ABSTRACT
Angina pectoris is important because of its association with heart disease and risk of death. Historically after Heberden’s account of angina in 1772, the association of pain with coronary artery disease quickly followed. Within a few years, Burns suggested an etiological role for ischemia. Subsequently, theories of differential myocardial stretch dominated thinking until Lewis’ chemical hypothesis in 1932, in which the local release of chemical substances during ischemia was seen as the cause of pain.

This review considers how ischemia at the tissue level triggers activation of afferent nociceptive pain fibres. The afferent projections of sympathetic and vagal afferent fibres are described, with a number of methodologies cited (eg, injection of pseudorabies virus into the heart with mapping of the retrograde viral transport pathways; and elevation of neuronal c-fos synthesis in brain regions activated by capsaicin application to the heart). Our own functional neuroimaging studies of angina are also reviewed.

There are 2 intriguing features of angina. The first is the poor correlation between symptoms and extent of coronary disease. The spectrum ranges from entirely silent myocardial ischemia to that of a functional pain syndrome—the ‘sensitive heart’—of cardiac syndrome X. An even more difficult aspect is the wide variability in symptoms of functional pain syndrome—the ‘sensitive heart’—of cardiac syndrome X. An even more difficult aspect is the wide variability in symptoms experienced by an individual patient.

A new paradigm is presented which, besides considering myocardial oxygen supply/demand imbalance, also draws insights from the broader field of pain research. Neuromodulation applies at multiple levels of the neuraxis—peripheral nerves, spinal cord, and brain—and it invites exploitation, whether pharmacological or electrical, for the benefit of the cardiac patient in pain.

RÉSUMÉ
L’angine de poitrine est importante en raison de son lien avec la maladie cardiaque et le risque de mortalité. Historiquement, après les travaux d’Heberden sur l’angine, en 1772, le lien entre la douleur et la maladie coronarienne a rapidement été reconnu. En quelques années, Burns suggérait un rôle étiologique à l’ischémie. Subséquemment, les théories d’étirement myocardique différentiel ont dominé jusqu’à l’hypothèse chimique de Lewis, en 1932, selon laquelle la libération locale de substances chimiques durant l’ischémie était considérée comme la raison de la douleur.

Cette revue examine comment l’ischémie au niveau tissulaire déclenche l’activation des fibres nociceptives différentes. Les projections afférentes de fibres afférentes sympathiques et vagales sont décrites, avec un grand nombre de méthodologies citées (par exemple, l’injection du virus de la pseudoréférence dans le cœur avec cartographie des voies de transport viral rétrograde et l’augmentation de la synthèse neuronale de la protéine c-fos dans les régions du cerveau activées par l’application de capsaicine au cœur). Nos propres études en imagerie neurologique fonctionnelle sur l’angine sont aussi revues.


Historical Aspects
In the popular imagination, chest pain is probably the most significant symptom that an individual might experience because of its association with important heart disease and risk of death. As MacKenzie put it,1 “it is of all symptoms the most clamant, the most universal, and probably the most diagnostic, and one calling, above all others, on the resources of the doctor.”

Probably the earliest extensive symptomatic description of angina pectoris is that of Heberden in 1772:2

But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.
They who are afflicted with it, are seized while they are walking, (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this unaeasiness vanishes.

In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have passed their fiftieth year.

What is less well known is the fact that the ingredients of a comprehensive anatomical and physiological account of angina pectoris were in place within 30 years of that description. Early landmarks on this road include: (1) the realization in 1785 by Edward Jenner (of later repute for vaccination) that the coronary obstructions, demonstrated in postmortem examinations by his mentor, the surgeon John Hunter, were causative of progressive angina; (2) the observation by Jenner’s friend and colleague Caleb Parry in 1799 that a threshold might exist for the onset of angina, according to the prevailing level of physical exertion; (3) Allan Burns’ hypothesis in 1809, that the mechanism of angina might be that of a myocardial equivalent to the claudication pain demonstrable in skeletal muscles of a limb; and (4) and John Warren’s recognition of the relationship between ‘ossification’ of the coronary arteries and angina.

At the end of the nineteenth and beginning of the twentieth centuries there was a greater preoccupation with the pathophysiological mechanisms of angina. Novel views were those of Clifford Allbutt, who focused on the nerve endings in the aorta and, with considerable prescience, those of Colbeck, who in 1902 favoured differential stretch of the myocardium and coronary spasm as potential causes of pain generation. Support for the mechanical hypothesis was also afforded by other clinical examples (eg, the description of ‘pseudoangina’ in mitral stenosis by Graham Steell [of murmur fame]).

In his masterful Lumleian lectures, Osler surveyed the epidemiology and etiology of angina pectoris and clinical features, including interesting comments about stress and tobacco. There is a detailed exploration of extra-pectoral sympathetic cardiac nerves was being proposed by François-Franck, as a treatment for angina, after Langley had discovered that electrical stimulation of the cardiac sympathetic nerves generated pain.

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In contrast with the mechanical hypothesis of generation of anginal pain, Lewis, in 1932, proposed a chemical hypothesis, suggesting that the intramyocardial release of pain-producing substances during ischemia might be the trigger for the painful sensation. Indeed, chemical hypotheses have largely prevailed ever since Lewis (see Tissue Level Effects of Ischemia section).

The overall historical development of understanding of the mechanisms through which coronary artery disease (CAD) contributes to myocardial ischemia and angina has been reviewed in detail by Bing.

### Angina’s Anatomical Substrate: From the Myocardium to the Cerebrum

#### Myocardial ischemia

The key factor mediating myocardial ischemia (Fig. 1) is an oxygen supply/demand imbalance and, typically, in the patient with CAD this is due to a critical stenosis of an epicardial artery. Such a stenosis sharply reduces coronary flow reserve (CFR) (the ratio of maximal to baseline myocardial blood flow) in the myocardial territory subtended by the stenosed vessel. Oxygen supply cannot increase adequately to satisfy the increased myocardial demand and aerobic metabolism can no longer be sustained downstream.

Ischemia may also be generated under conditions of increased demand without epicardial stenoses but with reduced CFR, for example, in left ventricular hypertrophy.

#### Tissue level effects of ischemia

At the tissue level, ischemia has a number of consequences. These include: (1) a build-up of adenosine from the breakdown of adenosine triphosphate (ATP), as well as the products of anaerobic metabolism, in particular hydrogen ions; (2) altered function of ionic transport mechanisms, increasing intracellular calcium loading and allowing leak of intracellular potassium ions; and (3) changed local mechanical forces, most acutely in the border zone between ischemic and nonischemic myocardium.

#### Sensory nerve endings in the myocardium

This topic has been described elegantly by Foreman. The sensory nerve endings in the myocardium are not specific, but rather are the endings of mixed myelinated (Aδ) and unmyelinated (C) fibres ‘forming bundles that can be traced through the septa between the muscles.’ Gradually these fibres form nerve branches that coalesce into the cardiac sympathetic and vagal components, with some evidence that sympathetic afferent fibres are distributed over the left ventricular wall, closer to the epicardial surface and vagal fibres are closer to the endocardial aspect and are distributed inferoposteriorly. (These localizations fit with certain clinical correlates of anterior vs inferior myocardial infarctions.)

At the myocardial tissue level, both chemosensitive and mechanosensitive nerve endings display responsivity to bradykinin. The chemosensitive endings are additionally sensitive to potassium ions, prostaglandins, leukotrienes, and adenosine and exhibit chemosensitization to bradykinin. Adenosine, its actions mediated through A1 and, to a lesser extent A2 receptors, has served as model for the generation of cardiac pain and
has been investigated in patients and normal subjects by Sylven and colleagues.\textsuperscript{26} It is likely that, besides the question of pain, adenosine plays an important role in the physiological regulation of the coronary microcirculation.\textsuperscript{27}

More recently, capsaicin sensitivity, via transient receptor potential vanilloid-1 (TRPV1) receptors has been the subject of intensive study. They respond to capsaicin, heat, and hydrogen ions at the myocardial (and spinal cord) level. The activation of these receptors leads to an influx of cations and a release of calcitonin gene-related peptide (CGRP) and substance P.\textsuperscript{28} Interestingly, these receptors may play a significant role in myocardial protection and preconditioning as well as algogenesis (the generation of pain).

The spatial and/or temporal patterns of activation of myocardial nerve endings have been considered by Malliani\textsuperscript{29} and others to have potential, according to their firing rates, in coding for ischemic pain. A more comprehensive conception of the cardiac neuronal system and its hierarchical arrangement has been presented by Armour,\textsuperscript{30} who contrasts the regulatory role of these neurons acting via cardio-cardiac reflexes in health, with their remodelled function in disease.

At the spinal cord level

From several lines of research, it has become established that the cell bodies of sympathetic afferent fibres are in the dorsal root ganglia of the C8 to T9 spinal segments, especially T2-T6. The dorsal root ganglion cells ascend via Lissauer’s tract and progress, principally via the spinothalamic tracts and medial pain pathway, to the posterior thalamus. Many more somatic fibres enter these tracts than do visceral pain fibres. In addition, a significant number of vagal fibres, connecting to the nucleus of the tractus solitarius and thence to the posterior thalamus, are also involved in the afferent conduction of painful stimuli. Foreman\textsuperscript{24} has pointed out that convergence of somatic inputs from the chest and upper arm tends to be with the sympathetic pathways, in contrast with the neck and jaw somatic convergence that accompanies the vagal pathways. The much greater number of somatic afferent pain fibres that accompany the visceral (sympathetic and vagal) fibres, as well as the longer time course of the somatic referral means that the actual painful episode (ie, angina), may be outlasted by the referred sensation (eg, local hyperalgesia).

The ascending fibres continue mostly within the spinothalamic tracts, having crossed over to the contralateral side, an terolateral quadrant, within 1 or 2 segments of entry to the cord. A minority of fibres remain ipsilateral as they ascend and some are in the dorsolateral quadrant. It is of interest that viscero somatic convergence, studied in detail in electrophysio-
logical studies involving stimulation of the cardiac nerves, suggests that there is little effect of such stimulation on the cell bodies in the C7 and C8 segments (forearm and hand representation) compared with C5 and C6 (upper arm) and C1 and C2 (jaw and neck). Besides the anatomical correlates of this, in terms of sites of referred pain etc, the considerable extent to which somatic afferents outnumber visceral ones also contributes to the poor localization of visceral pain and the rather spatially diffuse percept that it generates. As well as the afferent pathways described, several others may make a contribution but will not be discussed further here.

Projection of pathways to the brain

The forward projections of the neural pathways have been determined via a number of elegant methodologies applied to animals. Particular techniques include recording with microelectrodes at specific brainstem and cortical sites to assess the effect of discrete peripheral stimuli; secondly, the method of retrograde neuronal transport has been exploited, using agents such as horseradish peroxidase or localized injection of pseudorabies virus into the heart with immunocytochemical mapping of the retrograde pathways of transportation of the virus. Albutaihi and colleagues have reported on the elevation of neuronal c-fos synthesis in brain regions of rats as an indication of activation by capsaicin-induced cardiac pain. Heat shock proteins have also been measured in the brain in response to the same stimulus. As described in a number of major reviews, sympathetic afferent fibres travel predominantly via the dorsal columns to the ventral posterior lateral thalamus. Ventral posterior lateral neurons also receive visceral afferent inputs via the spinothalamic tracts. Vagal fibres mainly connect to the nucleus of the solitary tract and from there to the parabrachial nucleus in the pons and to the paraventricular region ventral to the ventral posterior thalamus. Rostral to the thalamus, cardiopulmonary inputs have been shown to activate neurons in the ventral and caudal (agranular) zone of the insular cortex. The insula is also connected to medial prefrontal cortical regions and to the contralateral agranular insular cortex. There is good evidence that the insula is involved in the monitoring of common visceral sensations and in modifying and integrating autonomic responses. As well as this, there are projections to the ventrolateral orbital cortex and to the primary somatosensory cortex. The parabrachial nuclei also have efferent connections to the hypothalamus and amygdala. A simplified schema is shown in Figure 3.

The central nervous system in cardiac pain perception: evidence from clinical studies

To explore the role of the higher centres of the brain in vivo, we adopted an interdisciplinary approach employing positron emission tomography (PET). PET is a powerful technique for the assessment of regional brain function. The actual parameter quantified by the PET method is regional cerebral blood flow (rCBF); however in most circumstances, rCBF is a reliable index of cerebral glucose consumption, which rises regionally when a given cerebral territory is activated. The glucose consumption is, in turn, coupled with Na/K dependent ATPase and therefore with neuronal firing rates. rCBF measurements have been employed to investigate many aspects of brain function, for example, responses to motor tasks or auditory or visual stimuli. In the 1990s, we applied the approach to the investigation of cardiac pain, initially reporting a study using PET with oxygen-15 labelled water to define the functional central nervous pathways activated by dobutamine-induced angina pectoris.

Compared with the resting state, angina was associated with increased rCBF in the hypothalamus, periaqueductal grey, bilaterally in the thalamus and lateral prefrontal cortex, and left
inferior anterocaudal cingulate cortex. In contrast, rCBF was reduced bilaterally in the mid-rostrocaudal cingulate cortex and fusiform gyrus and right posterior cingulate and left parietal cortices (Fig. 4). Several minutes after stopping dobutamine infusion, when the patients no longer experienced angina and the electrocardiographic changes had resolved, thalamic, but not cortical activation could be demonstrated. We proposed that the central structures activated constituted the pathways for perception of anginal pain. An important finding was that there was persistence of thalamic activation after the cessation of the symptoms and signs of myocardial ischemia. This prompted us to propose that gating of painful signals might occur at the thalamic level (Fig. 5).

**Variation in the Subjective Experience of Myocardial Ischemia**

Heberden's eloquent description of angina opened this article, but it is known that myocardial ischemia may also be painless or experienced as breathlessness and/or as overwhelming fatigue or just feeling 'very ill' in a rather undifferentiated way (see Other Affective Experiences Associated With Myocardial Ischemia section).

**Silent myocardial ischemia**

As noted above, Warren provided an early description of the relationship between 'ossification' of the coronary arteries and the development of (ultimately fatal) heart disease. However, he also made the equally important observation that the correlation between symptoms and the pathoanatomy was poor. It is back to this point that the much later recognition of the phenomenon of silent ischemia can be traced.

The relationship between pain and ischemia turned out to be more complex than might have been thought. It was found that myocardial ischemia and infarction could occur in the absence of pain, with infarction being discovered incidentally on electrocardiogram (ECG) monitoring or being inferred retrospectively after postmortem demonstration of significant CAD and/or scarring. The invention by Holter of a reliable recording device for ambulatory ECG monitoring led to the discovery that episodes of painless ST-segment depression were common and reflected reversible "silent" myocardial ischemia. Indeed up to 70% of episodes of myocardial ischemia in patients with CAD may be asymptomatic. In the case of acute myocardial infarction, the incidence of painless events has been estimated at approximately 30%. In that ischemia-related chest pain can be considered to be an early warning system for myocardial injury, silent ischemia can be viewed as a failure of that early warning system. Correspondingly, it is associated with a poor prognosis (eg, after unstable angina or myocardial infarction). Silent ischemia has also been assumed in patients in whom the first presentation of their coronary disease is sudden death. Silent ischemia has also been found during exercise in cardiac arrest survivors and in patients with life-threatening arrhythmias.

Several hypotheses arose to account for the silence of silent ischemia. These included: mildness of the ischemic episode, diabetes-related autonomic neuropathy, enhanced activity of central nervous opiate system, and central attentional factors. However, the fact that silent ischemia often coexists with painful ischemia in the same patient precludes any simple explanation.

Building on our earlier PET-based method we addressed the question as to whether the silence of painless myocardial ischemia was due to abnormal central nervous handling of afferent messages from the heart. In contrast to our earlier findings in patients with coronary disease and angina, we found that in nondiabetic patients who experienced silent myocardial ischemia (proven on stress echo), both thalami were shown to be activated, but cortical activation was limited to the right frontal region. A formal comparison of the 2 groups revealed significant differences for activation of the basal frontal cortex, ventral cingulate cortex, and left temporal pole (Fig. 4). In both groups, thalamic rCBF remained increased after the symptoms and signs of ischemia had ceased.

Because in both painful and silent ischemia, bilateral activation of the thalamus was shown, we considered that peripheral nerve dysfunction could not offer a complete explanation for silent ischemia. Frontal cortical activation appeared to be necessary for the sensation of pain. We hypothesized that the silence of silent myocardial ischemia might find its explanation in abnormal central processing of afferent pain messages and gating at the thalamic level might be key.

**Other affective experiences associated with myocardial ischemia**

Pain is quite a narrow part of the overall spectrum of negative affective experience that might be experienced by the patient with myocardial ischemia. In addition to the sense of imminent death (angor animi) long known to accompany angina, the symptoms also include a severe and all-pervasive fatigue, as well as shortness of breath and, at times, gastric or other abdominal pain, as well as the more classically 'vagal' feelings of nausea and sweating. The key point here is that this group of symptoms are genuinely associated with myocardial ischemia; we are not talking about the differential diagnosis of other etiologies of chest pain.

As to how the symptoms come about, we must return to the anatomical pathways described above. In particular, it should be remembered that the sympathetic afferents actually ascend as cardiopulmonary bundles rather than purely cardiac. However, there are other related phenomena. For instance, myocardial ischemia may evoke a rise in left ventricular end diastatic pressure, which may in turn activate peripheral afferent vagal fibres in the lungs.

Besides its occurrence at the peripheral nerve level as just described, afferent neural cross-talk also occurs at several levels of the neuraxis to expand the range of symptoms experienced. From a different, possibly teleological perspective, the fatigue and reduced effort tolerance might even be seen as an adaption to the inability to match myocardial oxygen demand with supply. It is well known to clinicians that patients with angina often improve symptomatically by subconsciously reducing their levels of physical activity.

**Modulation of Pain Pathways at Multiple Levels**

Chronic pain syndromes are common and present to some degree or other in up to 20% of the general population and the response to current treatment is rarely better than 40%. Several studies have contributed to an awareness
Figure 4. Regional cerebral blood flow changes in silent ischemia compared with angina pectoris. 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 anatomical localization of the activation foci. The latter are displayed as statistical parametric maps in the same stereotactic anatomical 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 patient groups according to the same linear colour scale (threshold for significance: 3.7). AC-PC, intercommissural plane; distances are expressed in millimetres from this reference (AC-PC) plane. (B) Transverse section of gross brain at thalamic level, labelled to aid orientation of the images in (A). (B) Reproduced from http://library.med.utah.edu/WebPath/HISTHTML/NEURANAT/CNS350A.html with the kind of permission of Edward C. Klatt, MD.
that modulation of the pain pathways can occur at any level of the neuraxis (Fig. 3).

At the tissue level

Modulation of the peripheral trigger of the myocardial pain stimulus can occur in several fascinating ways. Adenosine, acting via A2 receptors is a known mediator of pain and insensitivity to it has been posited as a contributor to the silence of silent ischemia. However, the same nucleotide can exert an analgesic effect via A1 receptors. Interactions of adenosine and substance P can amplify the algogenic stimulus.

Spinal cord neuromodulation

The notion that afferent pain traffic could be controlled at the spinal level is credited to Melzack and Wall who proposed their ‘gate theory’ in 1965. Important subsequent discoveries included that of endorphins and enkephalins, acting via spinal and central opiate receptors; Perl’s report of the sensitization of nerve terminals by inflammatory mediators and the finding of long-term potentiation at the hippocampal level by Bliss and Lomo in 1973.

An important role for γ-aminobutyric acid (GABA) receptor antagonists in the modulation of secondary hyperalgesia—a useful model of central sensitization—has been reported by Ianetti and colleagues. Electrical modulation of these pathways can also be achieved, particularly using spinal cord stimulation (SCS) and combinations of these treatments may be of value.

Neurophysiological studies of neuromodulation

Employing multichannel electroencephalogram to evaluate the responses to painful peripheral stimuli, it is possible to demonstrate negative and positive potentials (the peak early latency components N1 and P1 and later latencies N2 and P2) which can allow the discrimination of regions involved in primary registration of a painful stimulus, from other areas likely to mediate modulation or other processing. This allows quantification of the central nervous system’s ability to habituate to repeated stimuli.

The pain matrix

An important concept to emerge in the last few years is that of the pain matrix. Thus, rather than thinking in terms of a localized and specific ‘pain centre’ a more developed view is that of a looser network of different brain regions which, among a range of functions, subserve the perception of pain. Their interactions are complex, such that pain is not only registered, but can also be modulated. For example it is possible for an affenter pathway to evoke responses that imply origination from a different locus. In the case of visceral pain, a range of chest pains may be more evident through secondary hyperalgesia than the original trigger of repeated esophageal inflammation and/or distension.

The spectrum of modulation is extremely broad and can range from the complete blocking out of conscious pain sensations, to feelings of extreme pain with little or even no peripheral stimulation.

Pain modulation and central sensitization

Mood, cognitive set, context, and structural and neurochemical factors have all been shown to contribute to the modulation of pain perception. Depression and anxiety increase perceived pain. Foreman and Qin have described an impressive series of studies to demonstrate the presence of glucocorticoid-sensitive neurons in the central nucleus of the amygdala, a pathway from which descends to modulate nociception in upper thoracic spinal interneurons. This represents an important potential link between anxiety (which raises glucocorticoid levels) and hypersensitivity to nociceptive input from the heart. The N-methyl-D-aspartate (NMDA) receptor has also been implicated in heightened sensitivity to pain, a process antagonized by ketamine.

In addition, there are now hard data on the impact of expectation/anticipation, belief, and empathy. Critchley et al. have examined the role of attention and distraction, focusing on interoception; Dunckley and colleagues have also explored the influence of attention (Fig. 6).

Potential detrimental effects of efferent reflex responses to angina

Besides the intrinsically undesirable experience of pain, there are other detrimental efferent neural responses to myocardial ischemia. High levels of adrenergic activity can be evoked which, through a vicious cycle can increase myocardial oxygen demand, worsen ischemia, and produce more angina. There are data suggesting a reflex cardiac vasoconstriction evoked by the original chest pain. High central sympathetic tone is also proarrhythmic, in addition to any local myocardial proarrhythmic effects of ischemia. The broader question of brain–heart interactions in the genesis of arrhythmias has recently been comprehensively reviewed by Taggart, Critchley and Lambiase (Fig. 7).

Toward a functional cardiac pain syndrome—the ‘sensitive heart’

A relatively small number of patients experience angina-like chest pain, exhibit ischemic-like changes on the stress ECG but have angiographically normal coronary arteries; this disorder is widely known as cardiac syndrome X. (A restrictive definition has been chosen deliberately, to achieve a more clinically ho-
mogeneous patient group.) The epidemiology, clinical picture, and potential pathophysiological mechanisms of pain in this condition have been described in detail elsewhere. To the early literature on this topic was heavily focused on myocardial ischemia as the cause of pain and, in the absence of epicardial disease, Cannon and Epstein identified the coronary microcirculation as the likely site of dysfunction, coining the term ‘microvascular angina.’ Some more recent studies (eg, from the Women’s Ischemia Syndrome Evaluation [WISE] group) have also supported this point of view. However, several studies have very much weakened the case for ischemia (eg, failure to demonstrate either ischemia of any significance or the reduction in regional contractility that the latter would bring about) as well as clear evidence of abnormal pain perception (see list below) led Cannon (reference and personal verbal communication) and many others to

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**Figure 6.** Central modulation of afferent signals. CNS, central nervous system; GABA, γ-aminobutyric acid. Adapted from Tracey and Mantyh.

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**Figure 7.** Potential detrimental effects of efferent neural responses to angina. ECG, electrocardiogram.
repudiate the notion that ischemia made any meaningful contribution to the etiology of this disorder.

Historically, it is of interest that although the term 'syndrome X' was coined by Kemp in 1973,81 commenting on Arbogast and Bourassa's landmark report82 (which itself assumed a nonischemic etiology for the problem), the idea of an entirely functional cardiac pain syndrome was already envisaged by MacKenzie,1 60 years earlier, under the diagnostic label of 'secondary angina.'

The positive evidence in support of syndrome X being a neurophysiological rather than a cardiac ischemic disorder includes the demonstration of:

1. A lower threshold for cardiac pain between syndrome X patients during pharmacological stress, whether with adenosine, epinephrine, or dobutamine infusion;76,83
2. The absence of relationships amongst myocardial blood flow (measured by PET), chest pain, and ECG changes;76 and
3. Studies of direct cardiac stimulation, either with a cardiac catheter85 or pacing wire.86
4. More recent pacing studies have shown that syndrome X patients had both increased perception of pain for a given pacing voltage and a greater tendency to complain.87
5. Abnormal central nervous processing is demonstrable in cardiac syndrome X shown by neurophysiological measurement techniques to measure laser evoked potentials. Syndrome X patients were unable to habituate to the stimulus in contrast to normal subjects or to patients with CAD.88
6. The fact that the only effective treatment tested in a randomized control trial has been imipramine;89 and
7. Functional neuroimaging studies,90 with PET and O15 water during high dose dobutamine infusion in the manner described above, demonstrated greater right anterior insular activity in the syndrome X patients in comparison with our earlier published data from patients with angina due to CAD.

On the basis of our earlier studies of the central neural correlates of painful and silent myocardial ischemia in patients with CAD, we suggested that the thalamus may exert a 'gating' or filtering role in limiting the further afferent transmission of signals from the heart to the cerebral cortex. We might therefore have expected that in syndrome X the gate or filter would be less effective. However, the finding that both the syndrome X patients and the normal controls had substantial and equivalent increases in rCBF in the thalamus obviously refutes such a simple schema. In contrast, the findings support the hypothesis that the chest pain in syndrome X involves modulation of cardiac afferent signals by altered cerebral cortical activity. In particular, we suggested that the right insular activation might be specific for a perception of myocardial pain without ischemic injury and that this activation is the cortical expression of the abnormal percept.

Relevant to this, Brooks and Tracey have written an elegant summary of current thinking on the unique role of the insula in pain perception.91

It is of note that as well as our own work suggestive of a central neural origin to a functional cardiac pain syndrome, the feasibility of such a situation has also been shown by Lenz, who generated pain in the absence of remote disease92,93 by direct stimulation of relevant brain regions.94

**Implications for Treatment**

**The balance of myocardial oxygen supply and demand**

The classic concept of angina is, in essence, a unidimensional affair. Angina is the consequence of a supply/demand mismatch with respect to myocardial oxygen consumption. This paradigm95 has, for most of the last 50 years, totally dominated the therapeutic approach to angina, through drugs to reduce cardiac work, increase myocardial blood flow,96 or reduce peripheral resistance, or interventions (surgical97 or catheter-based98,99) to revascularize the heart.

**Newer medical approaches to ischemia**

Even assuming the optimization of anti-ischemic medical therapy, the means to increase myocardial oxygen supply are limited. From the aspect of managing myocardial oxygen demand, better rate control, most recently by use of the novel negative chronotrope, ivabradine, offers a little more scope. Areas for development include the use of pharmacological agents to improve mitochondrial efficiency (eg, trimetazidine100) or enhance diastolic relaxation (ranolazine101) and, longer-term, intravascular gene therapy may be a promising approach, through the promotion of angiogenesis.

Despite the many advances in per catheter or surgical techniques, studies have shown that at least 10% of patients with troublesome ischemia are rejected for conventional revascularization.95 Reasons for such rejection include: unsuitable coronary anatomy; numerous previous revascularization procedures; lack of available graft conduits; prohibitively high perioperative morbidity and mortality due to extra-cardiac diseases; and advanced age.

As a further measure to increase blood flow into the myocardial tissue, transmyocardial revascularization (TMR) was developed. When compared with medical therapy, initial studies reported that 3 of 4 patients who had undergone TMR improved 2 or more functional classes after 1 year102 of follow-up, as compared with 32% of the patients who received medical therapy alone although mortality did not differ between the groups. Other studies of TMR (performed surgically or percutaneously with a myocardial laser) suggested no benefit beyond that of a similar sham procedure in patients blinded to their treatment. Furthermore, measurement of regional myocardial blood flow and CFR by means of PET failed to show improved perfusion following this procedure.103 It was even suggested that the early beneficial effects may be analgesic, through an action on the intrinsic innervation of the heart, rather than a true improvement in myocardial perfusion.

Enhanced external counterpulsation is a nonpharmacological technique, the likely mechanisms of action of which include improvement of vascular endothelial function and recruitment of collateral vessels and possibly improvement in diastolic flow and load-independent ventricular function. Enhanced external counterpulsation has been the subject of 2 multicentre registries in the US. The technique is time-consuming—requiring 35 hours of active counterpulsation during a 4- to 7-week period. However, on treatment, anginal symptoms were improved in approximately 75% of patients.104
A new paradigm for intractable angina: neuromodulation

Two clinical features of angina merit consideration. They are: (1) the poor correlation between the severity of symptoms and the extent of CAD; and (2) the variability in symptoms experienced by an individual patient; it becomes clear that a more sophisticated paradigm is required. The requirement is in at least 2 domains—the intellectual and the therapeutic.

Intellectually, we require a satisfactory frame of understanding that can accommodate the 2 issues just raised. It is here that concepts of neuromodulation have most to offer. It can be seen from the description earlier in this report, that neuromodulation may apply at all levels of the neuraxis, between the heart and the cerebral cortex. As such there are now several new therapeutic targets in dealing with the problem of intractable angina. Of the following, some are becoming established treatments, some remain theoretical possibilities.

At the myocardial tissue level. Modulation of the trigger to cardiac pain at the tissue level could be achieved by antagonism of adenosine A1 receptors. Crea, Gaspardone, and colleagues have examined the selective adenosine A1-receptor antagonist bamiphylline and consider it of value.105

The action of substance P could be attenuated by neurokinin-1 receptor antagonists (eg, L-703606) although currently these agents are receiving attention for a wider range of aversive experiences (eg, pain and nausea in cancer patients).106,107

At the spinal cord level. Although the use of sympathectomy dates back more than a century, the results were of variable quality at best, so the procedure was abandoned for many decades. In the 1980s, there was a renewal of interest, in the form of thoracoscopic excision of the cervical sympathetic ganglia, but because an open thoracotomy was required, with its attendant morbidity and mortality, its attractiveness was limited. In 1995 Wettervik et al.108 evaluated the antianginal effect of ‘endoscopic transthoracic sympathectomy’ in 24 patients with intractable angina. There were no procedural complications and sympathectomy resulted in a significant reduction in the frequency of anginal attacks with 10 patients (42%) becoming free of angina.

Thoracic epidural anaesthesia has been attempted with limited success. However, more elaborate techniques—transcutaneous electric nerve stimulation and SCS—have probably the largest evidence base.25 While the primary beneficial effect has been analgesic, without necessarily any improvement in myocardial ischemia, some studies have reported a significant increase in the average exercise time. Interestingly, one of the mechanisms suggested for the efficacy of SCS has been increase in myocardial blood flow by overcoming efferent sympathetic vasoconstrictor tone.109

Effects of SCS in syndrome X patients

After SCS had been shown to be of benefit in patients with chronic CAD and intractable angina pectoris, the technique was applied with good effect by Lanza and colleagues to patients with syndrome X.110,111 Long-term treatment is also effective.112 In addition, by combining the technique of laser evoked potential measurement with the therapeutic use of SCS in syndrome X patients, Sestito et al. were able to show that SCS could restore the ability of the central nervous system of these patients to habituate to the painful stimulus.110

At the level of the brain. At the level of the brain, there are multiple opportunities for modulating the sensation of cardiac pain. A consideration of the pain matrix as discussed in the section on Modulation of Pain Pathways at Multiple Levels, showed that there were several elements of the matrix for which (1) abnormal modulation of afferent signals from the heart could lead to the establishment and maintenance of a chronic cardiac pain syndrome, even without any noteworthy innate cardiac dysfunction; or, conversely, (2) therapeutic neuromodulation might offer novel modes of treatment (Fig. 7).

Psychological interventions

Higher levels of depression have been reported in patients with more painful ischemia than silent ischemia;113 however, the topic is controversial in view of the potential etiological role of depression in ischemic heart disease.

Anxiety scores for patients with angina are also elevated, particularly patients whose symptoms are less predictable. Negative emotions—especially hostility—are also more prevalent in patients with angina and, of significance, psychological interventions to deal with these and to reduce distress have led to improved outcomes.49

Pharmacological approaches

Pharmacological interventions for depression have been proven in numerous clinical trials to have beneficial effects on mood, which could help patients with intractable angina. However, it has been known since the early trials of tricyclics that the drug class at lower doses has pain-modifying properties, which may or may not include peripheral neural inhibition as well as central effects.

The same considerations apply to GABA agonists, although somewhat in reverse, in that the role of GABA agonists as neuropathic pain modulators has been the main focus and only recently has low dose usage of these drugs been suggested as treatment for depression. Furthermore, combination therapy using tricyclics and GABA agonists is likely to be of greater value than each drug in isolation. A limiting factor in the use of GABA agonists has been that of tiredness, but there are attempts being made to develop agonists such as TPA023 to target the subunits of the GABA-A receptor implicated in nociception, but not the subunit implicated in sedation (ie, a specific α2 and α3 agonist but sparing α1 effect). The combined effect of GABA agonism plus SCS is superior to either modality separately.

Other neurochemical effects that merit further investigation are the potential of clonidine or newer central α-agonists to modify the experience of pain in patients with intractable angina in association with psychological interventions as just noted. It would also be important to assess the effect of such an intervention on heart rate variability, in the light of the arrhythmic risks that accompany adverse changes in sympathovagal balance (which also has implications for rhythm). Newer imidazoline 1-receptor agonists would also be of interest in this regard.

Since the publication of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) study,114 selective serotonin reuptake inhibitors appear to be safe in patients with ischemic heart disease. Besides their antidepressant action, they have value in treating anxiety and therefore should theoretically
be useful in the context of failure of habituation and/or excessive interoception.

**Electrophysiological measures**

As well as the application of SCS, neurostimulation—the use of microelectrodes implanted deep in the central nervous system—is increasingly being used to dramatic effect in a range of conditions including chronic pain, and could potentially find a role in intractable angina.

**Conclusion**

The concept of oxygen supply/demand imbalance remains central to the understanding of angina and its treatment. However, an appreciation of the complexity and subtleties of pain registration and modulation will lead to a much more creative approach to the treatment of complex cardiac pain presentations.

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