

# Is there such a thing as non-ischaeamic cardiac pain?

Nicholas Zareifopoulos

## Correspondence to

Nicholas Zareifopoulos,  
University of Patras School of  
Medicine, Rion, Patras, Achaia  
26504, Greece;  
nizareifopoulos@gmail.com

Over time, in the minds of clinicians and laypeople alike, cardiogenic pain is intimately associated with angina pectoris, the characteristic syndrome which accompanies myocardial ischaemia. However, in conditions such as myocarditis or cardiac sarcoidosis, both notorious for their silent clinical presentation, tissue damage is caused by inflammation, not ischaemia. One might wonder why there is no pain or angina-like syndrome accompanying these conditions. Recent insights into the molecular mechanisms underlying cardiac pain may provide an explanation.

Ischaemic or inflammatory damage of any tissue, including the myocardium, is accompanied by a series of metabolic changes and the release of a multitude of signal molecules from the affected cells. The end result is a change in the composition of the interstitial fluid, which can be detected by chemosensitive nerve endings.<sup>1 2</sup>

Specifically, in the case of ischaemia, once myocardial perfusion is reduced, aerobic glycolysis and lipolysis cease almost immediately, while anaerobic glycolysis is transiently stimulated. Thus lactate concentration increases and pH is lowered. If perfusion is not restored, cellular ATP stores are depleted and extracellular adenosine concentrations rise dramatically. Contractility is abolished and K<sup>+</sup> accumulates extracellularly, as Na-K ATPase activity is reduced.<sup>2</sup>

Among the immediate metabolic consequences of ischaemia, none is more intimately involved in the genesis of cardiac pain than the rise of interstitial adenosine concentrations. Its activity is most likely mediated by adenosine receptors located on the endings of unmyelinated C fibres.<sup>3</sup> As adenosine is typically released when nucleotide triphosphates are depleted, the notion that it is the most significant mediator of cardiac pain is in harmony with the hypothesis that angina is induced whenever myocardial oxygen demand greatly exceeds supply.<sup>2</sup> Increases of extracellular K<sup>+</sup> and H<sup>+</sup> concentrations could also alter neuronal excitability and constitute nociceptive stimuli. They may, however, act in synergy with other noxious stimuli, such as adenosine. Other substances which might contribute to the pathogenesis of angina pectoris include bradykinin, eicosanoids, serotonin (released from platelets) and substance P. Receptors for the aforementioned molecules are present in myocardial sensory endings. The former two do not directly stimulate the nociceptive fibres, though they may sensitise them to the actions of more potent mediators such as adenosine. The same probably applies for substance P.<sup>4</sup>

The molecular patterns of inflammation are not dissimilar, as bradykinin, eicosanoids and substance

P are crucial inflammatory mediators, and a local increase in K<sup>+</sup> and H<sup>+</sup> concentrations is typical of inflamed tissues. As these conditions contribute to the activation of nociceptive fibres in conditions of ischaemia, one would expect a similar response to be produced in response to inflammation (table 1). However, that does not seem to be the case.<sup>2</sup>

Cardiogenic pain is only uncommonly associated with other pathological entities afflicting the heart (myocarditis, endocarditis and cardiomyopathy), and it can usually be explained as a consequence of ischaemia.<sup>5</sup> In the case of hypertrophic cardiomyopathy angina is a common finding, and is attributed to the inability of the coronary circulation to meet the energy demands of the hypertrophic myocardium. In dilated cardiomyopathy, where hypertrophy is less pronounced and heart failure more so, the same principles apply. In the case of myocardial infarction, pain is present in the initial period of ischaemia until perfusion is re-established or irreversible necrosis of the entire affected area ensues. In the first week following an ST-elevation myocardial infarction (STEMI) there is marked inflammation of the affected tissue, which serves to clear cellular debris and enable scar formation.

However, this process is not typically associated with pain.<sup>2</sup>

Viral myocarditis may present silently, either asymptotically or with mild general symptoms of malaise. Its progress is also unpredictable, with most cases resolving automatically, and others progressing to dilated cardiomyopathy or even sudden death (due to fatal arrhythmias). For the above reasons, most cases are diagnosed too late or not at all. There are, however, cases of viral myocarditis presenting with typical anginal pain, resulting in prompt hospitalisations and diagnoses. In certain cases the cause is parvovirus B19, which can affect the endothelial cells of the myocardial blood vessels, causing haemorrhage, coronary insufficiency and myocardial ischaemia.<sup>6</sup> It may also contribute to myocardial ischaemia by inducing coronary vasospasm.<sup>7</sup> Thus patients experience typical anginal pain. However, myocarditis can also mimic acute myocardial infarction, even in the presence of a normal coronary circulation, further complicating the matter.

Sarcoidosis is an autoimmune disease characterised by non-caseating granuloma formation in various organs, most prominently the lungs. Cardiac involvement is not uncommon and presents a diagnostic challenge, as it may be asymptomatic or it may present with non-specific symptoms which can be associated with other conditions as well.<sup>8</sup> Patchy distributions of granulomas within the left ventricular myocardium with focal scarring



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**Table 1** Comparison between the microenvironments of ischaemia and inflammation

Ischaemic myocardium microenvironment	Inflamed myocardium microenvironment
Increased bradykinin, substance P, K <sup>+</sup> concentrations secondary to myocardial injury	Increased bradykinin, substance P, K <sup>+</sup> concentrations secondary to myocardial injury
Increased lactate concentration (produced by ischaemic cardiomyocytes)	Increased lactate concentration (produced by infiltrating leucocytes)
Increase in serotonin and thromboxane A <sub>2</sub> concentration (released by activated platelets)	Increased concentration of prostaglandins
Increased adenosine concentration (depletion of nucleotide triphosphates)	Local and systemic increase of proinflammatory cytokine concentrations (notably IL-1, TNF)
Rapid onset of changes	Gradual onset of changes

IL-1, interleukin-1; TNF, tumour necrosis factor.

in not uncommon at autopsy of patients suffering from the disease.

Cardiomyocyte necrosis and release of inflammatory mediators is typical of both myocarditis and sarcoidosis, contributing to the creation of a microenvironment similar to that of ischaemia. However, anginal pain is not commonly experienced in the context of myocardial inflammation, and whenever it is present, it may be insignificant in comparison with the rest of the symptoms of the condition.<sup>5</sup> The aforementioned findings shed light on an interesting question: since the sensory fibres innervating the heart are sensitive to ischaemia-induced alterations of the cardiac microenvironment, could they possibly be insensitive to the mediators of cardiac inflammation?

Clinical experience seems to vindicate the experimental findings that inflammatory mediators alone cannot induce anginal pain, the most important mediator of which, adenosine, is not typically increased in sites of inflammation. If an increase in the concentration of adenosine is necessary for the genesis of cardiac pain, one understands why myocarditis can present without pain. The microenvironment of the ischaemic myocardium is not the same as that of the inflamed myocardium, and perhaps the cardiac nociceptive fibres are sensitive only to the alterations typical of the former. Furthermore, in ischaemia the onset of tissue damage is immediate, while the process of inflammation is gradual, enabling perhaps the desensitisation of nociceptive fibres or the inhibition of the nociceptive pathway at the spinal level. Also, it is not unreasonable to assume that the

activation of central analgesic mechanisms, through endocrine signalling by cytokines (tumour necrosis factor (TNF), interleukin-1 (IL-1)) and glucocorticoids is also partly responsible for the painless clinical phenotype of myocarditis and cardiac sarcoidosis. In any case, cardiac innervation must be intact for cardiogenic pain to be experienced, as its absence (in the case of heart transplant patients) or dysfunction (in the case of diabetic neuropathy) is associated with silent myocardial ischaemia. To complicate the matter further, cardiac sensory nerve lesions may also cause angina in the absence of ischaemia, in the case of cardiac syndrome X, and oesophageal pathologies may also present with anginal pain, due to convergence of cardiac and oesophageal nociceptive pathways in the spinal cord.<sup>1</sup>

The microenvironments of ischaemia and inflammation overlap to a certain degree, but it seems there is only one signalling pathway for cardiac pain that is sensitive to ischaemic changes and, in some cases (notably, myocarditis presenting as acute myocardial infarction in the absence of coronary lesions), to inflammation. The phenomenon of painless ischaemia has been thoroughly studied, though the same is not true of painless cardiac inflammation. It may be a consequence of subtle differences between the changes induced by each cause of inflammation and the organism's response to it, which in certain cases may be able to activate the cardiac nociceptive fibres even in the absence of ischaemia. Further research is warranted to shed light upon the nature of such differences.

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