When the Heart Hurts

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Pain Perception and Cardiovascular Control

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Abstract

The relationship between the sensation of pain and cardiovascular system has been investigated only over the past decades, highlighting significant connections between various areas of our central nervous system and the heart, putting such organs at a very close distance.

The nociceptive pathways lead painful stimuli across the nervous system to specifically designated areas, involving the phenomena of transduction, transmission, perception, and modulation.

The autonomic response to pain is able to determine a series of systemic effects, and the cardiovascular system is primarily involved, through the rise in heart rate (HR), arterial

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blood pressure (BP), together with respiratory rate and muscle tension.

Acute postoperative pain is a good example of how powerful stimuli, if not properly treated, may seriously affect the whole organism, leading in the end to increased cardiac workload and potentially lethal imbalance between oxygen demand and supply. This becomes even more evident in case patients become chronically exposed to pain.

The positive impact of analgesia on cardiovascular control, finally, indicates that this heart-brain relationship is real and can be a therapeutic target in order to improve not only the patients' symptoms but also their cardiovascular health.

Keywords

Pain · Cardiovascular · Autonomic system · Nociception · Acute · Chronic · Takotsubo · Analgesia

Introduction

According to the International Association for the Study of Pain (IASP) [1], pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [2]. There are, however, a few characteristics that must be highlighted:

- Pain is always a subjective feeling: as such, it may exist without depending on the ability of each individual to express it verbally; however, there are specific neurophysiological pathways that have to be understood beyond the verbal communication, in order for physicians to target the symptom and treat it successfully. For example, a sedated and intubated patient is surely able to feel pain but has no means to directly transfer this information to the clinician; therefore, it is the clinician's task to collect all those indirect signs of pain (e.g., increased blood pressure, increased heart rate) that may guide the diagnosis.
- Pain is most often, but not always, due to tissue damage or any other biologic/organic/pathophysiologic causes; in those situations, where pain is reported in the absence of biologic tissue alterations, yet still regarded as a very unpleasant perception, it should be accepted as pain, even if it happens for psychological reasons.

A recent paper in 2016 proposed a revised definition [3]: "pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components," in order to acknowledge that this human feeling has a substantial value through a wide range of nonverbal behaviors.

These aspects are crucial in the setting of Intensive Care Unit (ICU), especially considering the cardiac ICU, where considerable amounts of patients arrive immediately after major surgical interventions and have to be kept sedated and intubated for at least 12–24 h.

Nearly half of patients interviewed after ICU hospitalization report moderate to severe pain, at rest and during routinary procedures; pain in the ICU may have multiple etiologies that can be either related to the underlying illness, performed surgery, invasive procedures, incisions, penetrating tubes and catheters. Moreover, daily patient care procedures such as tracheal suctioning, turning, mobilization, and dressing changes are pain sources, often underappreciated by caregivers. Immobility may cause musculoskeletal stiffness and wasting or pressure ulcers. Mechanical ventilation, sleep deprivation, and delirium may further enhance physical and psychological discomfort, leading to an even higher perception of pain [4].

Pain assessment in the ICU is often suboptimal, with infrequent evaluations, poor documentation, and discrepancy in the evaluation methods; as a matter of fact, this symptom has huge interindividual variability in terms of intensity, threshold, and linearity between injury and severity.

To address these challenges, validated assessment tools exist to objectively quantify and qualify pain for critically ill patients. Self-reporting is the gold standard for pain assessment: The Numerical Rating Scale (NRS) permits patients

to rate pain on a numeric axis from 0 (absence of pain) to 10 (highest level of pain) [4].

Vital signs (blood pressure, heart rate, and respiratory rate) are widely used by clinicians for pain assessment, but they can increase, decrease, or remain stable due to physiologic conditions unrelated to pain. In circumstances where self-reporting is not possible, pain assessment tools that incorporate behaviors and physiologic variables can be used. Of those developed and validated for ICU use, the behavioral pain scale (BPS) and the critical-care pain observation tool (CPOT) have the strongest evidence for reliability and validity. Both scales can be used in patients with artificial airways. The BPS evaluates three behavioral domains: facial expression, movement of upper limbs, and compliance with ventilation in response to movement and painful stimuli. Each behavioral domain is rated from one (no response) to four (full response), with a composite score ranging from 3 to 12. The CPOT evaluates four behavioral domains: facial expressions, movements, muscle tension, and ventilator compliance. Each component is rated from 0 to 2 with a composite score ranging from 0 to 8. If patients do not have an artificial airway, the BPS and CPOT include a vocalization domain to be assessed [4].

Nociception

Although now conceived as a wider and more complex entity, involving also emotional and cognitive elements, the biologic pathways through which a painful sensation is evoked and transmitted across the human body have been extensively studied.

The whole process defining how pain becomes a conscious experience is called "nociception."

It involves specific peripheral receptors, i.e., "nociceptors," that respond to a harmful stimulus or to a stimulus that may become harmful, if prolonged, repeated, or administered at higher intensity.

They are usually divided into chemical, mechanical, and thermal and act by collecting the stimulation and subsequently sending it to the brain through the nervous system. In the central nervous system (CNS), the stimuli are interpreted and elaborated to eventually produce the definitive symptom. Nociception is based on four main phases: transduction, transmission, perception, and modulation.

Transduction is the phase where the stimulus (thermal, chemical, or mechanical) is transformed into electrical impulses, able to be conducted across the peripheral nervous system (PNS); in this phase, the noxious trigger activates the nociceptors, causing ion channels to open and promoting the generation of action potentials. The nociceptors are characterized by the phenomenon of amplification, i.e., enhancing pain transmission by releasing chemical substances able to further involve new nociceptors; for example, prostaglandins are able to sensitize nociceptors through direct peripheral interaction and are the main target of nonsteroidal anti-inflammatory drugs (NSAIDs). Other chemicals, such as endorphins and enkephalins, are endogenous pain inhibitors.

Transmission is the process of conduction of electrical impulses along peripheral nerve axons to the CNS. Through a complex sequence of synapses, involving a number of excitatory and inhibitory interneurons, nociceptive impulses that have reached the dorsal horn of the spinal cord can ascend to the CNS along two different spinothalamic tracts. The thalamus is the main relay station of sensory stimulation, but the ascending pathways also connect to hypothalamus, limbic system, and the reticular formation. Finally, the thalamus projects nerve fibers to the somatosensory cortex, together with other areas, in order to obtain an integrated response to nociception.

Perception is defined as "decoding"/interpretation of afferent input in the brain that gives to the individual specific sensory experience [5]. It involves the cerebral cortex, therefore it is the phase of conscious awareness of pain and its interpretation, according to a number of personal, emotional, cultural, and experience-related factors; this explains why pain perception and its threshold differ so much among individuals.

Modulation, finally, is the overall process by which all sensory stimuli can be enhanced or

decreased, through the action of supraspinal impulses coming from the pons, medulla, and midbrain.

There are neurotransmitters (e.g., endothelin, enkephalin) released by supraspinal areas that can inhibit pain transmission to the thalamus and the somatosensory cortex; equally, norepinephrine and serotonin are released by the dorsal horn of the spinal cord. Modulation is able to make individuals feel the same type of stimuli with different intensity; it is thus another reason for the variability of pain threshold among human beings [5].

Autonomic Response to Pain

There is copious evidence, both experimental and clinical, that nociception and the autonomic nervous system (ANS) are closely interconnected; this is believed to be crucial for survival or, at least, adaptation to the environment.

Across the whole CNS, a complex network involving spinal and trigeminal dorsal horns, brainstem, amygdala, hypothalamus, thalamus, and insular cortex facilitates transmission of neural impulses coming from somatic and visceral sensation getting subsequently integrated and modulating autonomic responses; in other words, any painful sensation is able to initiate involuntary motor, endocrine, cardiovascular, and emotional reactions in our body [6, 7].

For example, the midbrain periaqueductal gray matter (MPAG), in its lateral component, is able to initiate fight-or-flight responses characterized by sympathetic activation, causing tachycardia, hypertension, blood flow redistributions to face and lower limbs; this whole neural output originates from well-localized nociceptive inputs from spinal and trigeminal dorsal horns [7].

Concurrently, the ventrolateral MPAG, receiving poorly localized visceral inputs, is able to originate an opposite set of responses: bradycardia, hypotension, hyporeactivity.

It is common knowledge that sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), the two main branches of ANS, generally determine opposite responses; however, with regard to cardiovascular activity, SNS and PNS may interact in a more complex and structured fashion; while PNS typically influences decreased heart rate variability (HRV) and increased heart rate, SNS is mainly responsible for increasing heart rate by reducing the interval between ventricle contractions [6].

As a matter of fact, there is consistent literature supporting the link between painful stimulation and ANS arousal, rising with increasing levels of stimulus intensity. The most common signs of ANS response to pain are changes in:

- Respiration rate (usually increased)
- Muscle tension (usually increased)
- HRV
- Peripheral vasoconstriction (usually increased)

Therefore, pain may substantially affect the cardiovascular system directly, by altering the pathways regulating heart rate, and by modulating the tone of peripheral blood vessels, which has an impact on blood pressure and, ultimately, on cardiac hemodynamic balances [6].

HRV, i.e., the physiological phenomenon of variation in the time interval between heartbeats, measured by the variation in the beat-to-beat interval, in particular, attempts to unravel the relative contributions of SNS and PNS activity, therefore representing an interesting measure of ANS reactivity to painful stimuli. According to Koenig et al., HRV may also be of interest as a biomarker for specific pain-related diseases or a potential outcome parameter to monitor pain relief after specific therapies [8].

Like many organs in the body, the heart has dual innervation. Although a wide range of physiologic factors determine HR, the ANS is the most significant. Chronotropic (i.e., the timing of heart cycles) control of the heart is achieved via the complex interaction of the SNS and PNS branches of the ANS. More importantly, PNS influences HR in an inhibitory fashion. The basic data for the calculation of all the measures of HRV are the sequence of time intervals between adjacent heartbeats, known as the interbeat interval (IBI). Relative increases in SNS activity are associated with HR increases, and relative increases in PNS

activity are associated with HR decreases. Since PNS changes occur in the scale of milliseconds rather than seconds, the PNS influences are the only ones capable of producing rapid changes in the beat-to-beat timing of the heart. Despite several methods to record the IBI sequence, electrocardiography (ECG) is the most prominent. Different software solutions are available for the analysis of prerecorded IBI sequences [8].

Although mean HR has some predictive power, particularly in predicting morbidity and mortality, HRV, rather than mean HR, has a number of experimental and theoretical advantages; it is a physiologically grounded, theoretically explicated, empirically supported, and computationally tractable measure of autonomic function. Because HR is a product of the complex interplay of the two divisions of the ANS – the SNS and the PNS – changes in mean HR are only partially illuminating. HRV, on the other hand, attempts to tease out the relative contributions of SNS and PNS activity and may therefore be more appropriate to investigate underlying autonomic reactions to nociceptive stimulation [8].

Operating Room: Acute Postoperative Pain and Its Effects on Cardiovascular System

The sensation of pain was selected throughout human evolution as a mechanism of protection; it notifies tissue injury or damage and stimulates an organism to act in order to heal them. This is the case for any spontaneously occurred lesion in the body, whether it is from a disease or accidental trauma.

Surgery provokes pain, but since tissue disruption is usually more significant, painful stimuli are more sustained. Generally, any response to postoperative pain is proportionate to the extension of the tissue trauma, though with variability among individuals.

Peripherally, an acute inflammatory response breaks out after surgery, involving the release of cytokines and other types of immunomediators, causing erythema, vasodilation, and enhanced vascular permeability with edema and activation of nociceptors (peripheral hypersensitivity). An analogous phenomenon occurs in the dorsal column of the spinal cord. Sustained peripheral nociceptive signals cause accumulation of neurotransmitters, which lower the nociceptive threshold and enlarge the sensitivity territory. This brings nociceptive sensitivity to its maximum level (central hypersensitivity).

Due to specific interneuronal connections in the spinal cord, a series of reflexes is generated, enhancing sympathetic activity, which is expressed through an increase in heart rate, stroke volume, and peripheral resistance.

Vasoconstriction applies to all peripheral vessels, including visceral districts; moreover, uncontrolled skeletal muscle activity may be observed.

As a result, cardiac workload is substantially augmented, with a consistent increase in oxygen demand; in such frail conditions, tachycardia favors shortened diastolic filling and decreased coronary artery perfusion. In those patients already affected by abnormal coronary arteries, this imbalance between oxygen supply and demand becomes potentially lethal, as it can trigger myocardial ischemia. Also, extreme sympathetic stimuli of vasoconstriction, triggered by severe acute pain, may even induce coronary vasospasm and induce acute coronary syndromes, from unstable angina up to acute myocardial infarction.

Hypercoagulability has been implicated in the genesis of angina and myocardial ischemia after major surgery. Analgesia has been associated with reduction of this hypercoagulability, presumably by prevention of activation of platelets or improved fibrinolysis; for example, it has been demonstrated that epidural analgesia is able to positively interfere with the postoperative impairment in fibrinolysis, which is commonly seen after lower extremity revascularization surgery. This, in the end, leads to a lower incidence of postoperative arterial thrombosis. The pathophysiological mechanism has been hypothesized as follows: since steroids are able to increase levels of plasminogen activator inhibitor-1 (PAI-1), and high levels of PAI-1 are associated with an increased risk of postoperative thrombotic

complications (due to a weaker plasminogen activation, thus weaker fibrinolysis), analgesia, by reducing cortisol and catecholamine production in response to surgical tissue stress, may therefore have a significant impact on postoperative hemostasis [9].

Peripherally, acute pain may reduce venous blood flow, causing stasis and deep venous thrombosis, of which the well-known cardiovascular complication, i.e., pulmonary embolism, represents another threat. Reduced renal and hepatic blood flow is observed and associated with organ failure, particularly in case of preexisting pathology.

Finally, severe acute pain has an impact on the neuroendocrine system, as well; the hypothalamic-pituitary-adrenal axis is activated and the adrenal glands may contribute to sympathetic tone enhancement through the release of catecholamines in the blood.

Both result in catecholamine secretion, catabolic hormone secretion, and increased oxygen demand.

In summary, severe acute pain may exacerbate the stress response increasing perioperative morbidity and mortality, especially in patients with cardiac disease [10–12].

Chronic Pain and Cardiovascular Disease

It is well known that many cardiac diseases usually cause pain: acute myocardial infarction or pericarditis are the most common examples.

However, there is still scarce knowledge about how, on the other hand, pain from other origins can specifically affect the cardiovascular (CV) system.

In fact, this happens by multiple mechanisms, up to a point for which sudden cardiac death may occur in chronic pain patients who experience a severe pain attack. One of the goals of pain therapy should be to address the patient's CV system and stabilize its homeostasis, and it particularly applies to elderly patients, who have either overt or covert cardiovascular disease or who may be at risk of developing it.

The consequences of pain may have deleterious effects both in the case of acute settings, such as after surgery, and during the course of a chronic disease, such as rheumatic syndromes; this setting is particularly dangerous, as the exposure of the patient's body to pain is long lasting and continuous, and its negative effects may cumulate over time.

Chronic pain is a potentially disabling condition affecting one in three people through impaired physical function and quality of life; its potential connection with CV disease has been demonstrated across a spectrum of chronic pain conditions including low back pain, pelvic pain, neuropathic pain, and fibromyalgia.

So far, a number of significant consequences of chronic pain on the human CV system have been characterized: the main ones are the effect on hemodynamics, on coronary artery disease (CAD), and the effect on lipidic metabolism.

Pain causes elevation of blood pressure and pulse rate by two basic mechanisms: the sympathetic nervous system is stimulated by electrical pain signals reaching the brain, as it occurs in acute pain, during flares, or breakthrough pain. The neuroanatomic brain changes that may occur with severe chronic pain appear to produce continuous sympathetic discharge.

Some chronic pain patients have persistent tachycardia, defined as a pulse rate over 100 beats per minute. The apparent cause is continuous sympathetic discharge from rearranged neuroanatomy which imbeds the memory of pain in its circuitry. Despite aggressive analgesic treatments (opioids), and adjuvants such as antidepressants or benzodiazepine, such symptom may not cease.

Painful stimuli can also cause significant release of epinephrine from the adrenal glands, mainly through a hypothalamic-pituitary-mediated signaling pathway. This not only increases cardiac inotropism and chronotropism but also enhances peripheral vascular tone, affecting cardiac afterload.

This explains why uncontrolled pain is hazardous in patients who have arteriosclerotic heart disease; sudden and dramatic vasoconstriction, affecting coronary arteries, may cause various degrees of acute coronary syndromes, that can even be lethal in patients suffering from

severe atherosclerotic burden or other forms of preexisting cardiopathy.

Finally, chronic pain states are known to raise serum lipids. Although the mechanism is not known, there is evidence of serum cortisol elevations during uncontrolled pain and elevated cortisol is known to elevate serum lipids and glycemia. Moreover, the majority of chronic pain patients eat a diet which is overloaded with carbohydrates and which might lead to obesity and elevated lipids.

The biological credibility of a model in which chronic pain predisposes to cardiovascular disease through sympathetic stress or inflammation would be strengthened by evidence of a dose-response relationship. In a recent systematic review and meta-analysis, the authors reported that all associations between chronic pain phenotypes and cardiovascular outcomes (cardiac disease, cerebrovascular disease, and cardiovascular mortality) appeared to be stronger (i.e., larger effect size); this represents mounting evidence that chronic stress or inflammation may provide a biologically plausible pathway from pain to cardiovascular disease [13, 14].

Neurogenic Stunned Myocardium and Takotsubo Syndrome

Acute stress-induced (takotsubo) cardiomyopathy has a dramatic clinical presentation, mimicking acute myocardial infarction (MI). The takotsubo syndrome is a fairly rare event, 1:36,000. The male/female ratio is about 1:3. It is more common in postmenopausal women, without significant cardiovascular risk factors. The main characteristic of this condition is the transient balloniform modification of the left ventricle, due to stimuli of neurogenic origin, due to physical or emotional stress. This deformation (clearly visible with echocardiography or magnetic resonance) makes the left ventricle assume the shape of a basket (tsubo) used by Japanese fishermen for octopus (tako) fishing. The syndrome presents with prolonged chest pain (angina), for an effort (50%) or at rest.

There is considerable variability in the ECG pattern at presentation, as it is for acute MI. The patients with takotsubo can present with a normal ECG, ST/T wave changes and ST-elevation, left bundle branch block (transient), and/or arrhythmias. Coronary angiography showed no significant stenosis. Laboratory tests (such as troponin) reveal an alteration of myocardial necrosis indices, but the values never reach high levels.

An important characteristic of takotsubo is the spontaneous recovery of the left ventricular ejection fraction, which returns to normal in all patients over a variable period of time (days to weeks) [15, 16].

Pain Therapy

Considering the significant connection between pain and the heart, it becomes crucial to analyze the effects of pain relief on cardiac homeostasis and hemodynamics.

We have seen that the heart is a major target of the adrenergic cascade of pain response, and it is easily affected in case of preexisting pathology.

Although any clinical scenarios would be suitable, particular interest is found in the setting of cardiac surgery, where the heart itself undergoes substantial stress and structural changes, becoming even more vulnerable to pain and its consequences.

In this setting, not only is the heart manipulated and traumatized but also the whole body goes through a massive release of proinflammatory mediators and adrenergic stimuli, triggered by a number of factors: sternotomy, thoracotomy, bone fracture and dislocation, artery dissection, tissue retraction, vein harvesting, and the need for numerous vascular catheters and thoracic drains, which usually have to be kept in place for several days.

Such clinical background represents a valid model of how pain relief may affect cardiac health.

Therapeutic Options

Postoperative pain (POP) after cardiac surgery is more intense within the first 2 days after surgery, and it is perceived stronger by younger

people, females, and patients who suffer from preoperative pain.

There are a number of therapeutic strategies to treat POP, but they may generally be divided into two main categories: systemic drugs and regional techniques.

Systemic Drugs

This category includes a series of pharmacological treatments that are usually administered intravenously; they spread through the whole body and have different targets, according to the type of molecule, and, consequently, a series of systemic side effects, due to the wide distribution of the drug.

Paracetamol is one of the most frequently used analgesic drugs; however, its mechanism of action is not totally understood. Paracetamol does not appear to inhibit the function of any cyclooxygenase (COX) enzyme outside the central nervous system, but it selectively inhibits COX activities in the brain, which may contribute to its ability to treat fever and pain [17].

Nonsteroidal anti-inflammatory drugs (NSAIDs) act as nonselective inhibitors of COX, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid. Prostaglandins act (among other things) as messenger molecules in the process of inflammation [18].

Opioids bind to specific receptors in the nervous system and other tissues. There are three principal types of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to 17 have been reported, and include the ε, ι, λ, and ζ (epsilon, iota, lambda, and zeta) receptors [19].

Regional Techniques of Analgesia

This category includes various techniques, usually through an invasive approach, that provide the administration of local anesthetics and/or opioids into predetermined areas; they allow selective targeting of confined anatomical sectors, thus a lower global dosage of drugs and their side effects. Compared to systemic drug administration, they require specific expertise, both for placement and for the following management.

Thoracic epidural analgesia (TEA) is the placement of a catheter in the epidural space, through which local anesthetics and opioids can be infused; according to the chosen vertebral space, different dermatomes may be involved.

Intrathecal morphine is the administration of low doses of morphine in the subarachnoid space; being morphine quite hydrophilic, it spreads across the cerebrospinal fluid, allowing a central and long-lasting (up to 24 h) analgesic effect.

*Local peripheral blocks (*e.g.*, parasternal, paravertebral, intrapleural)* provide the release of local anesthetics directly into the peripheral nerves or close to the surgical wound. They can be performed either as a single-injection procedure or as continuous drug infusion through a previously placed catheter.

The Impact of Analgesia on the Heart

Given the wide variety of pharmacological and technical options for analgesia, there is still no definitive consensus upon their impact on main cardiovascular outcomes.

This, at least, with regard to the setting of cardiac surgery.

Paracetamol seems effective at reducing pain, but it usually needs to be combined with another drug to obtain significant pharmacological synergy. NSAIDs have also been poorly studied so far, and their potential efficacy is counterbalanced by the widespread fear for the well-known side effects, among which bleeding, acute kidney injury, and increased risk for acute myocardial infarction (AMI) are worth reminding. Indeed, the link between NSAIDs and AMI represents a strong limitation to their use, but no definitive results are yet available; for example, it has been demonstrated that some molecules belonging to this class of drugs, such as ibuprofen, are not able to increase the risk of AMI significantly after cardiac surgery. In general, severe side effects

due to NSAIDs (and including AMI) do not seem to be significantly likely after cardiac surgery, but these results derive from a few small studies, and further data are necessary to confirm them. On the other hand, long-term use of NSAIDs, as it applies to the setting of chronic rheumatologic or immunologic diseases, is more clearly associated to severe cardiovascular complications, including hypertension, AMI, and atrial fibrillation; however, a potential confounding factor is the underlying chronic disease, which usually causes increased cardiovascular damage per se [20].

Opioids are traditionally used for analgesia in this surgical setting and are certainly better known for their respiratory side effects; however, recent evidence has come to attention about the potential link between opioids and the risk of coronary artery disease and cardiovascular death, again, in the setting of chronic diseases. Interesting hypotheses have been formulated to explain it: opioid receptors have been described in human myocardial cells and their chronic use or higher doses may increase ischemia and oxidative stress; remifentanil in rat myocardium demonstrated dose-dependent increased susceptibility to reperfusion injury. Chronic methadone and oxycodone use has been linked to prolongation of QT intervals and torsade's de pointes. Other studies have found increased inflammatory markers such as CRP and accelerated atherosclerosis in chronic opioid users. Methadone also increased platelet aggregation, decreasing protective effects of aspirin [21].

On the side of regional analgesia techniques, thoracic epidural analgesia (TEA) is the one showing the most promising results in terms of clinical benefits for the heart, being associated with a number of positive systemic effects besides the decrease of pain symptom itself. Various studies showed that TEA may improve respiratory and metabolic function, through the reduction of pulmonary atelectasis and through a better postoperative metabolic management with a lower degree of "stress hyperglycemia," respectively. Pulmonary and metabolic functions are directly connected to cardiovascular homeostasis and any positive impact on them may reflect on cardiac improvement as well.

However, TEA may also have specific and direct positive effects on cardiac performance, as it has been associated to increased stroke volume index and increased central venous oxygenation. Such benefits are probably due to the effect of TEA on systemic vascular resistance (SVR), which is usually decreased through the attenuation of sympathetic activity, mediated by local anesthetics [22, 23].

Systemic drugs and regional techniques, therefore, may certainly have a positive impact on the heart; the attenuation of adrenergic stimuli, obtained by the mitigation of pain symptoms, plays a key role. Moreover, treatments like TEA have shown potential further beneficial effects, both direct and indirect, on the heart.

Anyway, all current analgesic therapies have not yet shown a significant positive impact on major clinical outcomes, such as the length of stay in hospital, and may even determine severe adverse cardiovascular effects, especially if used in the long term.

Conclusions

In conclusion, it is now possible to investigate the close connection between the heart and the nervous system. There are various patterns of response to pain that determine different systemic effects, and the cardiovascular system is primarily involved. Acute pain and, above all, chronic pain, may carry on such stimulation, generating important consequences. The positive impact of analgesia on the cardiovascular system can be employed as a therapeutic target in order to improve specifically the patients' cardiovascular function and wellness.

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