of cardiac sympathetic afferents has been demonstrated using direct neural recordings during coronary artery occlusion. It is conceivable that the extent to which these afferent fibres are activated in the dog, simply from coronary occlusion, may be inadequate to provoke reflex responses. Coleridge *et al.*[15] have suggested that left ventricular sympathetic afferent endings may be more superficial in location and nearer to the epicardial surface of the left ventricle. This is

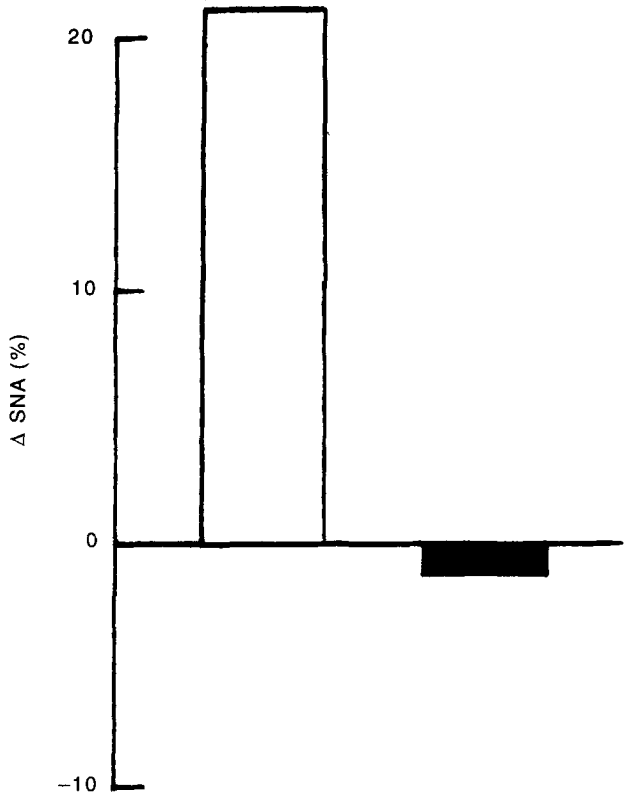

Fig. 1. Changes in renal sympathetic nerve activity (SNA) during coronary occlusion in cats (□; from Weaver *et al.*[14]) and of cardiac sympathetic nerve activity during coronary occlusion in dogs (■; from Felder & Thames[12]). In both sets of experiments arterial baroreceptor and vagal afferents were interrupted. Note that in the cat there was a significant increase in renal SNA during coronary occlusion. In contrast, there was no significant change in the dog.

consistent with observations made by Barber *et al.*[16] in which it was found that phenol applied to the epicardial surface of the left ventricle (apical to the atrioventricular groove) interrupts cardiac sympathetic afferent pathways but not vagal afferent pathways. Assuming that the endings lie close to the afferent fibres and considering the evidence reviewed by Coleridge *et al.*,[15] it is reasonable to suggest that the sympathetic afferents are indeed more superficial in location rather than deeper in the myocardium. Because of extensive collateral circulation in the canine heart, simple occlusion of a coronary artery may result in ischaemia that involves mainly the endocardium and spares the epicardial myocardium. The epicardial layers may receive sufficient blood flow by collateral vessels to prevent or limit ischaemia. As a result, coronary occlusion may provide only a minimal stimulus to sympathetic afferents located in these more superficial epicardial layers. Thus, it is possible that the failure to evoke reflex excitatory responses during simple coronary occlusion in dogs is merely the result of a failure to provide an adequate stimulus to the sympathetic afferent endings due to their location in relationship to the ischaemic myocardium. In contrast, cats are known to have little or no collateral vessels connecting the different branches of their coronary arterial tree. Coronary occlusion in this species is more likely to result in transmural ischaemia and adequate activation of these endings. Moreover, in both species coronary occlusion would result in subendocardial ischaemia, which should be an adequate stimulus for the vagal afferents as they tend to be located in the deeper layers of the myocardium.[16]

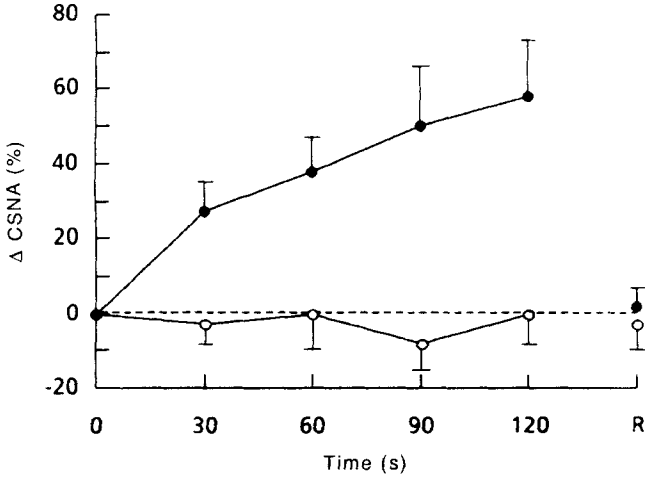

Fig. 2. Plot showing per cent change in efferent cardiac sympathetic nerve activity (CSNA) for left anterior descending coronary occlusion alone (○; LAD) and left anterior descending coronary occlusion with a circumflex stenosis (●; LAD + CIRC). Experiments were performed in dogs (n = 5) with sinoaortic denervation and vagotomy. Observations were made at baseline (B) before each coronary occlusion and during each 30 s period of the two minute occlusion. A recovery observation (R) was made 5 min after release of the occlusion. Changes in CSNA were significantly greater during LAD + CIRC than during LAD. Both coronary occlusions resulted in modest decreases in arterial pressure (not shown) that were not different. (From Minisi & Thames.[17])

examined the responses of efferent renal and cardiac sympathetic nerve activity to simple occlusion of the left anterior descending (LAD) coronary artery and to left anterior descending occlusion with a flow limiting stenosis placed on the circumflex coronary artery. The circumflex stenosis was adjusted to abolish coronary vasodilator reserve without reducing basal flow. This provided a mechanism for reducing or minimizing collateral flow from the branches of the circumflex coronary artery to the occluded left anterior descending coronary bed. As shown in Fig. 2, they observed significantly greater reflex increases in cardiac sympathetic nerve activity during LAD occlusion plus circumflex stenosis than during LAD occlusion alone. A similar augmentation was observed for renal nerve activity. They also demonstrated that during simple occlusion of the LAD, epicardial blood flow in the LAD distribution was still approximately 50% of basal values. This level of flow may have been sufficient to prevent ischaemia severe enough to stimulate cardiac sympathetic afferents. Addition of the circumflex stenosis to LAD occlusion increased the transmural myocardial ischaemia so that epicardial flow was now reduced to less than 30% of basal values. These experiments showed that ischaemia that is sufficiently transmural provides an adequate stimulus to cardiac sympathetic afferents located in the left ventricular myocardium and results in reflex sympathoexcitatory responses. It also was shown that these reflex responses were abolished by cardiac sympathetic deafferentation, thus establishing the afferent pathway for these responses. These studies further demonstrated that reflex sympathoexcitatory responses can be elicited during coronary occlusion and can be mediated by cardiac sympathetic afferents in dogs with intact spinal cords. However, these responses were significant only during ischaemia that was sufficiently transmural to involve the more superficial epicardial layers of the left ventricle.

Unlike the vagal afferents, which appear to be preferentially distributed to the inferoposterior wall,[13,18–20] cardiac sympathetic afferents appear to be more uniformly distributed throughout the wall of the left ventricle, at least in the canine heart. Minisi and Thames[33] used the technique of LAD coronary occlusion with concomitant circumflex stenosis and compared the reflex responses to those resulting from circumflex occlusion with LAD stenosis ('reverse experiment'). They observed similar increases in renal sympathetic nerve activity in response to both of these interventions.

MECHANISMS RESPONSIBLE FOR ACTIVATION OF VENTRICULAR SYMPATHETIC AFFERENTS DURING MYOCARDIAL ISCHAEMIA

The mechanisms for activation of cardiac sympathetic afferents during myocardial ischaemia have not been definitively determined. Kimura *et al.*[21] demonstrated nearly 20 years ago that there are increases in coronary sinus bradykinin concentrations after experimental coronary artery occlusion in dogs. Epicardial and, in some instances, intracoronary bradykinin results in increases in blood pressure, tachycardia and sympathoexcitation, which can be shown to be mediated by cardiac sympathetic afferents.[21] These results have served as the basis for the

hypothesis that bradykinin is the agent responsible for activation of cardiac sympathetic afferents during myocardial ischaemia in humans[22] leading to a combination of efferent autonomic responses of the type seen in dogs along with the perception of chest discomfort (widely known as angina pectoris). The results of preliminary experiments performed in our laboratory show that bradykinin antagonists do not reduce the sympathoexcitatory response provoked by myocardial ischaemia and activation of cardiac sympathetic afferents. Moreover, preliminary observations from our laboratory also suggest that blockade of kininases with the angiotensin converting enzyme inhibitors enalaprilat and captopril fails to alter the reflex sympathoexcitatory responses to activation of cardiac sympathetic afferents during myocardial ischaemia. Blockade of kininases would be expected to augment these responses by increasing local bradykinin concentrations, if bradykinin were indeed responsible for the activation of cardiac sympathetic afferents during myocardial ischaemia. Thus, it seems unlikely that bradykinin is the culprit for the activation of ventricular sympathetic afferents during myocardial ischaemia.

Recent clinical reports indicate that adenosine injected into the coronary arteries elicits angina-like chest discomfort in patients, even when injected into non-diseased coronary arteries.[23] The results of recent experiments support the view that adenosine may well be the principal agent responsible for activation of cardiac sympathetic afferents resulting in both the sympathoexcitatory, vasopressor responses that occur during myocardial ischaemia in animals and humans as well as for the sensation of angina pectoris in patients. Thames *et al.*[24] reported recently that the reflex sympathoexcitatory responses to transmural myocardial ischaemia induced by left anterior descending coronary occlusion and during rapid atrial pacing were nearly abolished following treatment with aminophylline, an adenosine receptor antagonist (Fig. 3). Conversely, administration of dipyridamole, an inhibitor of the uptake of adenosine, significantly potentiated the sympathoexcitatory responses to induced myocardial ischaemia in the same model (Fig. 4). In addition, these investigators have shown that the intracoronary administration of adenosine, in the presence of dipyridamole, results in reflex sympathetic activation[25] mediated by cardiac sympathetic afferent fibres (Fig. 5). Moreover, they showed that these responses are due to activation of adenosine A_1 but not A_2 receptors[25] by using selective agonists. This is particularly interesting because it appears that sympathetic afferents are activated by adenosine receptors (A_1) which differ from those mediating vasodilation (A_2).

The clinical implications of the activation of cardiac sympathetic and vagal afferents during myocardial ischaemia are addressed in the section that follows.

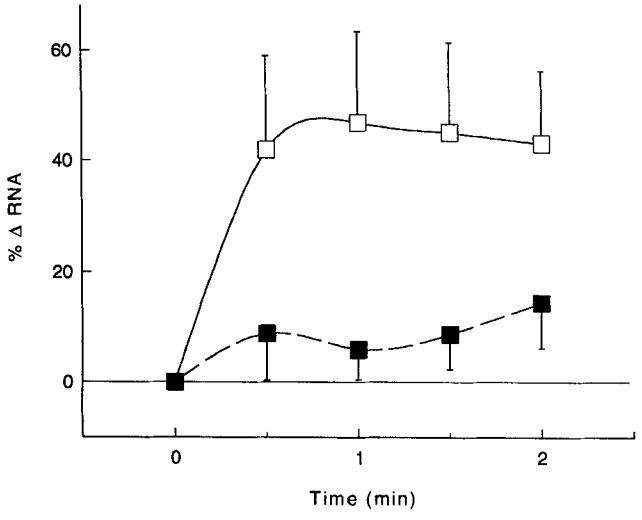

Fig. 4. Graph showing changes of renal nerve activity (% Δ RNA) during left anterior descending coronary occlusion and rapid atrial pacing under control conditions (■) and after treatment with dipyridamole (□). The increases in RNA was significantly augmented after dipyridamole treatment. (From Thames *et al.*[18])

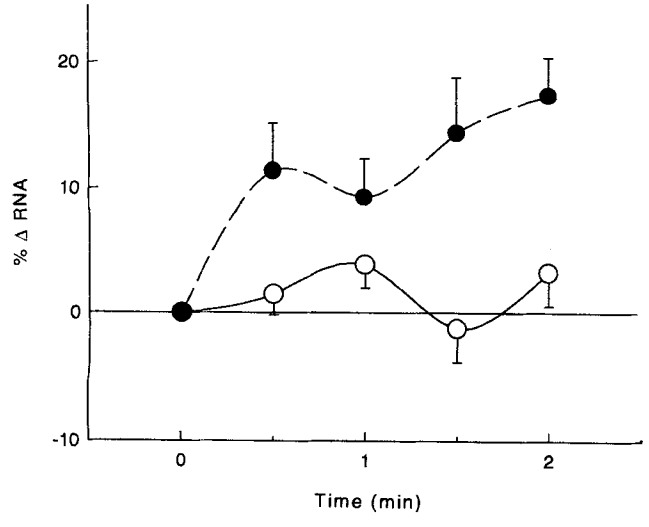

Fig. 3. Changes in renal nerve activity (% Δ RNA) during left anterior descending coronary artery occlusion and rapid atrial pacing under control conditions (●) and after treatment with aminophylline (○). The increases in renal sympathetic nerve activity were significantly reduced after treatment with aminophylline. (From Thames *et al.*[18])

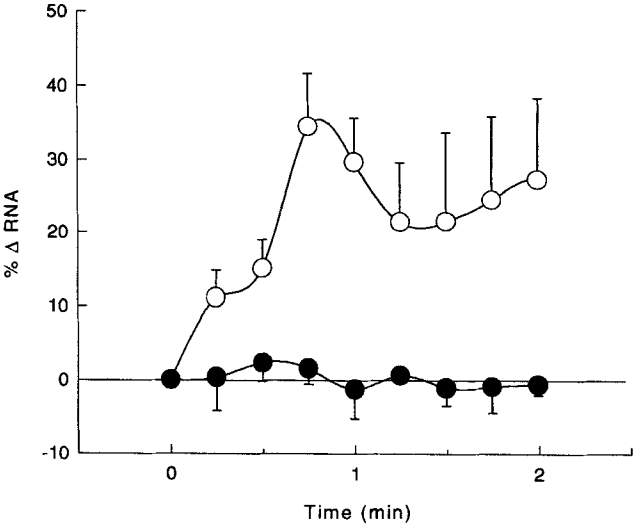

Fig. 5. Response of renal nerve activity (% Δ RNA) during intracoronary adenosine (2 mg) before (●) and after (○) pretreatment with dipyridamole (0.57 mg/kg, i.v.). After dipyridamole, RNA was significantly increased during intracoronary adenosine. (From Dibner-Dunlap *et al.*[25])

EVIDENCE FOR REFLEX RESPONSES TO MYOCARDIAL ISCHAEMIA IN HUMANS

Although there are clearly identifiable reflex responses to myocardial ischaemia and infarction in humans, the afferent pathways mediating these responses can only be suggested based on the similarity of these responses to those demonstrated in animals and for which the afferent pathways are clearly defined.

Adgey *et al.*[26] reported that bradyarrhythmias occurred far more commonly early in the course of myocardial infarction during inferoposterior injury (61%) than during anterior injury (14%). These investigators subsequently noted that signs of autonomic imbalance were present in 92% of 74 patients who were evaluated within 30 min of the onset of an acute ischaemic episode.[27] Sympathetic overactivity, as defined by the presence of sinus tachycardia and increases in blood pressure or both, was noted in 54% of patients with anterior injury but only in 20% of patients with inferoposterior injury. Conversely, parasympathetic overactivity, as defined by bradyarrhythmias, hypotension or both, occurred in nearly 80% of patients with inferoposterior myocardial infarction but only in 33% of patients with anterior injury. Perez-Gomez *et al.*[28] have documented a similar phenomenon in humans during myocardial ischaemia that resulted from coronary artery spasm. When the coronary spasm produced anterior wall myocardial ischaemia, significant increases in heart rate were noted during anginal pain. When coronary spasm produced inferoposterior ischaemia, significant decreases in heart rate occurred. Finally, Shani *et al.*[29] have described forearm vasodilation during ischaemia of the inferior wall, during occlusion of the right coronary artery in patients subjected to percutaneous transluminal coronary angioplasty. The cardioinhibitory vasodilator responses to inferoposterior myocardial ischaemia have been attributed to activation of cardiac vagal afferents that are thought to be preferentially distributed to the inferoposterior wall of the left ventricle in humans, just as has been observed for animals.

Further evidence of activation of these vagal afferents has been demonstrated during reperfusion of the ischaemic myocardium following the administration of thrombolytic therapy. Wei *et al.*[30] examined heart rate and arterial pressure following the intracoronary administration of streptokinase or urokinase in patients with anterior and inferior wall infarction. They found that reperfusion of an occluded right coronary artery supplying the inferoposterior wall of the left ventricle resulted in significantly greater bradycardia and hypotension than when the anterior descending coronary artery was reperfused with lytic therapy. They interpreted their results to suggest that reperfusion of the ischaemic myocardium is associated with activation of a cardioinhibitory vasodepressor reflex similar to that of the Bezold-Jarisch reflex.

There are two types of evidence that cardiac sympathetic afferents are activated during myocardial ischaemia in humans: one is the presence of anginal chest discomfort reported by patients during periods of myocardial ischaemia and the second is the presence of an increase in blood pressure and tachycardia during periods of ischaemia that may or may not be associated with angina.[31] There is little doubt regarding the role of cardiac sympathetic afferents in the mediation of anginal pain. It was shown many years ago[32] that anaesthesia of the stellate ganglia could interrupt anginal chest discomfort. One issue that is not clear is whether the sensory fibres responsible for the sensation of anginal pain are the same as those that result in reflex pressor and cardioaccelerator responses. This tissue is particularly important as it has been shown that patients with silent or painless myocardial ischaemia often demonstrate increases in blood pressure and heart rate during monitoring in an intensive care unit environment. In addition, increases in blood pressure and heart rate often are observed in patients who experience angina, but the cardiovascular responses often precede the development of anginal discomfort.[8,31] This is an area in which significant additional work is needed.

At this point, we would like to suggest a conceptual framework for understanding the role of cardiac vagal and sympathetic afferents in the autonomic responses to myocardial ischaemia and acute myocardial infarction. First, it should be clear that autonomic responses will depend on which region of the myocardium is rendered ischaemic. This is based on the preferential distribution of left ventricular vagal afferents to the inferoposterior wall of the heart in humans. Thus, the syndrome of bradycardia and hypotension in the setting of an acute inferoposterior wall myocardial infarct may be best explained on this basis. In addition to this regional difference in the distribution of vagal afferents, there appears to be a difference in the distribution of vagal versus sympathetic afferents across the wall of the ventricle. It appears that the vagal afferents are located nearer to the endocardial than the epicardial surface, while the reverse is true for sympathetic afferents.[17] Thus, subendocardial ischaemia would be expected to be an adequate stimulus for vagal, but not for sympathetic afferents. Ischaemia, which is more transmural rather than subendocardial, appears necessary to activate cardiac sympathetic afferents, at least based on animal studies. This may help us to understand an important mechanism for silent or symptomless myocardial ischaemia. Most episodes of myocardial ischaemia in humans that are not associated with anginal chest pain occur during activities of daily life. Indeed, as many as 70% of these episodes are not associated with angina. Most myocardial ischaemia that occurs during activities of daily life affects mainly the subendocardial region and is not transmural in distribution. Thus, it would not be surprising that patients experiencing ischaemia in this distribution may not experience angina pectoris. Subendocardial ischaemia releases adenosine in the subendocardium, which fails to activate ventricular sympathetic afferent endings because they are located nearer to the epicardium than to the endocardium.[17] Thus, it would be expected that most episodes of myocardial ischaemia that occur during activities of daily life and which provoke mainly subendocardial ischaemia are painless. Finally, the presence of cardiovascular responses to activation of cardiac sympathetic afferents as opposed to the perception of anginal discomfort may represent activation of different populations of receptors or may represent differences in the sizes of the populations that must be activated in order to provoke these different types of responses (cardiovascular responses versus anginal chest discomfort). Clearly, there is much left to be learned about the responses to activation of cardiac vagal and sympathetic afferents during myocardial ischaemia, their mechanisms of activation and their functional significance.

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