The elusive link between transient myocardial ischemia and pain

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"There is perhaps no symptom familiar to clinicians that has given rise to more speculation than that of anginal pain."1 Lewis, the author of this sentence, was merited with having initiated a critical evaluation of the link between muscular ischemia and pain but, as often occurs, better knowledge was soon transformed into a choral certainty. Entire generations of physicians lived, and still perhaps do, with the conviction that acute myocardial ischemia, as a rule, leads to pain. Cardiac pain hence became a reliable warning symptom, reflecting tissue damage and its natural history.

The purpose of this article is to outline the capital elements forming the traditional interpretation of cardiac pain and to consider them in relation to the new experimental findings. A great amount of uncertainty will be reestablished in the interpretation of this cornerstone symptom, and its reliability to supply a sound basis for deep clinical reasoning will be doubted. The hope is to contribute to a clinical method based on the contradictions of experimental pathophysiology rather than on more reassuring monolithic views.

The symptom

It is a symptom of antique description. The philosopher Lucius Annaeus Seneca, who suffered from chest pain likely to have been anginal, perhaps slightly related to the not totally rewarding task of having to be Nero’s teacher, wrote about twenty centuries ago: “The attack is short and the impetus like a storm; it usually ceases within an hour: who could indeed be expiring for a long time? I have experienced all other illnesses and dangers... to have any malady is only to be sick, to have this is to be dying. Therefore doctors call it ‘meditation of death’” (Epistulae morales ad Lucilium, Liber VI, Epistula II).

After the symptom was indisputably described and attributed to coronary disease, and this was only two centuries ago,1 it progressively assumed the vest of the most alarming message from the jeopardized heart.

The traditional interpretation. This view is based on a complex net of highly heterogeneous notions.

The afferent pathway. The concept that the afferent fibers running in the cardiac sympathetic nerves were the only essential pathway for the transmission of cardiac pain arose from observations on both humans and experimental animals. In man, thoracic sympathectomy or section of the higher thoracic dorsal roots was found to be a maneuver capable of relieving anginal pain,2 while thoracic sympathectomy could abolish behavioral reactions accompanying coronary occlusion in acute experiments.3,4 These observations were consistent with Langley’s statement that “most of the afferent fibers, which on electrical stimulation give rise to pain, pass by the sympathetic strands and not by the vagus.”5 More in general, Langley’s opinion was that the sympathetic nervous system was a pure outflow. The afferent nerve fibers contained within it were considered with no reflex function, merely subserving nociception and somatic in nature, since they had their cell bodies located in the dorsal spinal ganglia together with somatic neurons.5

From this conceptual matrix originated the holistic view according to which pain of somatic and visceral origin was due to the “direct stimulation of a common system of pain nerves.”6

The adequate stimulus. One day Harvey and Charles I, a highly sophisticated team, touched the beating heart of the young Viscount Montgomery, incredibly exposed through a large thoracic wound, and they had to acknowledge “that the heart was without the sense of touch; for the youth never knew when we touched his heart except for the sight or the sensation he had through the external integument.”7 This experiment, often cited for its fallacy, provided the dawn of a future certitude: touch and pain were not to be equated.

When Sherrington8 individuated in the “nocuous” event, threatening the integrity of a tissue, the stimulus capable, by definition, of triggering nociception, he
furnished more a general concept for the interpretation of somatic pain than a universal key for predicting all types of nociception. For instance, as to the heart, in the same period it became known that "in acute endocarditis pain is rarely present, and ulceration of valves or of the wall may proceed to a most extreme degree without any sensory disturbance." That is to say that for the heart an ambiguous relationship between damage and pain has long been known.

Around the thirties the problem of the adequate stimulus for cardiac pain was sharply focused in experimental terms. On the side of chemical stimuli the foreground was occupied by Lewis’ appealing proposal of a “factor P” capable of inducing nociception and accumulating in the tissue spaces when a muscle is exercising under ischemic conditions. However, at the same time, evidence was equally available on the adequacy of a pure mechanical stimulus to elicit pain from the heart.10, 11 Although the problem was far from being solved, Lewis’ prestige transformed his hypothesis into a common belief and the abnormal accumulation of chemical substances became the nub of the traditional view of how the adequate stimulus is engendered in the ischemic myocardium.

“Intensity” or “specificity”? The general problem concerning the afferent code transmitting nociception has assumed, through the years, the vest of two main hypotheses proposing respectively “intensity” or “specificity.”10, 11

The “intensity” mechanism, the most obvious and probably the first to be formulated, assumes that pain results from an excessive stimulation of receptive structures. Alternatively, pain may be conceived of as a “specific” sensation,12 that is, the product of the excitation of a well-defined nociceptive apparatus, the functional characteristics of which make it responsive only to a limited class of events, the “nocuous” stimuli that threaten the integrity of a tissue.

After these premises, it should be clear that the “specificity” theory was also in the epicenter of the traditional interpretation of cardiac pain. Indeed, the assignment of the afferent sympathetic path to the exclusive transmission of pain coincided with the most committed conceptualization of a specific nociceptive channel, not only in the usual terms of a peculiar contingent of small diameter afferent fibers,12 but as the whole sensory input contained in an ensemble of nerves. Hence, the sympathetic sensory endings within the heart were “specific” nociceptors.

The new experimental findings

Do cardiac-specific nociceptors exist? This question can be explored experimentally. Peripheral sensors purely nociceptive in function should have no background discharge12 as a consequence of their high threshold, which renders them unresponsive to normal events and excitable only with strong stimuli, likely to be noxious. Thus the recruitment of their silent fibers by a peripheral stimulus could represent an unambiguous signal to the centers. It is well known, for instance, that on the somatic side there is a population of afferent fibers, innervating the skin, which have receptors that seem to fit the criteria for specific nociceptors12: no background discharge and recruitment only with strong mechanical or thermal stimuli.

Recently an intense electrophysiologic investigation13 was carried out into the properties of either the small myelinated or unmyelinated ventricular sympathetic afferent fibers, i.e., the afferent fibers that are more likely to convey cardiac nociception. It was found that these fibers possess a mechanosensitivity that makes them tonically active and responsive to normal hemodynamic events. Coronary occlusion or intracoronary administration of bradykinin, i.e., possible algesic stimuli, increased markedly their tonic impulse activity, but a recruitment of silent afferent fibers could not be appreciated.

It was concluded that the “intensity” mechanism appeared as the most likely candidate to account for the properties of the neural substrate subserving cardiac nociception.10, 11, 13 Hence, ventricular sympathetic sensory endings are not “specific” nociceptors, but low-threshold polymodal receptors.11, 13

Experimental preparations and adequacy of the stimulus. Pain is a conscious experience that can be explored only indirectly with experimental preparations; accordingly, different opinions on peripheral nociceptive mechanisms are often the result of different preparations.

In animals lightly anesthetized or recovering from anesthesia, it is quite easy to obtain behavioral reactions by applying stimuli likely to be noxious to the heart.3-4 Decades ago Sutton and Lueth observed that traction on a ligature placed around a coronary artery could elicit “evidence of severe pain” after a very few seconds, this latency suggesting a mechanical nature of the stimulus. On the contrary, in long-term experiments, coronary occlusion performed through implanted occluders does not produce pain reactions, at least during the initial minute of occlusion.11 Clearly, in all these cases it is difficult to quantify how “noxious” the stimulus is.

The nonapeptide bradykinin was likely to furnish a remarkable tool for the experimental analysis of this subject since it could be quantified when used as a
stimulus. Indeed, the initial observations by Guzman et al. \(^4\) appeared extremely sound and easy to interpret when describing that intracoronary injections of bradykinin produced very effectively overt pain reactions in dogs recovering from recent surgery. However, when the intracoronary injections of bradykinin were administered to conscious dogs after full recovery from the operation necessary for their instrumentation, a marked pressor sympathetic reflex was elicited, but in the absence of any pain reaction.\(^5\) The importance of recovery from anesthesia and recent surgery, in explaining these apparent discrepancies, was explored in a few experiments by injecting bradykinin during the first week after surgery. At that time the animals' recovery was still incomplete and some animals exhibited vocalization and agitation suggesting a pain reaction. This behavioral response was no longer present when the same animals were tested again, later on, at a time of complete recovery.\(^5\)

Thus, a similar stimulus appears algogenic or not, depending exclusively on the specific experimental set. The observation that, under appropriate experimental conditions, an excitation of the cardiac sensory supply, likely to be massive, did not elicit pain appears to represent total defeat for the “specificity” theory, at least if nociceptors were postulated to be exclusively sensitive to algogenic substances. On the other hand, the “intensity” theory also appears, as such, too naive.

As a working hypothesis we proposed\(^3\) a modified version of the intensity mechanism. Cardiac pain would result from the extreme excitation of a spatially restricted population of afferent sympathetic fibers; hence from an afferent code based on a peculiar spatiotemporal pattern. More explicitly, an intense excitation of afferent sympathetic fibers would be more likely to reach the effectiveness of a nociceptive code when characterized by spatial heterogeneity. Thus, besides the extension and severity of ischemia, which would determine the background of the afferent excitation, further crucial stimulations of the sensory endings could occur in those regions where mechanical stretching is maximal or where an abnormal vasomotion takes place. Indeed, it should be recalled that it was observed that ventricular sympathetic receptors could be excited to an extreme degree by a light but abnormal mechanical motion such as that occurring during ventricular fibrillation.\(^3\)

According to this hypothesis, when the activation of the cardiac sympathetic afferent fibers is widely and homogeneously distributed, as in the case of intracoronary injections of bradykinin or, more currently, during inhibitory modulations\(^6\) will prevent the onset of pain. Conversely, recent thoracic surgery, by inducing a localized somatic afferent barrage, could decisively contribute, through mechanisms of convergence at spinal level, to genesis of the peculiar algogenic code.

Finally, the contribution by vagal afferent fibers to the mechanisms of cardiac nociception should be considered with caution and further explored. Indeed, the anginal pain referred to the jaw, head, and neck, more frequent after sympathectomy (the phenomenon of “migration of pain”\(^7,8\)) may indicate an additional central site, besides the spinal cord, where the mechanisms for referred pain would be activated, in this case by cardiac vagal afferent fibers. Moreover, even when nociception is transmitted through afferent sympathetic fibers, an important modulatory role on threshold and characteristics of pain may be exerted by vagal afferents.

Clinical observations. In recent years, it has been abundantly documented that in patients exhibiting spontaneous and reversible electrocardiographic changes typical of episodes of transient myocardial ischemia, the hemodynamic profile of the crises can appear substantially similar whether or not they are accompanied by pain.\(^9,10\) A careful analysis revealed that several factors are likely to be implicated in the genesis of pain, such as duration of the episode or severity of ischemia. For instance, ischemic crises were usually painless when shorter than 3 minutes and associated with increases in left ventricular filling pressure smaller than 7 mm Hg.\(^11\) However, above these values the onset of pain was unpredictable. In brief, duration and severity of ischemia appeared as necessary but not sufficient factors. Be that as it may, the temporal sequence of ischemic episodes, sometimes more than one per hour, about 70% of which are unaccompanied by pain,\(^11\) seems to furnish a most intriguing clinical puzzle, in which what appears to be a stochastic absence of pain cannot be attributed to peripheral neuropathies or to any other stable condition of the individual.

Since this article only deals with transient myocardial ischemia, painless myocardial infarction will not be analyzed, although reports on this possibility pioneered, as early as the thirties, the clinical suspicion that cardiac pain could fail to signal tissue damage.\(^11\) The point is that we should not equate anginal pain, for which mechanical factors could be prevalent, and pain in the course of myocardial infarction, when accumulation of chemical substances and direct destruction of nerve fibers are likely to provide quite different conditions for nociception.
The elusive link

The link between pain and tissue damage is the basis of a conception that assigns to pain a primordial and protective value for living organisms. While this principle seems corroborated by most common observations on somatic injuries, it seems unlikely to be valid, as such, for the heart where the link is much more elusive.11

This elusiveness has recently been attributed to a “defective anginal warning system.”19 In my opinion warning is a state of consciousness that depends not only on afferent inputs but also on the degree of awareness and culture: similarly cardiac pain embraces a whole spectrum of sensations.20 In this regard, it is worthwhile recalling an old debate between James Mackenzie, who claimed that surgical relief of cardiac pain would endanger patient’s life because angina was an important warning symptom of overexertion, and White,2 who maintained that even after cardiac sympathectomy the patient continues to experience warning signals such as constriction, dyspnea (Seneca’s “difficult breath,” suspirium), and palpitation. In short, warning should not depend on a unique afferent pathway when the warning signal does not belong to a specific sense.12

Cardiovascular sympathetic afferent fibers are tonically active and mediate reflexes that are mainly excitatory in nature with positive-feedback characteristics. It is thus likely that the primary role of this afferent channel is to contribute to the neural regulation of circulatory functions.13 The capability of their cardiac sensory terminals in detecting ischemic damage or abnormal changes related to it and their connection with the central structures elaborating the perception of pain has, on pathophysiologic finalistic grounds and in the absence of better knowledge, suggested as basic an accessory function. However, by the Darwinian or a similar hypothesis, of no less value in physiology than in morphology, it is hard to understand the biologic strategy and hence the development of a system providing the wild animal with hundreds of fibers exclusively designed for signaling unlikely coronary emergencies. Even more surprising is a warning system that lets filter so many dangers: this porosity seems to denote a different biological purpose. More simply, physiology and pathophysiology are unlikely to share the same finalistic organization.

Conclusions

Little is known on cardiac nociception, which is a receptive process, and still less is known of the mysterious step from nociception to pain, which is a conscious experience. In clinics, cardiac pain sometimes appears as an ally but more often is just unreliable testimony to some damage. The site of this elusiveness could be in the heart, where apparently similar ischemic episodes could in fact activate quite different afferent codes as a result of the extreme complexity of the mechanical and chemical events; in terms of our “spatiotemporal pattern” hypothesis no stimulus acting on the heart should be expected, because of its quality, to elicit pain as a rule. The waxing and waning could also be determined by the highly complex modulatory influences that are exerted on pain mechanisms, at spinal and brain level, through neural circuits and humoral substances.16

Physiologists know that sensation is an abstraction, not a replication of the real world. Clinicians should be aware that cardiac pain more than an abstraction is only a possibility, and yet a cornerstone symptom.

References

5. Langley JN: The autonomic nervous system. Brain 26: 1, 1903
7. Willis R: The works of William Harvey. London, 1847, Sydenham Society
9. Osler W: The Lumleian lectures on “angina pectoris” (lecture II), Lancet 1: 839, 1910
14. Guzman F, Braun C, Lim RKS: Visceral pain and the pseudoaffec-
18. Masieri A, Chierechia S, Davies G, Glazier J: Mechanisms of ische-
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