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Contribution of Baroreceptor Function to Pain Perception and Perioperative Outcomes

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Abstract

Baroreceptors are mechanosensitive elements of the peripheral nervous system that maintain homeostasis by coordinating physiological responses to external and internal stimuli. While it is recognized that carotid and cardiopulmonary baroreceptor reflexes modulate autonomic output to mitigate excessive fluctuations in arterial blood pressure and to maintain intravascular volume, increasing evidence suggests that baroreflex pathways also project to key regions of the central nervous system (CNS) that regulate somatosensory, somatomotor and CNS arousal. In addition to maintaining autonomic homeostasis, baroreceptor activity modulates the perception of pain, as well as neuroimmune, neuroendocrine, and cognitive responses to physical and psychological stressors. In this review, we summarize the role that baroreceptor pathways play in modulating acute and chronic pain perception. The contribution of baroreceptor function to postoperative outcomes is also presented. Finally, methods that enhance baroreceptor function, which hold promise in improving postoperative and pain management outcomes are presented.

Summary Statement:

We discuss the evidence that baroreceptor function modulates acute and chronic pain perception and contributes to perioperative outcomes. As such, these little-studied associations represent an opportunity to investigate a novel process that impacts: 1) our understanding of physiological factors that mediate chronic pain and perioperative outcomes and 2) the implement novel interventions that will improve pain management and perioperative outcomes.

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Introduction

The central (CNS) and peripheral (PNS) nervous systems work in concert to maintain homeostasis in response to psychological and physical stressors. An ensemble of coordinated biological processes modulates sensory, emotional, motor, autonomic, neuroendocrine, and immune responses to tissue damage, including surgery.[1–5] Mechanosensitive baroreceptor afferents mediate physiological responses to internal stimuli by integrating and modulating PNS and CNS responses to internal stimuli and stressors to maintain homeostasis. These receptors respond to changes in arterial pressure (AP), venous pressure, and respiratory dynamics.[6–8] Baroreceptor afferents transmit information to discrete regions of the brain stem nucleus tractus solitarius (NTS), via afferents coursing in or with the vagus nerve (aortic depressor nerve and cardiopulmonary afferents) and glossopharyngeal nerve (carotid arterial baroreceptors). Carotid and cardiopulmonary baroreceptor reflexes modulate autonomic output to maintain resting blood pressure, buffer excessive fluctuations in AP (carotid sinus baroreceptors), and to maintain intravascular volume (cardiopulmonary baroreceptors). Baroreceptor activity engages CNS networks that regulate somatosensory, somatomotor, CNS arousal, as well as autonomic, neuroimmune, and neuroendocrine responses to physical and psychological stressors.[2] An important, but under-investigated, area of study is whether changes in baroreceptors contribute to pathological conditions in a variety of clinical settings. In this review, we summarize the neurobiology of the baroreceptor function and how baroreflex mechanisms are thought to contribute to acute and chronic pain conditions as well as perioperative outcomes.

Baroreceptor Reflex

Baroreceptor activation: Arterial, carotid sinus, baroreceptors are mechanoreceptors that are located in the aortic arch and carotid sinuses and are “tuned” to changes in systemic arterial pressure. These receptors have terminals associated with both myelinated (Aδ) and unmyelinated (C) afferent fibers in the inner adventitial layer of the arterial wall that respond to stretch generated by transmural pressure on a beat-to-beat basis.[8] Stimulation of arterial baroreceptors modulates transient changes in blood pressure to maintain a homeostatic set point for AP by dynamically adjusting sympathetic and parasympathetic output to the heart and the peripheral vascular system. Arterial baroreceptor mechanoreceptors respond to increases in intramural pressure depending on resting AP, mainly systolic and pulse pressure. As resting AP increases, a given incremental change in AP evokes greater activation of carotid sinus baroreceptor afferents, thereby promoting a greater increase in parasympathetic tone and a decrement in sympathetic tone. For normotensive individuals, the threshold for baroreceptor activation is at a carotid mean arterial pressure of approximately 60 mmHg[9], and it is active across the whole range of normal blood pressures.[10] This threshold changes with aging with lower carotid sinus pressure thresholds observed for young subjects (45 mmHg at 22 ± one year) compared to older subjects (80 mmHg at 61 ± two years).[11]

Nucleus tractus solitarius and cardiovascular response: The NTS is the central projection site for baroreceptors and modulates the activity of spinal and supraspinal networks that coordinate the responses to environmental stressors. The NTS sends excitatory

glutamatergic projections to the caudal ventrolateral medulla[12], which projects GABAergic inhibitory fibers to the rostral ventrolateral medulla.[13] This short neural circuit converts the baroreceptor excitatory input to NTS into an inhibitory output that reduces the descending excitatory tone originating in the rostral ventrolateral medulla that projects to the intermediolateral region of the spinal cord.[12,13] Activation of this pathway produces a reduction in cardiosympathetic tone and vascular resistance.[14] The NTS also sends direct excitatory projections to the dorsal vagal motor nucleus and nucleus ambiguus, which enhances parasympathetic output.[15,16] This baroreceptor-elicited shift in autonomic balance towards the parasympathetic side results in a reduction in heart rate, AP, and adrenal secretion of adrenaline.[17,18]

Assessment of Baroreflex Sensitivity and Influencing Factors

One way of assessing baroreceptor function is through the measurement of the baroreceptor sensitivity (BRS), which is typically defined by the relationship between the change in AP and the associated effect on inter-beat interval[19,20] and most procedures measure the change in heart rate as a function of the change in systolic AP (SAP). The development of reliable methods to estimate BRS has opened a window that enables the investigation of the role of baroreflex dysfunction in many medical conditions. The gold-standard procedure for assessing BRS is to measure the ratio of change in heart rate to the change in SAP in responses to the intravenous administration of a low dose of a vasopressor agent (e.g., phenylephrine).[21–26] In addition, non-invasive methods have been developed to allow for the assessment of BRS in response to the small natural continuous variations in blood pressure, i.e., 'spontaneous BRS.'[27] In Fig. 1 illustrates how the simultaneous recording of beat-to-beat SAP and heart rate is used to estimate BRS by the sequence method (For more details on the methods for the estimation of BRS see the Supplemental Digital Content 1).

Thresholds for normal and abnormal spontaneous BRS have been proposed by the Autonomic Tone and Reflexes After Myocardial Infarction Study.[25,28] In general, a normal BRS is defined as > 6 ms/mmHg a moderate dysfunction as 3–6 ms/mmHg, and severe dysfunction as < 3 ms/mmHg. However, estimates of BRS must be interpreted in the context of gender, age, and circadian rhythm. Female subjects have 50% lower cardiac baroreflex sensitivity than men[29], which is associated with lower AP and estrogen-mediated central sympathoinhibition and peripheral vasodilation.[30] BRS fluctuates across the reproductive cycle with increases during the mid-luteal phase when estrogen and progesterone levels are elevated[31,32] and around the ovulation[33] whereas it is markedly suppressed during pregnancy[34], contributing to pregnancy complications such as orthostatic hypotension and severe hypotension with peripartum hemorrhage.[31] Also, there is an age-related decline in BRS that results from increased arterial wall stiffness and a subsequent reduction in the ability of baroreceptor mechanoreceptors to process changes in arterial pressure.[35] This leads to increases in sympathetic nerve activity and SAP with aging.[36] Finally, diurnal variations in BRS have been identified in humans, with reduced sensitivity after waking compared to sleep, although other more complex patterns have also been described.[37]

Baroreflex Regulation of Pain Perception

Influence of arterial and venous blood pressure on pain perception: To date, most studies have indirectly examined the relationship between BRS and pain perception by examining the association of pain perception with experimentally-induced changes in AP and venous blood pressure (i.e., physiological events that activate baroreceptor afferent activity). In animals, vasopressor mediated arterial hypertension in response to vasopressor agents[38] or abdominal aortic occlusion produce hypoalgesia or antinociceptive behaviors.[39] Similarly, genetically hypertensive rats are hypoalgesic, which is reversed by lowering arterial blood pressure via ganglionic blockade or by right vagatomy.[40] Similarly, chronic hypertension induced by renal artery clipping or increasing dietary salt in salt-sensitive rats[41] induces a hypoalgesia that is reversed by lowering blood pressure.[42] Noteworthy, spinal nociceptive transmission is diminished in genetically hypertensive rats[43], and the observed hypoalgesia can be reversed with pharmacologic procedures that lower AP. Similarly, elevating arterial pressure in normotensive rats impairs spinal nociceptive transmission[39] and in normotensive animals lowering AP induces hyperalgesia.[40] Elevating venous pressure by volume expansion activates cardiopulmonary volume vagal afferents and evokes a profound hypoalgesia in rats.[44–46] In addition to venous blood pressure, the activation of vagal afferents with intravenously administered morphine, met-enkephalimamide, or other vagal afferent stimulants, produces an almost immediate cardiopulmonary mediated hypoalgesia in rats that appears to be independent of CNS penetration.[46–48]

An association between AP and pain perception has also been demonstrated in humans, with evidence that healthy normotensive individuals experience decreased pain sensitivity as a function of increasing resting AP.[49–58] In contrast, individuals with chronically low resting AP are prone to thermal hyperalgesia.[59] As observed in rats, hypertension-associated hypoalgesia in humans is correlated with systolic AP as opposed to diastolic AP.[57] The processing of nociceptive stimuli also varies throughout the cardiac cycle such that during systole (e.g., maximal baroreceptor load) pain sensitivity is diminished compared to during diastole.[60–63] There is a greater effect size of systolic AP compared to diastolic AP on pain sensitivity.[49,50,56,64–67] This further suggests a pain-modulatory role for arterial baroreceptors although the relative contribution of slowly and rapidly adapting baroreceptor afferents to sustained versus phasic changes in blood pressure on pain perception remains an open question.

Changes in AP have also been reported to contribute to the suppression of pain perception measured in conditioned pain modulation paradigms, procedures which assesses the strength of endogenous pain regulatory systems.[68,69] The strength of endogenous inhibitory pain positively correlate with increases in AP elicited by a noxious conditioning stimulus.[70] Considering that reduced conditioned pain suppression has been linked with the development of chronic pain[71], it remains to be determined if reduced baroreceptor function and blood pressure are risk determinates for acute perioperative and chronic pain.

It should also be noted that some studies have not observed a reciprocal relationship between AP and pain sensitivity. The hypoalgesia exhibited by hypertensive patients persists after

reductions of AP with medical treatment.[72] Hypoalgesia is already present in borderline hypertension and is antecedent to established hypertension.[72] Normotensives with a family history of hypertension, and a presumed genetic risk for hypertension, also have reduced responsiveness to acute pain despite having a normal resting AP[73–76], although this has been reported for males but not for females[77] and has not been observed by others investigators.[72] Moreover, pain tolerance measured in normotensive individuals at age 14 predicts ambulatory blood pressure later in life.[78] It has been proposed that mechanisms independent of AP, such as venous hypertension, which is antecedent to the expression of essential hypertension, may explain the temporal discordance between early life AP and pain sensitivity.[40] In support of this hypothesis, an increase in venous pressure – a stimulus that stimulates low-pressure cardiopulmonary baroreceptors and induces hypoalgesia - occurs before the onset of arterial hypertension in genetically hypertensive rats.[40] Furthermore, low-pressure cardiopulmonary baroreceptors, unlike arterial baroreceptors, do not reset and continue exerting a modulatory influence on pain processing in the presence of sustained elevation in AP.[79]

In summary, there is evidence that supports an association between AP and pain perception: pain sensitivity is correlated with responses to acute episodic changes in AP, is diminished in chronic hypotension, and is inversely correlated with resting AP in normotensive individuals. Also, a substantial body of functional and anatomical evidence supports the causal nature of this association. The temporal and causal relation between AP, BRS, and pain perception requires further investigation that promises to reveal a better understanding of the pathophysiological processes that contribute to aberrant pain perception and autonomic function.

Baroreflex stimulation and pain perception: The demonstrated relationship between pain perception and carotid sinus and cardiopulmonary baroreceptor activation[1,46,58,80,81] implies that this relationship can be affected by changes in BRS; however, the relationship between BRS and pain perception has been much less studied. Spontaneous BRS has been shown to be inversely correlated with ischemic and thermal pain responses in normotensive human subjects.[82] Similarly, a reciprocal relationship between BRS assessed during cold noxious stimulation has been reported in normotensive human subjects.[83] It should be noted that the relationship between BRS and pain is temporally dynamic and influenced by the individual's physiological and emotional status. For example, the magnitude of the relationship between BRS and cold pain perception is inversely associated with resting AP.[83] Moreover, BRS assessed with rises in AP increases versus decreases in AP are differentially associated with experimentally-evoked pain in normotensive subjects.[82]

In an attempt to provide insight into the causal nature of these associations, investigators have used direct mechanical or electrical manipulations of baroreceptors, which allow more stimulus control than other indirect methods of stimulation (e.g., tilt-table, pharmacological, and volume-induced AP changes). The mechanical stimulation of carotid baroreceptors with external neck suction, which simulates an AP increase, reduces mechanical pain[84] although it has no effect on thermal[84], electrically-induced pain[61], or experimentally-induced ischemic pain[85] in normotensive human subjects. In contrast, external neck compression, which mimics a reduction in AP, reduces electrically-induced pain ratings in normotensive

adults.[61] The electrical stimulation of the cervical vagus, which activates baroreceptor afferents, produces antinociceptive effects at high intensities and pronociceptive effects low intensities of stimulation in rats[86], cats[87], and humans.[88] Thus, carotid baroreceptors and vagal afferents exhibit a complex and dynamic influence on nociceptive processing.

Collectively, these findings provide evidence to support the view that baroreflex function modulates pain perception. The occurrence, efficacy, and directionality of baroreceptor reflex activity as indexed by BRS on pain perception is influenced by many factors, such as level of resting AP, pain modality, method of baroreceptor stimulation, among many other factors. At present, we do not know if alterations in baroreflex function contribute to chronic pain syndromes where BRS is known to be substantially reduced (see below section 'Clinical Implications of Impaired Baroreceptor-Mediated Pain Modulation').

Physiological mechanisms mediating baroreflex inhibition of pain: The mechanisms and pathways by which elevations in arterial and venous blood pressure decreases pain sensitivity are not fully understood. Arterial and venous blood pressure-related hypoalgesia have been associated with carotid sinus[46,62,89,90] and cardiopulmonary baroreceptors.[47,91,92] Several studies have documented an attenuation of hypertension-associated hypoalgesia by decreasing or interrupting the sinoaortic afferent limb of the baroreflex.[38,45,91,93] Volume expansion induces hypoalgesia that is partially reversed by right vagotomy.[44–46] In addition, noxious heat-evoked responses of wide-dynamic-range and high-threshold lumbosacral spinal dorsal horn neurons are reduced in spontaneously hypertensive rats compared to normotensive controls.[43] In agreement with this observation, spontaneous BRS correlates with the temporal summation of pain since higher resting systolic AP and greater BRS are associated with significantly lower temporal "wind-up" of heat pain in healthy human subjects.[94] These findings suggest that (a) AP-mediated hypoalgesia requires an intact baroreceptor afferent input and (b) the activation of second-order spinal nociceptive neurons by primary nociceptive afferents is inhibited by baroreceptor stimulation evoked by increases in AP.

Animal studies support a role for endogenous opioid activity as one of many possible endogenous neurotransmitter systems involved in hypertension associated hypoalgesia.[41,42,95–98] Maixner and colleagues demonstrated that naloxone reverses the hypoalgesia observed in spontaneously hypertensive rats in both pre-hypertensive neonatal and hypertensive adult animals.[40] Similarly, sympathetic inhibition resulting from baroreceptor stimulation is mediated by endogenous opioid networks in rabbits[99] that appear to originate in the NTS and rostral ventrolateral medulla.[100] Hypertensive rats exhibit neurochemical markers of elevated opioid activity in the spinal cord and other CNS nuclei.[41,101] Interestingly, it has been proposed that in the presence of essential hypertension there is reduced hypothalamic sensitivity to endogenous opioids, which leads to (a) a reduction in baroreflex-inhibition of the sympathetic output, (b) an increase and prolongation of AP response to environmental stimuli, (c) prolonged baroreceptor stimulation, and finally, (d) an excessive release of endogenous opioids.[102] The proposed excessive release of endogenous opioids, whether elicited by baroreflexes or by non-baroreflex mechanisms (e.g., a primary brain stem nuclei dysfunction[103]), may mediate the hypoalgesia seen in hypertensive conditions. In human studies, hypertensive subjects exhibit enhanced levels of circulating

endorphins and diminished sensitivity to noxious thermal stimuli.[104] Of note, pain-relieving actions of angiotensin II, which is increased several hypertensive conditions, have been related to the AT2-receptor-mediated central release of endogenous opioids.[105] However, a conclusive role for endogenous opioids in hypertension-associated hypoalgesia remains to be established, as naloxone fails to reverse hypoalgesia in hypertensive humans.[50,106]

A second likely mediator of hypoalgesia under hypertensive conditions and baroreceptor stimulation is the activation of α_2-adrenergic receptors in brain regions involved in both autonomic and sensory processing. Noteworthy, NTS, rostral ventrolateral medulla, and caudal ventrolateral medulla contain noradrenergic and adrenergic neurons.[100,107] Microinjection of the α_2-adrenergic receptor agonist clonidine into NTS produces analgesia mediated by opioid receptors in normotensive rats and spontaneously hypertensive rats.[108] Of note, morphine administration to the region of the NTS produces naloxone-reversible analgesia in rats.[109] Both analgesia induced by increased AP and hypoalgesia in spontaneously hypertensive animals are abolished following α-adrenergic blockade.[46,97,110] Again, the translation to humans is lacking, although there is indirect evidence that subjects with elevated AP within the normotensive range demonstrate increased pain tolerance along with higher circulating levels of norepinephrine.[111]

Clinical Implications of Impaired Baroreceptor-Mediated Pain Modulation

Baroreceptor Dysfunction and Chronic Musculoskeletal Pain: Emerging evidence suggests that diminished BRS not only augments the perception pain to experimental noxious stimuli but also contributes to the etiology of chronic musculoskeletal pain conditions, such as fibromyalgia, temporomandibular disorders, and chronic back pain.[58,64,112,113] In these patients, changes in the sensitivity to experimental pain and the perceived intensity of ongoing clinical pain correlates with diminished BRS and resting AP.[94,112,114] These chronic pain states share several features including altered autonomic nervous system function.[115] Specifically, many fibromyalgia patients show a high prevalence of orthostatic hypotension.[116] Fibromyalgia patients also exhibit a negative correlation between BRS sensitivity and clinical pain intensity and the severity of clinical complaints, and there is a reduction in resting BRS by nearly 35% in fibromyalgia patients compared to healthy control women.[113] Furthermore, systolic, diastolic, and mean arterial pressures are correlated with thermal and ischemic pain in males but not females, with higher blood pressure associated with lower pain sensitivity in males.[117,118] The observed sex difference in the blood pressure-pain sensitivity relationships coupled with a reduction in BRS in females may represent an important risk pathway that partially explains the female predominance of common chronic pain conditions like fibromyalgia[119] and sex differences in responses to both pharmacologic and non-pharmacologic interventions for pain.[120]

At the population level, there is a lower incidence and prevalence of common musculoskeletal pain conditions in individuals with elevated AP, supporting a relationship between hypertension and hypoalgesia in various chronic pain states. In a large headache study, higher systolic and diastolic blood pressures were associated with a reduced risk for non- migrainous headache[121] and chronic musculoskeletal complaints.[122] Moreover, there is a significant negative relationship between several self-reported chronic pain conditions and

hypertension.[123] The association between AP and the prevalence/incidence of chronic pain could be mediated by an impaired baroreceptor function that disrupts the normal modulatory effect of AP on pain processing. Whether altered baroreflex function represents a risk factor for the onset and persistence of chronic musculoskeletal pain and whether strengthening of baroreflex function represents a resilience factor that protects from common chronic pain conditions are questions that remain to be answered.

Baroreflex Dysfunction and Inflammatory Mediated Pain: BRS is inversely associated with carotid atherosclerosis inflammatory markers[124], subclinical hypothyroidism[125], and pregnancy-induced hypertension.[126] Baroreflex dysfunction can occur secondary to autonomic dysfunction in response to focal or systemic pathologies.[127] While autonomic dysfunction is generally thought to be a consequence of chronic inflammation, new research indicates that in many cases autonomic dysfunction actually precedes the development of some of these conditions. Compared to healthy controls, patients at risk of developing rheumatoid arthritis (i.e., positive for multiple auto-antibodies) have lower cardio-parasympathetic activity and elevated cardio-sympathetic activity, manifested by reduced HRV and elevated resting heart rate. Individuals at risk for rheumatoid arthritis display a cardio-parasympathetic/sympathetic profile similar to patients with established rheumatoid arthritis as well as higher serum levels of norepinephrine, an indicator of augmented sympathetic nervous activity.[128] In patients with rheumatoid arthritis who have suffered a stroke, inflammation is reduced on the paralyzed side.[129] Moreover, sympathetic tone is positively correlated with plasma IL-6 levels in hypertensive postmenopausal women.[130] Consistently, central sympathetic inhibition in hypertensive patients reduces systemic TNFα levels in young healthy non-pregnant women.[131] Thus, these clinical studies demonstrate a clear baroreflex and systemic autonomic dysfunction association with inflammation.

Animal studies suggest that the association between autonomic dysfunction and inflammation depends on the bi-directional communication between the autonomic nervous system, neuroimmune, and inflammatory processes (reviewed in detail elsewhere[132,133]). Thus, the severity of inflammation is not merely immune-mediated but is also modulated by the nervous and endocrine systems. Peripheral mediators of inflammation, specifically interleukin IL-1β and TNFα activate vagal afferents. The efferent limb of this reflex involves vagal parasympathetic fibers that release acetylcholine, which deactivates macrophages, preventing the secretion of inflammatory cytokines, and inhibits the synthesis of TNF-α in innervated immune organs, including the liver, spleen, and heart.[23,134] Moreover, baroreflex activation diminishes neutrophil migration and synovial concentrations of inflammatory cytokines TNFα, IL-1β, and IL-6 in the rat by inhibiting sympathetic drive to the knee in an experimental arthritis model.[135] Unlike parasympathetic anti-inflammatory effects, sympathetic stimulation is associated with pro-inflammatory effects mediated by that activation of adrenergic receptors on immune cells or indirectly via numerous mechanisms, including the production and distribution of lymphocytes and modulation of the release of pro-inflammatory peptides.[136] In a rat model of stroke, infection rates are reduced after sympathectomy, which attenuates sympathetically-mediated immunosuppression.[137]

Emerging evidence suggests a direct causal relationship between baroreflex function and inflammatory reflex arcs. The electrical activation of baroreflex pathways attenuates joint inflammation in experimental arthritis induced by the administration of zymosan into the femorotibial cavity in rats with lumbar sympathectomy, adrenalectomy, celiac subdiaphragmatic vagotomy or splenectomy.[135] Baroreflex activation attenuates neutrophil migration and the synovial levels of pro-inflammatory cytokines TNF, IL-1β, and IL-6 but not anti-inflammatory cytokine IL-10.[135] Baroreflex and autonomic dysfunctions also modulate local and systemic inflammatory in animal inflammatory models.[138] The autonomic regulation of inflammatory mediators act either directly on nociceptors or indirectly on sympathetic nerve terminals to produce and release inflammatory substances that contribute to the perception of pain[139] and chronic inflammatory pain conditions like arthritis.[140] In addition, afferent pain signaling can directly modulate other components of inflammation, including plasma extravasation and neutrophil function, which are modulated by vagal afferent activity.[141] The sympathetic contribution to hyperalgesia has also been demonstrated in humans[142], and it is well-described in neuropathic pain conditions such as complex regional pain syndromes.

Baroreflex Dysfunction and Perioperative Pain: The putative causal relationship between baroreflex dysfunction and exaggerated inflammation in human subjects is of substantial relevance to perioperative outcomes. Baroreflex dysfunction is observed preoperatively in patients with several comorbidities and postoperatively, particularly after endarterectomy or other neck surgeries affecting the carotid sinus nerve.[127] In a prospective surgical study [143] that examined thirty patients undergoing carpal tunnel surgery who underwent preoperative BRS testing and postoperative pain assessments at 6 weeks (acute pain) and ~1 year (persistent pain), there was a significant negative correlation between a measure of heart-rate variability (i.e., the square root of the mean squared differences of successive R-R intervals, RMSSD) and acute postoperative pain. Preoperative resting AP, and presumably, baroreceptor activation, has also been reported to be associated with postoperative pain intensity at 24 h and 48 h postoperatively in men undergoing prostatectomy, even after accounting for patient-controlled opioid use.[144] Similarly, there is a negative correlation between resting preoperative AP and postoperative pain after cesarean section.[145]

Baroreceptor dysfunction associated with impaired autonomic homeostasis increases the vulnerability to the hypotensive effects of general anesthesia.[146,147] Chronic hypertensive patients have lower baseline values of BRS and exhibit a more pronounced decrease in both systolic and diastolic AP following propofol administration.[148] Furthermore, endotracheal intubation, which is a sympathetic stimulus that should raise AP, decreases AP in chronic hypertensive patients.[148] Intraoperative hypotension caused by diminished baroreceptor activation is likely to contribute to augmented inflammatory reactions to surgical trauma, and as a result, to exaggerate acute postoperative pain and an increased vulnerability to chronic postoperative pain. Further work is required to establish the contribution of diminished BRS to perioperative adverse events, postoperative pain and the likelihood of developing persistent pain following common surgical procedures.

The Association of Medical and Health Conditions with BRS

Significant alterations in BRS have been observed in several diseases and health conditions (Fig. 2). Low BRS is commonly seen in patients with hypertension and diabetes[149,150], carotid atherosclerosis[151,152], obesity[153], in smokers[154], and high alcohol consumption.[155] Patients with obstructive sleep apnea have an attenuated BRS[156], which is associated with increased blood pressure variability[157], increased sympathetic activity[158], desensitization of vascular adrenergic receptors, and decreased peripheral vascular adrenergic responses.[159] In the context of perioperative outcomes, this autonomic dysfunction is of relevance since it is linked to cardiovascular morbidity and obstructive sleep apnea.[160] Autonomic dysfunction is also prevalent in patients with chronic kidney disease who have an increased risk of sudden cardiac death associated with reduced spontaneous BRS.[161] Interestingly, BRS dysfunction is correlated with glomerular filtration rate[162], suggesting that there is a direct association between reduced BRS and declining renal function. All of these BRS-associated events can be further aggravated by the fact that prolonged bed rest induces rapid detrimental changes in baroreflex function.[163] Congruent with a baroreflex-mediated modulation of pain, there is an increased prevalence of chronic pain and/or greater pain perception in patients with conditions with reduced BRS as well as obstructive sleep apnea[164], diabetes[165], obesity[166], chronic kidney disease [167], smoking[168], alcoholism[169], and hypertension[170], although the mechanisms mediating these associations are not yet well understood. (see Fig. 2)

Baroreflex dysfunction expressed as a reduced BRS has been reported in several cardiovascular conditions such as essential hypertension, impaired cardiac contractility[171], post-myocardial infarction sudden death[172], heart failure[173,174], coronary artery disease[25], and atrial fibrillation.[175] Baroreflex function has also been implicated in modulating muscle tone[62], sensorimotor performance[176], startle reflex[177], cortical activity[3], and sleep[178], cognitive performance[179–182], and cortical arousal.[80] Of note, about fifty percent of cardiac surgery patients[183,184] and up to 26% of elderly non-cardiac surgery patients[185] experience early postoperative cognitive dysfunction, which can persist in the long-term, significantly diminishing the life quality. The etiology of postoperative cognitive dysfunction is multifactorial and known to be associated with several patient-related factors.[186] It is not known if BRS contributes to postoperative changes in cognition. The pathophysiological processes involved in postoperative surgical outcomes are complex; however, it is clear that postoperative outcomes do not solely result from surgical insult but instead are strongly influenced by the patient's preoperative physiologic status that is regulated, at least in part, by baroreceptor function and BRS.

Is BRS a Modifiable Risk Factor?

While there are several interventions that can modify BRS, the most extensively assessed approach is vagal nerve stimulation, which has been evaluated for the treatment of a variety of conditions: neurological (partial seizures[187], drug-resistant epilepsy[188], tinnitus[189,190], traumatic brain injury[191,192], stroke[193]), psychiatric (Alzheimer's disease[194,195], cognitive decline[196], posttraumatic stress disorder[197], treatment-resistant anxiety disorders[198]), painful/inflammatory (headaches[199,200], rheumatoid arthritis[201,202], fibromyalgia[203], chronic pelvic pain[204], Crohn's disease[205]), and cardiovascular/metabolic (coronary artery disease[206], heart failure[207], hypertension[208–211], obesity[212]). Among these conditions where

pain, inflammation, cognitive impairment, and cardiovascular events are likely to occur, vagal nerve stimulation has been proposed as a preoperative optimization procedure with the goal of reducing the incidence of adverse postoperative outcomes.

Other less invasive procedures that have been suggested to increase BRS in a clinically meaningful way include increasing venous pressure via fluid management[45,213,214], acupuncture or somatic afferent stimulation[215–218], the stimulation of cranial vagal afferents arising from the ear's concha[219,220], cardiovascular conditioning[221–223], operant learning procedures[224], intraoral appliances[114], and relaxation/biofeedback therapies[225–228]. Future studies are required to assess the effects of these procedures on BRS, acute and chronic pain perception and perioperative surgical outcomes.

Conclusions

We have summarized the evidence suggesting a role for baroreceptor function in both acute and chronic pain conditions as well as perioperative outcomes. While the measurement of baroreflex function in the perioperative period currently remains mostly relegated to the research environment, the assessment of perioperative BRS is highly likely to yield important clinically meaningful information that leads to novel strategies for organ protection and pain management. Preoperative recognition of impaired baroreflex function as an important modifiable risk factor requires exploration. Further research in this field is warranted since it is likely to provide actionable information that will reduce the sequelae of surgical stress and improve the management of chronic pain, and adverse surgical outcomes. Existing non-invasive interventions known to increase BRS should be explored for managing patients with chronic pain and implemented preoperative to optimization surgical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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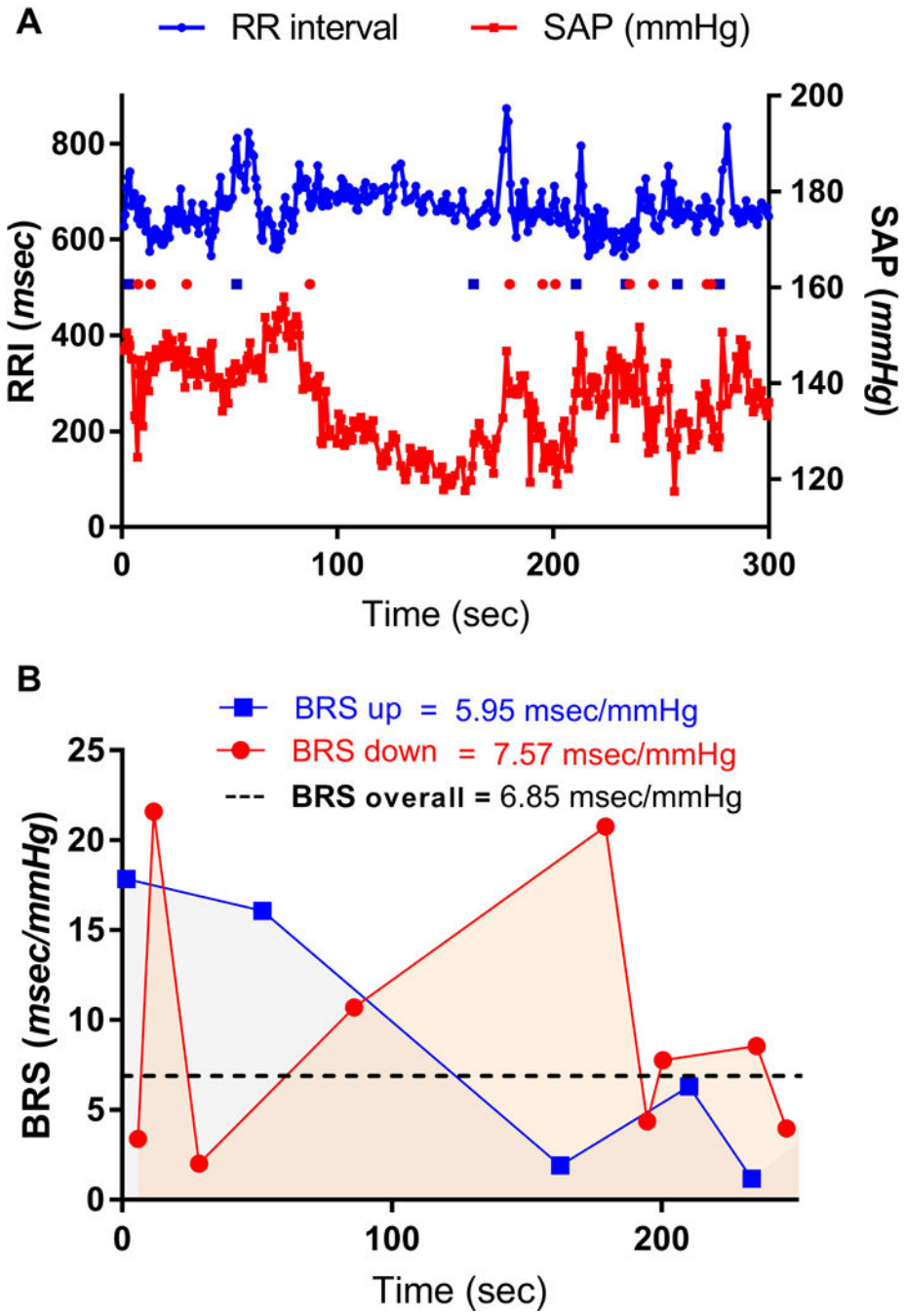

FIGURE 1:

Estimation of BRS using the sequence method. ECG and SAP waveforms are recorded simultaneously, then beat-to-beat SAP and the calculated R-R intervals (RRI) are plotted against time course. **Panel A:** SAP and RR interval signals and the baroreflex sequences acquired using the sequence method. Closed squares indicate UP sequences. Open squares indicate DOWN sequences. Sequence selection criteria: SAP > 0.5 mmHg, RRI > 1 ms, sequence > 3, a significant correlation coefficient (r > 0.9). Note that the significant sequences cluster in segments where SAP and RRI signals apparently oscillate more

coherently (in this case, at the start and the end of this recording.). **Panel B:** Within-subject variability of the BRS. Mean UP, DOWN, and overall BRS calculated from the sequences shown in panel A.

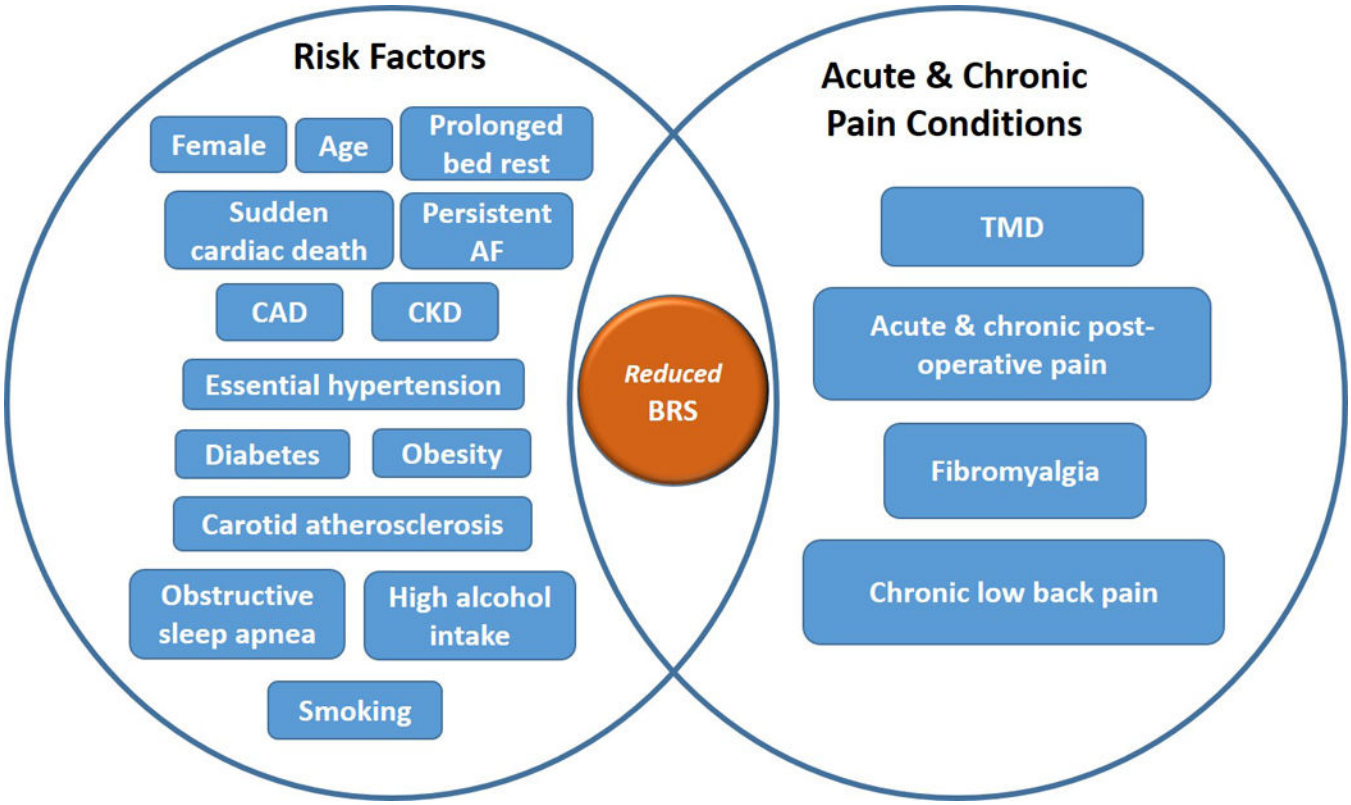

FIGURE 2:

Reduced BRS is frequently observed in patients with cardiovascular, renal, sleep, and metabolic disorders, a feature that is shared with acute and chronic pain conditions, and that is associated with high prevalent chronic pain in these disorders. AF: atrial fibrillation. CAD: coronary artery disease. CKD: chronic kidney diseases. TMD: Temporal mandibular disorders.

TABLE 1:

Association between BRS and AP with persistent postoperative pain

AP or BRS measurements	Surgical procedure	Outcome
Preoperative BRS	Carpal tunnel release	Negative correlation with both acute and persistent postoperative pain.[143]
Presurgical systolic AP	Prostatectomy	Negative correlation with 24h and 48h postoperative acute pain.[144]
Resting preoperative blood pressure	Cesarean section	Negative correlation with postoperative pain.[145]