Editorial

Cardiac Nociception

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Modern cardiovascular medicine, following Harvey's inspiration, positions the heart indisputably at the center of a hemodynamic model. More deeply rooted in our cultural heritage are chronicles, such as Seneca's own description of anginal attacks, or the account of Anania's and Sapphira's sudden death for fear of God's punishment, clearly hinting at some less visible, more subtle, yet critical functions coupling the heart with life and death. These functions are now recognized as attained by the autonomic nervous system.

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A relationship between anginal pain and the heart was first described by Heberden more than 200 years ago.[1] The role of sympathetic afferents[2] in cardiac nociception was recognized a century later, and the causal contribution of reversible myocardial ischemia was suggested by Keefer and Resnik[3] in 1928. Subsequent patient studies have demonstrated that the sensation of pain is not directly related to the degree of disease in the coronary artery subtending the ischemic territory or to the severity and duration of myocardial ischemia.

Most visceral pain research has been invasive and has used animal models. This research has established that adequate peripheral painful stimuli are transmitted through sympathetic afferents[4] to the dorsal root ganglia and then, principally via the spinothalamic tracts and medial pain pathway, to the posterior thalamus. A significant number of vagal fibers connecting to the nucleus of the tractus solitarius and from there to the posterior thalamus are also involved in the afferent conduction of painful stimuli.[4] Beyond this, the central connections mediating visceral pain perception and the affective response to it are unclear, although more recent studies in patients with coronary artery disease have shown that anginal pain perception requires activation of specific areas of the brain and that abnormal central processing of afferent pain messages from the heart plays a role in episodes of myocardial ischemia not accompanied by pain (ie, silent).[5,6] Using dynamic positron emission tomography with oxygen-15–labeled water used in patients with stable angina pectoris and angiographically proven coronary artery disease, it has been possible to measure changes in regional cerebral blood flow (rCBF) during anginal pain induced by intravenous infusion of dobutamine. Compared with the resting state, angina was associated with increased rCBF in the hypothalamus, periaquaductal gray, bilaterally in the thalamus and lateral prefrontal cortex, and left inferior anterocaudal cingulate cortex. In contrast, rCBF was reduced bilaterally in the midrostrocaudal cingulate cortex and fusiform gyrus and right posterior cingulate and left parietal cortices[5] (Figure, A). There are important differences between these findings and those for somatic pain.[7,8] In the latter, increases in rCBF were found in the contralateral dorsal cingulate cortex, thalamus, and lenticular nucleus, and also the prefrontal, contralateral insular, and prefrontal cortices. In contrast, angina evokes a bilateral thalamic increase in rCBF with activation of the periaquaductal gray and hypothalamus, but with reduction in dorsal cingulate cortical flow bilaterally. Compared with the patients with angina, an equivalent stress on the hearts of patients with silent ischemia produced the same degree of thalamic activation but significantly less cortical activation, especially with respect to the anterior and ventral cingulate and basal frontal cortices (Figure, A).[6] These findings show that afferent stimuli from the heart do reach the central nervous system in patients with silent ischemia. Accordingly, the absence of a sensation of chest pain is unlikely to be caused by failure of transmission by the peripheral nerves, but it is likely to depend on the specific properties of the ischemia-induced neural activation.[6] Following this approach, the sensory code for cardiac pain[4] might be based on intensity (pain is produced by very intense, suprathreshold stimuli), specificity (stimulation of specific receptors, recruited only by painful stimuli), other modalities (such as the intense stimulation of specific afferent channels), or a combination of these.

Considering the critical role of the input signal, the presence of specific nociceptors has not been unambiguously demonstrated in the myocardium, although they may be more probable in the coronary arteries. The issue, which is partly semantic, stems from the implicit assumption of a neural code based on quantity, and thus it revolves around the definition of the adequate stimulus, as related to a very high mechanical threshold (very scarce action potentials for normal mechanical events, and a clear activation only with noxious stimuli) or to sensory fibers responding only to chemical stimuli. Often, however, the same sensory fibers might be polymodal and have both a preferential sensitivity for chemical stimuli and a simultaneous limited sensitivity to normal mechanical stimuli. Notably, chemical stimulation of the coronary bed with bradykinin (simulating the chemical message of ischemia) in conscious dogs,[9] while evoking positive feedback, sympathoexcitatory reflexes did not elicit behavioral equivalents (agitation, vocalization) of cardiac pain (Figure, B). Moreover,

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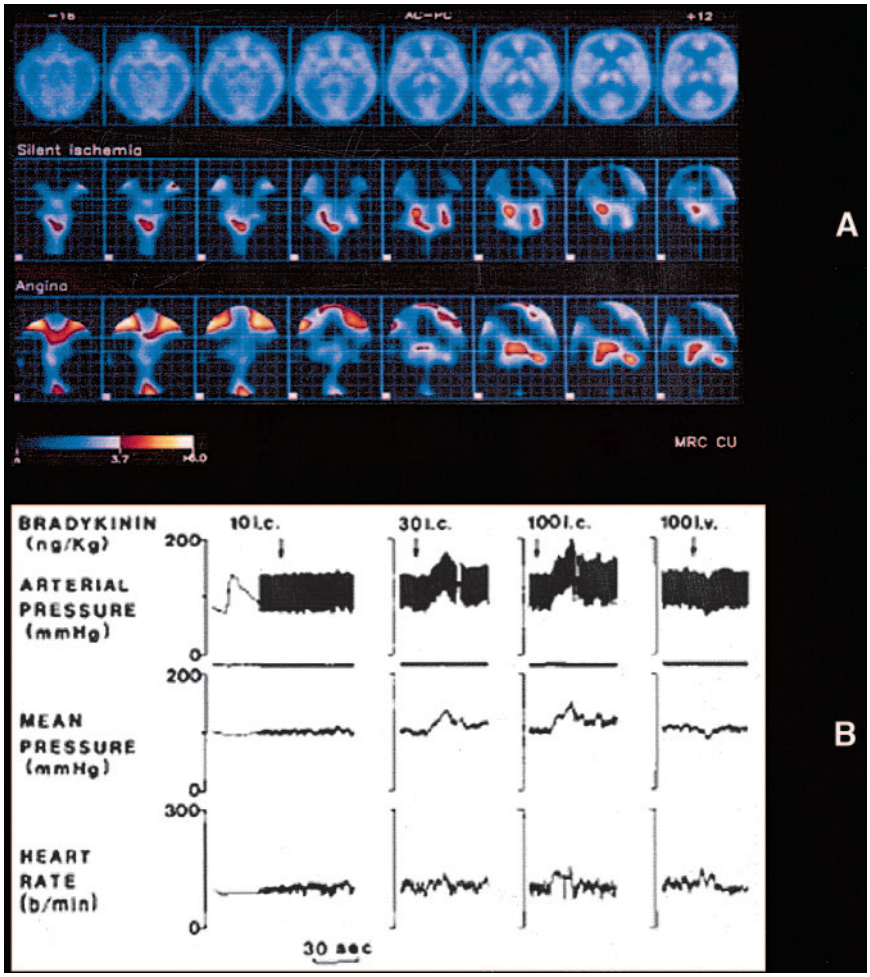
(*Circulation.* 2006;114:2309-2312.)

***Circulation* is available at http://www.circulationaha.org**
DOI: 10.1161/CIRCULATIONAHA.106.665042



A, Cerebral areas activated during angina pectoris and silent ischemia. The top row shows averaged blood flow maps from all subjects and all conditions normalized into a standard stereotactic space. These pictures can be used for anatomic localization of the activation foci. The latter are displayed as statistical parametric maps in the same stereotactic anatomic space shown in the above averaged blood flow maps. Results for the silent ischemia patients are shown in the middle row and results for the angina pectoris patients are shown in the bottom row. The magnitude of the *z* scores is displayed for both patients groups according to the same linear color scale (threshold for significance: 3.7). AC-PC indicates the intercommissural plane. Distances are expressed in millimeters from this reference (AC-PC) plane. Reprinted from Rosen et al,[6] with permission from The American College of Physicians. Copyright 1996. B, Effects of graded doses of intracoronary bradykinin in a conscious, fully innervated dog. Notice the large increase in arterial pressure and tachycardia in the absence of any apparent signs of pain. A slight decrease in pressure is produced by IV injections of bradykinin. Reprinted from Pagani et al,[9] with permission from The American Heart Association. Copyright 1985.

the application of hemodynamic stimuli in the physiological range activates cardiac sympathetic (and vagal) afferents,[2,10] thereby initiating sympathosympathetic reflexes, even when the circuitry is limited to the spinal cord. These findings suggest that cardiac function is governed, beat by beat, by autonomic reflexes initiated by stimulation of peripheral afferents: positive-feedback sympathetic excitatory reflexes from the heart and the aorta, interacting with negative-feedback vagal and baroreceptor mechanisms, or excitatory ergoreflexes from exercising muscles. Accordingly, the continuous changes in cardiovascular performance attending activity and quiet, emotions and rest, and arousal and sleep are accompanied by corresponding variations in autonomic activity, partly through variations in central command, and partly in response to attendant changes in sensory cardiovascular stimulation and to reflexes thereby initiated. By abnormally activating the cardiac sensory substratum, pathological events such as myocardial ischemia initiate reflexes that at times might veritably produce autonomic storms, inclusive of dramatic occurrences such as sudden arrhythmic death. Usually, only these storms are capable of piercing through consciousness and generating the experience of pain, whereas the majority of sensory processing from the heart goes unnoticed and remains unconscious. However, new theories of consciousness[11] elucidate why the occurrence and integration of additional information from other areas (convergence) or from different contexts (arousal) might lead to the experience of cardiac pain in absence of ischemia.

Until recently, the exploration of the substratum underlying neural regulation of the heart was based on the study of reflexes (eg, Bainbridge, Bezold-Jarisch) using traditional neurophysiological techniques, such as selective ablation, stimulation, and electrophysiological recordings of afferent (ie, sensory) or efferent (ie, motor) fibers, belonging to either the vagal or the sympathetic branch of the autonomic nervous system. A major limitation of these techniques is their fundamental invasiveness and, despite technological advances, particularly in imaging techniques, the difficulty of exploring humans in everyday, real-life conditions. Accordingly, it is not surprising that neurocardiology still struggles to become a serious component of medical practice.

In the last 2 decades, the study of the autonomic nervous system has been expanded by the application of spectral analysis to quantify the hidden oscillations present in beat by beat variations in heart period, usually obtained from a single-lead ECG (RR variability). This new tool provides the opportunity to functionally explore the continuum of effects of cardiovascular innervation in intact conscious animals or behaving humans.[10,12] From RR variability, 2 major oscillatory components usually can be extracted (in addition to a noise component at about 0 Hz): one centered around 0.1 Hz (low frequency) and a second one (high frequency) at about

0.25 Hz, synchronous with respiration. These components are strongly coherent with similar components present in the directly recorded efferent muscle sympathetic nerve activity.[13] In normal humans at rest, pharmacological or physiological increases in sympathetic activity (and simultaneous decreases in vagal drive) are associated with a leftward shift in the balance between these 2 components; the opposite occurs with decreases in sympathetic drive. Although a consensus document[14] has proposed standards of technique and interpretation for clinical use in normal and abnormal conditions, there is some disagreement on strict physiological interpretations that might delay clinical applications of this noninvasive approach. System analysis[15] and multiple parameters,[16] such as the addition of arterial pressure and respiration, provide new windows into the secrets of cardiovascular neural regulation.

The fact that specific autonomic imaging techniques (such as positron emission tomography of noradrenergically innervated areas) are more directed toward research, coupled with paucity of targeted pharmacological treatments, probably accounts for the limited interest in neurocardiology among clinical cardiologists, despite the relatively large scientific database. However, arrhythmias and sudden death, myocardial contractility, oxygen consumption, exercise response, and cardiac perception all depend on an intact (or altered) cardiac innervation.

In the last few years, novel attention has been devoted to cardiac neural mechanisms, with a specific focus on cardiac nociception, probably because chest pain, the hallmark of myocardial ischemia, is such a critical clinical symptom.[4] The availability of new pharmacological tools and expanded knowledge on details of molecular signaling at the level of sensory endings has permitted better definition of the role of capsaicin-sensitive vanilloid receptors, which are being proposed as relatively specific sensors for tissue ischemia.[17] There has been much work and debate in this novel area, and although pain is not a physiological stimulus, the production of lactic acidosis and liberation of lipid and other inflammatory mediators[18] may well act through stimulation of VR1 cation channel expressing cardiac sensory neurons.[19]

In this issue of *Circulation*, Ieda et al[20] project a new bridge between molecular and functional research in the broad area of sensory innervation of the heart. In their study, they focus on the role of nerve growth factor (NGF) in the regulation of the cardiac sensory nervous system, and they analyze the mechanism of silent myocardial ischemia in mice with and without streptozotocin-induced diabetes mellitus (DM). The technique used for the assessment of cardiac sensory nerve density in mice was based on immunostaining for calcitonin gene-related peptide, a marker for nociceptive sensory nerves, although calcitonin gene-related peptide positive nerves preferentially innervate cutaneous regions. Cardiac sensory nerves that were immunopositive for calcitonin gene-related peptide, dorsal root ganglia, and the dorsal horn were markedly retarded in NGF-deficient mice, whereas cardiac-specific overexpression of NGF reversed these deficits. Down-regulation of NGF, calcitonin gene-related peptide–immunopositive cardiac sensory denervation, and atrophic changes in dorsal root ganglia were observed in naive mice with DM, whereas the abnormalities were reversed in NGF transgenic mice with DM. Cardiac sensory function, assessed by myocardial ischemia-induced c-Fos expression in dorsal root ganglia, was also reduced in naive mice with DM, whereas it was preserved in NGF transgenic mice. Direct gene transfer of NGF in diabetic rat hearts improved impaired cardiac sensory innervation and function, as determined by electrophysiological activity of cardiac afferent nerves during myocardial ischemia. The authors conclude that correct development and regulation of the cardiac sensory nervous system are strictly dependent on cardiac production of NGF and that the reduction of NGF associated with DM is the main cause of cardiac sensory neuropathy.

These novel findings are important not only because they help reveal the molecular origins of cardiac pain, but also because they open the way to a new molecular understanding of cardiac innervation. An integration of neural principles in everyday cardiology will, however, require changing from deterministic physiology to system analysis[15] of complex integrated finalistic structures. Molecular techniques will have to be incorporated with bioengineering to achieve a fuller understanding of the clinical implications of neurocardiology, because there seems to be more than just ischemic pain in cardiac innervation.

Disclosures

None.

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KEY WORDS: Editorials ■ angina ■ nervous system ■ molecularbiology