■ REVIEW ARTICLE

Clinical Relevance of the Bezold–Jarisch Reflex

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THE idea that reflexes originating in the heart can play a role in normal physiology dates to the 1860s.[1] Until the 1950s, these reflexes, and the Bezold–Jarisch reflex (BJR) in particular, were regarded largely as pharmacological curiosities with the only practical application of the study of the BJR being the clinical use of a veratrum alkaloid as an antihypertensive agent. Since the 1860s, it had been known that injection of minute amounts (0.005 mg) of veratrine or its pure alkaloid components (veratrum) initiates a reflex which causes a rapid fall in blood pressure and heart rate in association with apnea.[1] This "Von Bezold reflex" was classically defined in association with arrest of breathing, but more recently, it has been called the BJR and includes the triad of bradycardia, hypotension, and peripheral vasodilation.[2]

It is now understood that certain inhibitory reflexes, which have origin with cardiac sensory receptors, play a role in cardiovascular homeostasis. Activation of a subset of these receptors by diverse stimuli increases parasympathetic nervous system activity, inhibits sympathetic activity and is responsible for eliciting the BJR. Some anesthesiologists have suggested that the BJR may explain cardiovascular collapse reported during regional anesthesia techniques.[3–9] This review focuses on the physiology of the BJR and its possible physiologic role in a number of clinical situations. It also provides discussion of the limited relevance of this reflex in regional anesthesia. The topic of clinical management will not be addressed given the paucity of data on this matter, but suggestions for future experimental direction are offered.

History of the BJR

The BJR

In 1867, von Bezold and Hirt[1] observed that an intravenous injection of veratrum alkaloids caused a profound decrease in blood pressure and heart rate in con-

junction with apnea. In 1915, Cramer (as cited in Dawes and Comroe[2]) described apnea, hypotension, and bradycardia following intravenous injection of veratrum viride extracts in cats. In the late 1930s, Jarisch and Richter[10,11] studied cats in which veratridine was injected before and after interruption of the cardiac branches of the vagus nerves; they confirmed that the depressor effect initially observed in 1867 was, in fact, reflex in origin. Cramer believed that the receptors for this effect were in the lung, but Jarisch argued that the receptors were located in the ventricle of the heart.[10,11] It was not until 1947 that Dawes *et al.*,[12] using veratridine in cats, showed that the reflex apnea was caused by a mechanism separate from that mediating the hemodynamic changes. Various terms since 1867 have been used to describe these events. Today, the BJR connotes the reflex as described by Dawes in the mid twentieth century: bradycardia, vasodilation, and hypotension resulting from stimulation of cardiac receptors.

Anatomy and Physiology of the Reflex

The BJR is an inhibitory reflex usually denoted as a cardioinhibitory reflex (table 1). Early clues as to the mechanism of the BJR came from observations that cooling or sectioning the vagus nerve (the afferent limb of the reflex) could abolish the aforementioned triad of bradycardia, hypotension, and peripheral vasodilation in response to injection of veratrum alkaloids.[2] Many subsequent studies have been devoted to the identification and localization of the receptors in the heart mediating this response and to defining the afferent pathways that mediate the BJR.

Afferent fibers of cardiac receptors that course in the vagus nerves are composed of two major fiber types: approximately 25% are myelinated fibers originating in the walls of the atria and in the atrial-caval junctions, and 75% are nonmyelinated fibers distributed in the walls of all cardiac chambers.[9,13,14] Animal experiments using selective stimulation and interruption of nerve activity have shown that the BJR has its origin in cardiac receptors with nonmyelinated, type C vagal fibers constituting the afferent limb of the reflex.[9,15,16]

The receptors in the walls of the four cardiac chambers are the nonencapsulated terminals of the C-fiber afferents and are heterogeneous in terms of their responsiveness to mechanical (pressure, inotropism, volume) and chemical (veratrum alkaloids, adenosine tri-phos-

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Table 1. Important Cardiovascular Reflexes

Eponym	Receptors/Afferent innervation	Effect(s)
High pressure receptors Baroreceptor reflex	Stretch receptors in the walls of arteries, carotid, and aortic bodies Afferent impulses carried via the nerve of Hering and vagus nerve to the medulla	Stimulation results in increased firing of the afferent limb with an increase in efferent vagal and decrease in efferent sympathetic nerve activity. Overall effect is to decrease heart rate, blood pressure, contractility and total peripheral resistance.
Low pressure receptors Atrial stretch type Bainbridge reflex	Stretch receptors of the atria sensitive to blood volume Afferent signals through the vagus nerves to the medulla	Stimulation of these receptors (via increased blood volume) stimulates heart rate and presumably contractility. Overall effect serves to pump 'extra' blood returning to the heart.
Atrial stretch reflex	Stretch receptors in endocardium of atrium release atrial natruretic factor, inhibit anti-diuretic hormone secretion from pituitary and decrease renin release.	Overall effect is to promote diuresis and natruresis
Cardioinhibitory type Bezold–Jarisch reflex	Receptors in walls of ventricles, both mechanosensitive and chemosensitive Afferent signals via the unmyelinated components of vagus nerve	Maintains tonic inhibition on vasomotor centers. Activation causes inhibition of sympathetic outflow coupled with bradycardia, peripheral vasodilation and hypotension.

phate, serum, amidine derivatives, capsaicin and venoms from snakes, insects and marine animals) stimuli, and most respond to veratrum alkaloids, the classic pharmacologic stimulus for the BJR (fig. 1).[9,15,17–23] Injection of veratrum alkaloids in the left or right coronary circulation causes not only bradycardia and a reduction in cardiac output, but also peripheral vasodilation.[2,24] This is accomplished *via* excitation of receptors in the cardiac wall supplied by the coronary artery.

The slowing of the heart is not the sole cause of the depressor response. Though the veratridine-induced bradycardia in dogs is abolished by atropine, the decrease in blood pressure is only partially attenuated.[2,25] Cutting or cooling the vagus nerve has a more pronounced effect than atropine administration, veratrum alkaloid being hemodynamically benign under such conditions,[25] suggesting that the BJR inhibits vasomotor output independent of heart rate modulation. These data are in accord with other evidence in cats, which also supports the idea that the BJR can independently modulate blood pressure and heart rate.[22]

Fig. 1. Classic activation of the Bezold–Jarisch reflex (BJR) by veratrum alkaloids. Originally characterized as a pharmacologic reflex, the BJR is activated by a variety of veratrum alkaloids. BJR activation leads to decreased vasomotor output, bradycardia, and hypotension. Hypotension and bradycardia occur in the presence of other intact reflexes, such as the baroreceptor reflex, which implies that BJR activation includes some type of inhibitory action on the baroreceptor reflex at either the afferent or efferent pathways. In this capacity, pharmacologic stimulation of the BJR makes it a dominant effector of blood pressure. In this and subsequent figures, the BJR is represented on the *right* and the baroreceptor reflex on the *left*. The *thick arrows* to the left of the text indicate change (increased or decreased activity). + = activation; − = inhibition; X = abolition of that particular step; the international "no" *circle* (crosshatched with line) indicates complete abolition of that pathway.
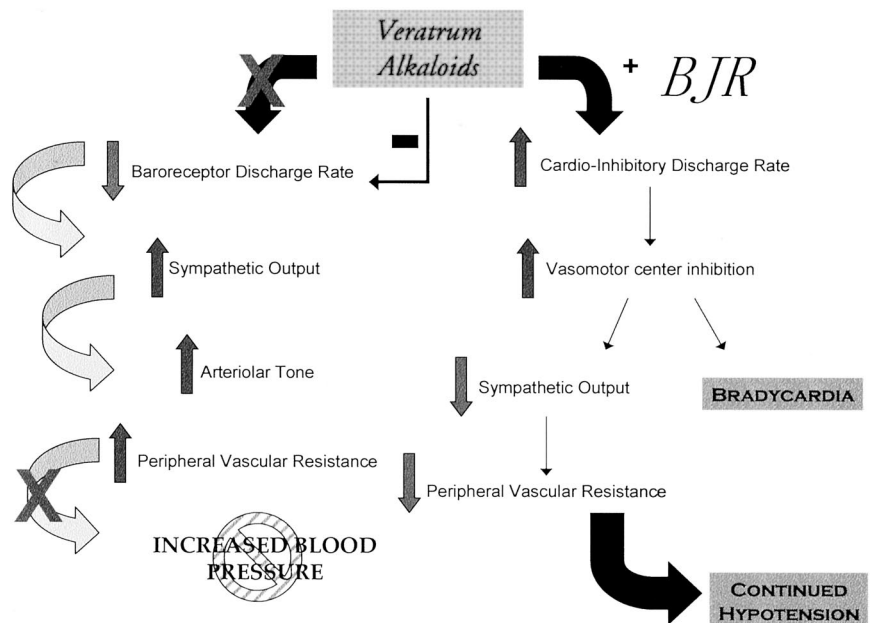
Table 2. Possible Physiologic Roles of the Bezold–Jarisch Reflex Process Strength of Evidence

Process	Strength of Evidence
Blood pressure regulation	*
Homeostatic response to hypovolemia	†
Effector of hemodynamic changes during myocardial ischemia	†
Hemodynamic changes during coronary angiography	†
Syncope associated with aortic stenosis	‡
Vasovagal syncope	‡

Evidence is discussed in text.

* Large body of animal and human data.   † Good animal data with some human data.   ‡ Minimal animal or human data.

Current Understanding of the Role of the BJR

Although the Veratrum alkaloids vigorously elicit the BJR, these compounds are not present in animals. The same question, therefore, that arose in the 1940s still vexes investigators today: what are the normal stimuli to these sensory nerve endings? Although not yet answered definitively, there has been great progress in our understanding of the triggering of this reflex and the role it plays in normal and abnormal circumstances (table 2).

Blood Pressure Regulation

The regulation of blood pressure in normal and pathologic states is complex with multiple systems participating in maintaining hemodynamic stability.[26] These multiple systems are integrated such that output from the medullary vasomotor centers (final common pathway) is tightly regulated in response to a variety of stimuli and perturbations. Vasomotor center output consists primarily of sympathetic nervous system activity and, during normal conditions, keeps blood vessels partially constricted; what is commonly referred to as *vasomotor tone*. Modulation of vasomotor tone is more complex than simple augmentation or attenuation of sympathetic tone. Local intrinsic regulation of arterioles (carbon dioxide, oxygen tension, and pH) combined with extrinsic vasomotor modulation, which integrates multiple systemic reflexes participate in the regulation of vascular tone.

The baroreceptor reflex (fig. 2), a primary homeostatic mechanism, includes stretch receptors in the carotid and aortic bodies whose afferent impulses are carried *via* the nerve of Hering and the vagus nerve, respectively, to the medulla. Firing frequency of the receptors is enhanced during increases in arterial pressure, resulting in an inhibition of vasoconstriction and peripheral vasodilation. Another systemic reflex is the BJR. The cardiac receptors mediating the BJR have very low basal firing rates in the absence of any stimulation,[13,27,28] and output from these cardiac receptors contributes tonic inhibition to the vasomotor centers.[9,13,15,16,29-31] These receptors, when stimulated by electrical excitation, show increased firing frequency with subsequent inhibition of the vasomotor centers, promoting vasodilation.[16,29]

It is well established that these BJR cardioinhibitory receptors, in conjunction with the aortic and carotid baroreceptors, participate in blood pressure regulation. There is an interaction between the two systems in blood pressure control such that they are complementary.[9,32] Animal preparations, where the baroreceptors can be isolated from the systemic circulation, have
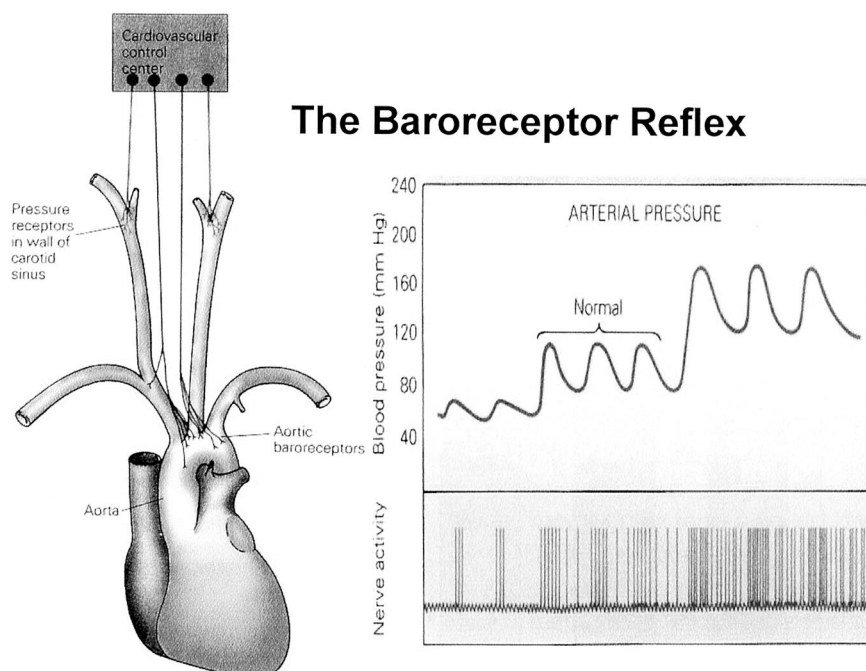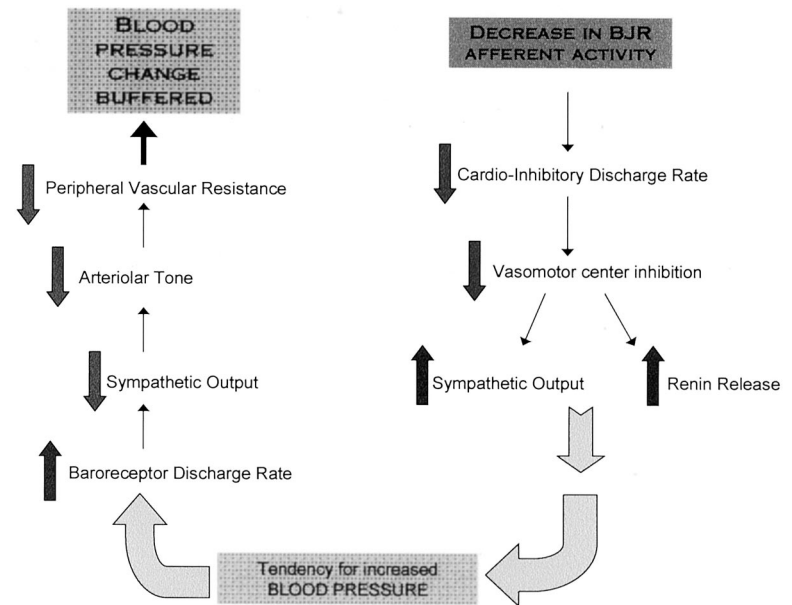

The Baroreceptor Reflex

Fig. 2. Anatomic configuration of the baroreceptor reflex (*left*). Pressure receptors in the walls of the carotid sinuses and aorta detect arterial pressure changes in the circulation. These signals are conveyed to afferent receptive regions of the medulla *via* Hering and the vagus nerves. Output from effector portions of the medulla modulates peripheral tone and heart rate. Increase in blood pressure results in increased activation of the reflex (*right*), which effects a decrease in blood pressure.

Fig. 3. Interaction between the baroreceptor and Bezold–Jarisch reflexes (BJRs) in blood pressure regulation. Decreased activity of the afferent limb of the BJR results in decreased firing of the afferent fibers of the BJR. This leads to a release of vasomotor inhibition with augmented medullary outflow and a consequent increase in blood pressure. However, with the baroreceptor reflex present, this increased blood pressure response is attenuated and the expected effect of withdrawal of BJR activity does not occur and there is no change in systemic blood pressure.

proved useful in delineating this relationship. In normal intact animals, vagal cold block produces only mild increases in systemic blood pressure. In the experimental preparations, when the baroreceptors are active (*i.e.*, fully able to buffer blood pressure alterations), and cardioinhibitory receptor activity is lessened *via* cold block of the vagus nerve, there is no or minimal vascular response (as with normal, intact animals; fig. 3). As baroreceptor activation is progressively withdrawn (*i.e.*, less able to modulate blood pressure changes), withdrawal of cardioinhibitory receptor activity produces increasing degrees of systemic hypertension, increased renal and mesenteric vascular resistance, decreased splanchnic capacitance, increased serum renin levels, and tachycardia.[29,32,33] When free to exert buffering influence, the baroreceptor reflex can inhibit the blood pressure increase and renin release seen with vagal cold block (cardioinhibitory receptor withdrawal).[14] Thus, when both systems are free to interact, the baroreceptor reflex appears to be the dominant regulator of blood pressure. That veratrum alkaloids can produce such a dramatic blood pressure response in the presence of an intact baroreceptor reflex (fig. 1) suggests that this relationship can be uncoupled, and the BJR activity can become dominant.

Hypotension

The cardioinhibitory receptors are also involved in the restorative response to systemic hypotension. As early as the 1970s, it had been shown that with comparable decreases in arterial pressure, there was more pronounced renal vasoconstriction with hemorrhagic *versus* cardiogenic hypotension.[34–37] This is somewhat surprising in that during hypotension, irrespective of cause, baroreflexes should trigger reflex systemic vasoconstriction and tachycardia to lessen the decrement in pres-

sure. It is evident therefore that the actual physiologic response to hypotension is more complex than initially had been appreciated.

The sympathoinhibitory response of the BJR cardioinhibitory receptors is somewhat more active in the renal vascular system than in the vasculature of the limbs.[30] In dogs, the renal vascular bed is under preferential control of these cardioinhibitory receptors, whereas the vascular beds of skeletal muscle are primarily under carotid baroreceptor control.[38–40] Thus, the differential engagement of the carotid and BJR cardiac receptors with the central neuronal pool governing sympathetic outflow to the periphery dictates the relative role of each system in countering various stresses.[32,41–43] This may explain why, in humans, renal vessels constrict with hypovolemic hypotension, whereas renal vessels dilate with cardiogenic hypotension.

Mild and Moderate Hypovolemia

The baroreceptor and cardioinhibitory receptor systems interact with one another during the maintenance of normal blood pressure, and this suggests that they also may have integrated responses to various degrees of hypovolemic insult. This interaction is shown by a series of experiments in dogs where mild hypovolemia was induced by bleeding (4 ml/kg). In animals with intact baroreceptors, there was no change in mean systolic, diastolic, and arterial pressures, but there was an increase in serum renin levels.[14,44,45] These same studies also showed that the BJR cardiac vagal afferent fibers decrease their firing, thus partially releasing their tonic inhibition of vasomotor centers and increasing sympathetic traffic to the renal nerves. This occurs with no change in traffic from the carotid baroreceptors and without any clear activation of the sympathetic system as measured by change in heart rate or blood pressure.

Thus cardioinhibitory receptors respond to decreases in blood volume to which baroreceptors are insensitive. The result of mild hypovolemic insult is a decrease in cardiac receptor activity (thereby augmenting vasomotor output). However, *because the baroreceptor reflexes are intact*, the expected response of tachycardia and increased vasomotor tone is blunted. During these conditions, the sole manifestation of decreased cardioinhibitory receptor activity is an increase in renin release.[14,44,45]

Despite this animal data[27,44] and clinical data in healthy humans, which document unchanged heart rate and blood pressure during mild hemorrhage,[46–48] the exact role that the cardioinhibitory receptor system plays in human hypovolemia is less clear.[41,42] In humans with mild to moderate hemorrhage (400–650 ml) that decreases right atrial and pulmonary capillary wedge pressures (but not mean arterial pressures), there is no change or a slight decrease in renin release.[45] With larger hemorrhage or with negative pressure (-40 mmHg) applied to the lower limbs, there were changes in heart rate and arterial blood pressure in conjunction with an increase in plasma renin levels.[49] Therefore, it seems that a large enough hemorrhage can provoke increased renin release in humans and, in contrast to canine studies, this response is late and seen in conjunction with decreased mean arterial pressures and increased heart rates.[14,49] The relative contributions of the baroreceptor and cardiac receptor systems to these changes have not been clarified.

Profound Hypovolemia

The literature is replete with reports documenting bradycardia during *severe* (greater than 600 ml) hemorrhage in humans.[50–57] The mechanism behind this response is unclear. There were attempts to link the BJR to the bradycardia observed during severe hemorrhage during the period between the 1930s and 1970s. Presumably, during mild and moderate hemorrhage in humans, the vasomotor inhibition exerted by cardioinhibitory afferent fibers and baroreceptor systems is released (as occurs in animals), resulting in an increase in blood pressure (fig. 4A). The issue is that during *profound* hemorrhage, the expected hypotension can be accompanied by profound bradycardia. A paradoxical activation of the BJR could explain this occurrence. Specifically, the expected decreased activity of cardioinhibitory receptors (release of vasomotor inhibition) during profound hemorrhage does not occur and there is instead *increased* receptor activity that further inhibits vasomotor output and triggers bradycardia (fig. 4B). There is some evidence for this notion in animals.

During severe hemorrhage in cats, increased firing of cardioinhibitory receptors has been recorded[58] and a vigorous contraction of a relatively empty ventricle can trigger the cardiac vagal afferent fibers, which have been shown to lead to bradycardia, vasodilation, and hypoten-

sion.[59] In humans, a sudden decrease in peripheral resistance coupled with decreased venous return triggers bradycardia presumably to preserve cardiac filling.[52] These observations taken together suggest that the cardioinhibitory receptors *may* become active during profound hypovolemia.

Myocardial Ischemia

Persons with myocardial ischemia and infarction display several autonomic disturbances, including arrhythmia, hypotension, and hypertension.[60] A large number of people who suffer myocardial ischemia die from sudden cardiac death presumed secondary to cardiac arrhythmia. Bradyarrhythmias and hypotension are seen more commonly in patients with inferior or posterior wall myocardial ischemia and infarction, in contrast to anterior wall ischemia that often elicits tachyarrhythmias and hypotension.[60] These discrete manifestations of hemodynamic responses to ischemia suggest different underlying mechanisms mediating them and a *possible* role for BJR components. The distribution of the cardioinhibitory C fiber afferent receptors in the myocardium correlates well the coronary anatomy affected during myocardial ischemia[19,61–63] with the concentration of cardiac inhibitory receptors greatest in the inferior and posterior walls of the heart,[23,63] locations corresponding to the anatomic territory where myocardial ischemia is associated with hypotension and bradycardia. In addition, when veratridine is injected into the coronary circulation of dogs and cats, a greater degree of hypotension and bradycardia is seen during injections of the posterior/inferior circulation than with left anterior descending artery injections.[19] The stimulus for reflex triggering during myocardial ischemia is not known, but there is some evidence for molecules generated during ischemia and reperfusion, such as oxygen-derived free radicals and prostaglandins.[64–66] There is also evidence that the stimulus may be mechanical secondary to the aneurysmal bulging of myocardium that occurs during transmural ischemia.[18,20,67]

The purpose of this response during myocardial ischemia is unclear. As detailed previously, the same reflex has been implicated as a mechanism of sudden cardiac death during ischemic injury.[62] At least one of the studies on humans details termination of electrocardiographic alterations consistent with ischemia by an episode of hypotension, bradycardia, and nausea.[68] Those investigators have suggested that such a mechanism is protective. It also has been argued that the profound bradycardia and renal vasodilation reduces myocardial oxygen demand and augments renal perfusion that is beneficial in ischemia.[19,69]

Coronary Reperfusion

The concept that reperfusion of previously ischemic tissue is associated with unique morbidity has been recog-
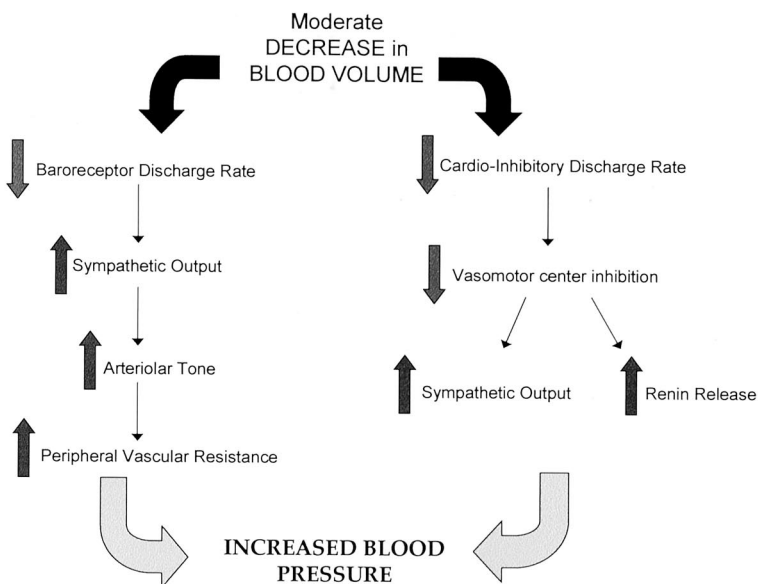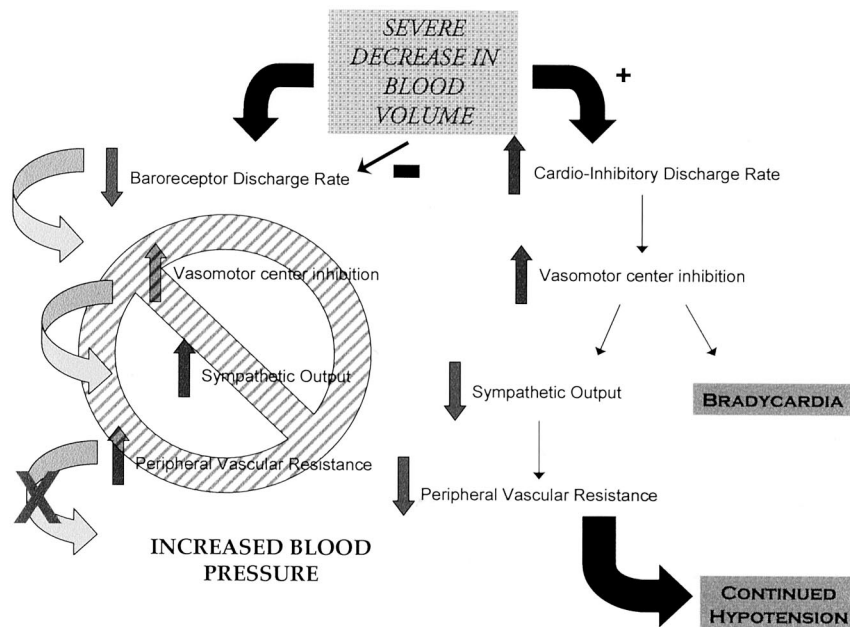
A.

B.

Fig. 4. Activation of the Bezold–Jarisch reflex (BJR) during hypovolemia. (*A*) During conditions of moderate hypovolemia, the BJR and the baroreceptor reflex are synergistically active. The BJR activity is withdrawn simultaneously with activation of the baroreceptor reflex leading to an increase in blood pressure. (*B*) During conditions of severe volume loss, not only is the BJR presumably paradoxically activated but the baroreceptor fails to exert its dominant blood pressure control effects either due to failed sensing at the afferent limb or inhibition of its efferent limb from some component of the BJR pathway. The net result is bradycardia and further hypotension.

nized secondary to the advent of coronary reperfusion techniques utilizing intravenous lytic drugs and coronary angioplasty.[70] Since the 1970s, it has been known that acute coronary occlusion and reperfusion in animal models could stimulate the cardioinhibitory receptors and potentially trigger the BJR,[18,20,65,67,71] and this phenomenon is most pronounced with inferior or posterior reperfusion events.[63] There also is evidence that the BJR may be involved in mediating the hypotension and bradycardia often seen during human coronary angiography with the injection of contrast media into the right coronary artery.[72]

Aortic Stenosis

The traditional teaching concerning exertional syncope in patients with aortic stenosis stresses the inability to increase cardiac output in the face of a fixed outflow obstruction. Of late, there has been a revival of an early twentieth century hypothesis that the cause of exertional syncope in aortic stenosis may be secondary to reflex activation of the BJR.[69,73–75] The origin of this idea lies in observations that increases in left ventricular pressure could trigger cardioinhibitory reflexes and promote hypotension.[19,75] It is argued that the cardiac vagal receptors,

stimulated by vigorous contraction of the ventricle, triggers the BJR and may be responsible for this event.[69] Exercise causes an increase in left ventricular pressure, which then triggers a cardiac reflex–mediated syncopal event. Further evidence for BJR involvement comes from observations made in the early 1970s in people with severe aortic stenosis. Normally, with exercise, the somatic pressor reflex causes peripheral vasoconstriction that serves to maintain mean arterial pressure and venous return in the face of augmented blood flow through the musculature.[26,76] During skin blood flow testing of patients with severe aortic stenosis, a vasodilation, not vasoconstriction, in response to exercise was observed. Therefore, it was postulated that the initiating event for syncope in these patients may be a left ventricular–mediated reflex withdrawal of vasomotor tone in association with a loss of somatic pressor reflex.

Vasovagal Syncope

There is no clear consensus on either a mechanism or teleologic explanation as to the benefit of vasovagal syncope. Recall that during moderate systemic hemorrhage, decreased ventricular filling lessens the tonic activity of vagal afferent fibers causing increased sympathetic vasomotor activity resulting in "reflex" vasoconstriction and tachycardia.[27,45,49] During severe hemorrhage, however, vigorous contraction of the empty ventricle may precipitate bradycardia and hypotension.[59] The latter mechanism may account for the appearance of vasovagal syncope in the setting of orthostatic stresses. This is supported by the observation that treatment with β adrenergic blocking drugs has been shown to be effective in preventing some forms syncope.[77] Many studies have attempted to tie such observations of bradycardia seen with hemorrhage to vasovagal mechanisms and therefore to the BJR.[3,4,8,53,78]

However, it remains unclear if this relationship truly exists. Cardiac transplant patients have had classic vasovagal syncope, even though there is no clear evidence for reinnervation of the transplanted heart.[79,80] More recent experiments using echocardiography also fail to demonstrate either an empty ventricle or a more vigorous contraction as measured by end-systolic length or fractional systolic shortening during syncopal episodes.[81-83] Therefore, vasovagal syncope is not synonymous with the BJR nor is it necessarily dependent upon cardioinhibitory receptor activation or the formal BJR.

Is the BJR Involved in Cardiovascular Collapse during Regional Anesthesia?

The Clinical Problem

There is accumulating evidence in the forms of case reports, closed claims analyses, and randomized trials that cardiovascular complications associated with regional anesthesia can include hypotension and bradycar-

dia which can progress to complete cardiovascular collapse. These complications are not predictable and there exists neither a firm understanding of the cause of cardiac arrest nor any entirely effective interventions to counter such an event when it occurs.[84,85] For these reasons this problem needs to be investigated more carefully.

Spinal and Epidural Anesthesia

The mechanisms of action, the pharmacology of the agents, and the clinical outcomes associated with regional anesthesia are all undergoing various forms of basic science and clinical investigation. A better understanding of many of the known side effects and risks associated with these techniques has evolved. The most common side effects from spinal and epidural anesthesia are cardiovascular. Hypotension and bradycardia are the most frequent with an incidence estimated to be 33 and 13% in nonobstetric populations, respectively.[86-88] The incidence of cardiac arrest during spinal anesthesia has been estimated to range from 1/1600 to 1/250,000[89,90] with a relatively greater incidence in younger, healthier males.[85] Several case reports[6,7,86,89,91-100] and closed claim analyses[101,102] support the idea that severe circulatory complications are more frequent than had been appreciated. These reports share the common denominator that patients receiving spinal or epidural anesthesia were observed to have profound bradycardia with hypotension. This cardiovascular collapse was not anticipated, and in many cases, not treated effectively.[84,85,103] Mortality from these events is low, but this does not negate the fact that these complications are severe and pose a significant threat to patients.

Etiology of the Bradycardia and Hypotension

The relative hypotension commonly associated with neuraxial blockade is secondary to sympathetic block. The block results in decreased systemic vascular resistance, peripheral vasodilation with redistribution of the central blood volume to the splanchnic circulation and lower extremities[104-106] in conjunction with a possible slight decrease in myocardial contractility.[107,108] The etiology of the bradycardia is less clear. There is some specific evidence from heart rate variability tracings[109] as well as conjecture[84] that there is a shift towards vagal predominance with neuraxial anesthesia. Supportive data are absent but it is conceivable that the cardioinhibitory receptors of the BJR may be responsible for the bradycardia. There is some evidence that cardiac afferent fiber activation may help to preserve diastolic filling time during relative decreases in venous return[52] and that bradycardia is associated with echocardiographic evidence of smaller left ventricular chamber size.[110] This mechanism implies that the bradycardia and hypotension in humans are not causally related to the true BJR but that the *hypovolemic* (redistributive) hypotension

invokes a *protective* bradycardia mediated by cardioinhibitory afferent fibers. The BJR is a reflex that causes the triad of vasodilation, bradycardia and hypotension, and cardioinhibitory receptor-mediated bradycardia alone is not equivalent to the BJR. The appearance of bradycardia with hypotension may appear like BJR "mediated" syncope, but the bradycardia in these circumstances is actually the compensatory mechanism for some *other* cause of peripheral vasodilation. This line of conjecture supports the conclusion that the bradycardia and hypotension observed during these clinical scenarios are manifestations of, *at least*, two separate processes. Whether the cardioinhibitory receptors *actually* participate on any level has yet to be demonstrated.

Cardiac Arrests

Bradycardia also is a common feature of profound circulatory collapse under neuraxial anesthesia[50,51,53–57,111] When explanations are offered in the literature, a wide variety of theoretical causes of cardiovascular collapse have been presented. These include activation of the baroreceptor reflex,[85,103] sudden shifts in cardiac autonomic balance,[109] activation of a reflex arc within myocardial pacemaker cells,[6] the Bainbridge reflex,[84,112] hypoxia and respiratory insufficiency,[101] triggering of the cardioinhibitory receptors, and, ultimately, the BJR.[97,113] When explanations of the BJR being responsible for the cardiovascular collapse are offered, they are presented as either a vasovagal mechanism that is stated as synonymous with the BJR, or as a "direct trigger" mechanism whereby the BJR is activated by some amalgam of factors present during regional anesthetic delivery. There are many possible explanations for these arrests, but with minimal supportive data in the literature, it is unclear whether the BJR or even the cardioinhibitory receptors have any role in their etiology.

Peripheral Nerve Blockade.

Reports of cardiovascular collapse are not limited to persons having neuraxial anesthesia. Patients undergoing peripheral nerve block techniques have been reported to have cardiovascular instability with dominant features of bradycardia and hypotension. In particular, shoulder procedures done during interscalene block with the patient in the sitting position appears to be the most common regional block technique associated with this presentation.[3,4,7,8] It was hypothesized that the cause of the hypotension and bradycardia was based on a combination of peripheral vasodilation from the sitting position, increased contractility of the heart secondary to absorbed epinephrine from the injection of the block, and vigorous contraction of an empty ventricle.[3,4,6–8,78] It is claimed that the three components resulted in activation of the BJR.

However, there are no convincing data in the literature to support these prerequisites. Oberg and Thorn[59] hypothesized that vigorous mechanical contraction of an empty ventricle is sufficient to trigger the afferent fibers in the wall of the ventricle and, therefore, the BJR. Some support for this empty ventricle concept during *epidural* anesthesia is found in humans studies[114] and by observations in humans made during tilt-table testing with venous pressure measurements, which showed a decreased ventricular volume.[115–117] Other evidence obtained during lower extremity venous pooling[118] or acute hemorrhage[47] fail to demonstrate such changes and, in fact, reveal augmented cardiac output with increased chamber volume. Echocardiography data fail to demonstrate either an empty ventricle or more vigorous ventricular contraction during syncopal episodes.[81–83] No evidence for venous pooling exists in the setting of *peripheral* nerve blockade. The α adrenergic receptor agonist drugs such as phenylephrine can activate cardioinhibitory receptors,[119] but there is no evidence of increased contractility in response to concentrations of epinephrine seen in local anesthetic mixtures for nerve block exists.[120] In our institution, one patient experienced multiple episodes of hypotension and bradycardia associated with initiation of an infusion of 0.1% bupivacaine *without* epinephrine *via* a supraclavicular brachial plexus catheter during a two-day interval. In fact, one of the events occurred with the patient *supine* (unpublished observations, February 1999, C. Carter M.D., Boston, Massachusetts, visual data). This case lends further doubt to the contention that the mechanism of cardiac arrest requires either augmentation of contractile function secondary to venous pooling induced orthostatically or by exogenous inotropism. In fact, taken as a whole, we believe that the literature support a mechanism *other than the BJR* for the cause of the hypotension and bradycardia seen during shoulder surgery performed during interscalene block.

Conclusion

It is likely that Bezold–Jarisch cardioinhibitory receptors are involved in some manner in maintenance of normal blood pressure and in the response to hypovolemia. The same system may be active during myocardial infarction and coronary reperfusion. The BJR is not synonymous with vasovagal syncope, and there is no evidence that the cardioinhibitory receptors or the BJR *per se* have a primary role in this type of syncope. Very little data exist that demonstrate cardioinhibitory receptor participation in the hemodynamic events observed during neuraxial anesthetics. The hemodynamic embarrassment seen in shoulder surgery during interscalene block appears not to be related to BJR activation.

An important issue to consider is to what extent is the BJR a physiologically dominant reflex? When triggered by Veratrum alkaloids, the subsequent hypotension and bradycardia suggest that the BJR is dominant under these

conditions. That is, Veratrum alkaloids produce profound hypotension and bradycardia despite the presence and likely functioning of other homeostatic reflexes, such as the baroreceptor reflex. More "physiologic" stimuli, such as changes in blood pressure or intravascular volume, produce changes in pressure and heart rate that are balanced, integrated outcomes of multiple cardiovascular reflexes. Under these conditions, the BJR is not dominant, and profound cardiovascular collapse, as seen following the administration of Veratrum alkaloid, is not observed. No other documented effectors of the cardioinhibitory receptors have been shown to activate the BJR to the same dominant extent as Veratrum alkaloids. It follows that in order for the BJR to be a primary contributor to the cardiovascular collapse detailed in the anesthesia literature, whatever factors are present during the anesthetic techniques that stimulate the cardioinhibitory receptors, *must do so to the same degree as veratrum alkaloids.* These stimuli must allow the BJR to be dominant and be able to overcome the buffering power, or even negate other important homeostatic reflexes. Therefore, despite the appealing theoretic relation between hypotension, bradycardia, and cardiovascular collapse seen during neuraxial and regional anesthetic blockade (interscalene block) and the BJR, there is little evidence to support a role for the BJR in mediating these hemodynamic events. General acceptance that the BJR is responsible for these events should be discouraged until more data become available.

Further laboratory and clinical investigation are required before the clinical events documented in the anesthesia literature can be attributed to the BJR. Stimulators and inhibitors (effectors) of the cardioinhibitory receptors in humans need to be characterized and the full spectrum of the human efferent response to these factors should be investigated. These data need to be reconciled with the existing data from animal studies. Once this foundation is established, definitive demonstration of these effectors in clinical scenarios can be sought and evidence for the activation of the BJR can be determined. Informed clinical therapeutic recommendations cannot be forthcoming in the absence of such an understanding. The role of the BJR in human pathophysiology and anesthetic morbidity remains unclear.

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