CME

The Bainbridge and the "Reverse" Bainbridge Reflexes: History, Physiology, and Clinical Relevance

George J. Crystal, PhD, FAHA, and M. Ramez Salem, MD

Francis A. Bainbridge demonstrated in 1915 that an infusion of saline or blood into the jugular vein of the anesthetized dog produced tachycardia. His findings after transection of the cardiac autonomic nerve supply and injection of the cholinergic blocking drug atropine demonstrated that the tachycardia was reflex in origin, with the vagus nerves constituting the afferent limb and a withdrawal of vagal tone the primary efferent limb. Subsequent investigators demonstrated that the increase in venous return was detected by stretch receptors in the right and left atria. In the 1980s, it was shown convincingly that the Bainbridge reflex was present in primates, including humans, but that the reflex was much less prominent than in the dog. This difference may be due to a more dominant arterial baroreceptor reflex in humans. A "reverse" Bainbridge reflex has been proposed to explain the decreases in heart rate observed under conditions in which venous return is reduced, such as during spinal and epidural anesthesia, controlled hypotension, and severe hemorrhage. The Bainbridge reflex is invoked throughout the anesthesia literature to describe the effect of changes in venous return on heart rate in patients in the surgical and critical care settings, but a critical analysis of the experimental and clinical evidence is lacking. Our main objectives in this review are to summarize the history of the Bainbridge reflex, to describe its anatomy and physiology, and to discuss the evidence for and against it having an influence on heart rate changes observed clinically. The interaction of the Bainbridge reflex with the arterial baroreceptor and Bezold–Jarisch reflexes is discussed. (Anesth Analg 2012;114:520–32)

The cardiovascular reflexes are neural feedback loops that regulate and modulate cardiac function and vascular tone. They are composed of an afferent (sensory) limb, integration in the medulla oblongata within the central nervous system, and an efferent (motor) limb. Table 1 lists major cardiovascular reflexes. The arterial baroreceptor reflex is a primary homeostatic mechanism that maintains arterial blood pressure within narrow limits. It accomplishes this function via adjustments within the circulation on the basis of feedback from high-pressure stretch receptors located in the aortic arch and carotid sinus. The Bezold–Jarisch reflex inhibits sympathetic outflow to blood vessels and the heart. These changes are mediated by mechano- and chemosensitive receptors located in the wall of the ventricles. The final reflex listed is the Bainbridge reflex, which is the focus of this article.

The Bainbridge reflex refers to the increase in heart rate secondary to an increase in central blood volume.[1] Although this reflex has been cited over the years to explain changes in heart rate in surgical and critical care settings, its very existence is a matter of debate.[2] The only previous review of the literature pertaining to the Bainbridge reflex appeared 24 years ago, and it focused exclusively on the animal studies performed up to that time.[3] An up-to-date critical analysis of the experimental and clinical evidence is lacking. The main objectives of this review are to summarize the history of the Bainbridge reflex, to describe its anatomy and physiology, and to evaluate the evidence for and against it having an influence on heart rate changes in the surgical patient. The interaction of the Bainbridge reflex with the arterial baroreceptor and Bezold–Jarisch reflexes is discussed.

HISTORY AND PHYSIOLOGY

In 1915, a British physiologist named Francis A. Bainbridge published an observation that bears his name, which demonstrated that an increase in inflow to the heart produced tachycardia.[1] Bainbridge's study was performed in dogs that were anesthetized with morphine, chloroform, and ether. Heart rate and arterial blood pressure were recorded via a catheter placed in the carotid artery; venous pressure was measured via a catheter placed in the iliac vein near its opening into the inferior vena cava. Venous return was increased by injection of either normal saline solution or blood, either undiluted or diluted with saline, into a jugular vein. The solution had been warmed to body temperature before injection. Bainbridge found that if 200 to 400 mL of fluid was injected into a 10-kg dog over a period of 1.5 to 4 minutes, heart rate increased. Bainbridge also observed that the increases in heart rate could be brought about by injections of smaller amounts of fluid, provided the rate of injection was sufficiently rapid. An original tracing from Bainbridge's paper illustrates this phenomenon (Fig. 1). A rapid injection of only 50 mL of saline caused a doubling of central venous pressure (CVP) associated with a rapid 30% increase in heart rate. Bainbridge demonstrated that the increase in heart rate after the IV infusions was consistently associated with a rise in CVP, and that its onset occurred when the rise of pressure was sufficient to increase ventricular end-diastolic pressure and cause ventricular dilation. He

From the Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, Illinois.

Accepted for publication July 15, 2011.

Funding: None.

The authors declare no conflict of interest.

Reprints will not be available from the authors.

Address correspondence to George J. Crystal, PhD, FAHA, Department of Anesthesiology, Advocate Illinois Masonic Medical Center, 836 West Wellington Avenue, Chicago, IL 60657. Address e-mail to gcrystal@uic.edu.

DOI: 10.1213/ANE.0b013e3182312e21

Table 1. Major Cardiovascular Reflexes

Reflex	Receptors and location	Afferent limb	Efferent limb and response
Arterial baroreceptor reflex	Stretch receptors in vessel wall of carotid sinus and aortic arch, which respond to changes in arterial blood pressure	Fibers in glossopharyngeal and vagus nerves to medulla	Homeostatic control of arterial blood pressure via changes in cardiac output and systemic vascular resistance mediated by the autonomic nervous system
Bezold–Jarisch reflex	Mechanical and chemosensitive receptors in ventricular walls	Nonmyelinated vagal C-fibers to medulla	Inhibition of sympathetic outflow resulting in bradycardia, peripheral vasodilation, and hypotension
Bainbridge reflex	Stretch receptors at junction of the vena cava and right atrium and at junction of the pulmonary vein and left atrium, which respond to changes in volume in central thoracic compartment	Fibers in vagus nerve to medulla	Inhibition of vagal outflow and enhancement of sympathetic outflow to sinoatrial node causing tachycardia

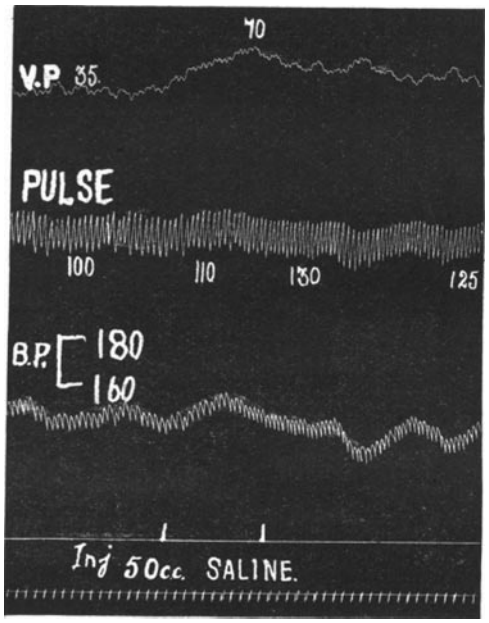

Figure 1. Tracing from Bainbridge's original study[1] demonstrating that a rapid injection of 50 mL of saline in an anesthetized dog caused a doubling of central venous pressure (CVP) associated with a rapid 30% increase in pulse rate. Permission has been obtained from John Wiley & Sons, Ltd.

Table 2. Experimental Studies Providing a Historical Perspective and Mechanistic Details to the Bainbridge Reflex

Year	Findings
1863	Marey[6] noted an inverse relationship between heart rate and arterial blood pressure.
1895, 1914	Frank[4] and Patterson et al[5] demonstrated that output of the left ventricle was determined by the volume of blood before contraction.
1915	Bainbridge[1] reported that IV infusions caused tachycardia in anesthetized dogs.
1937	Nonidez[12] provided morphological evidence for stretch receptors in the right and left atria, which could initiate cardiac acceleration.
1955	Coleridge and Linden[13] found that increases in heart rate during IV infusions in anesthetized dogs were more likely at low heart rates. In 1972, Horwitz and Bishop[14] extended this finding to conscious dogs (Fig. 3).
1965, 1967	Goetz[15] and Ledsome and Linden[16] demonstrated in anesthetized dogs that selective increases in right or left atrial pressure caused tachycardia.
1975	Vatner et al.[17] showed in conscious dogs that intravascular volume loading caused a reduced sensitivity of the arterial baroreceptor pathway (Fig. 4). This provided an explanation for the violation of Marey's law by the Bainbridge reflex (Fig 5).

demonstrated further that the tachycardia was reflex in origin because it was abolished by transection of the vagi and cardiac accelerator (sympathetic) nerves and ligation of the suprarenal veins. The latter excluded a role for circulating catecholamines from the adrenal medulla in the cardiac acceleration. Additional experiments using selective administrations of atropine or sectioning of the vagi showed that the vagus nerves were the afferent (sensory) limb and a reduction in vagal tone was the primary efferent limb of the reflex, although he proposed that increased activity of the cardiac sympathetic nerves may also play a role. Bainbridge suggested that the reflex mechanism would protect against excessive blood pressure levels in the veins, atria, and pulmonary circulation by transferring blood from the venous system to the arterial system and that it would contribute to the increase in heart rate during muscular exercise.

At the time of Bainbridge's article, little was known about reflex control of the heart (Table 2). The heart was considered a mechanical pump, whose output was determined primarily by the volume of blood filling the heart before contraction, i.e., the Frank–Starling mechanism.[4,5] In 1863, Etienne Marey had observed that heart rate was inversely proportional to arterial blood pressure, a phenomenon that became known as *Marey's law*,[6] but it was not known until almost 10 years after Bainbridge's article appeared that the induced changes in heart rate originated specifically in arterial baroreceptors.[7,8] The details of the baroreceptor reflex pathway and its role in the normalization of arterial blood pressure were later described (Fig. 2).[9,10] When viewed retrospectively, it can be appreciated that Bainbridge's work in the early 1900s was groundbreaking, and that it served as a stimulus for a period of intensive investigation on the reflex control of the circulation that has lasted to the present day.[11]

Subsequent basic researchers confirmed the existence of the Bainbridge reflex and clarified its anatomical and physiological features (Table 2, Figs. 3 to 5).[12–17] Although

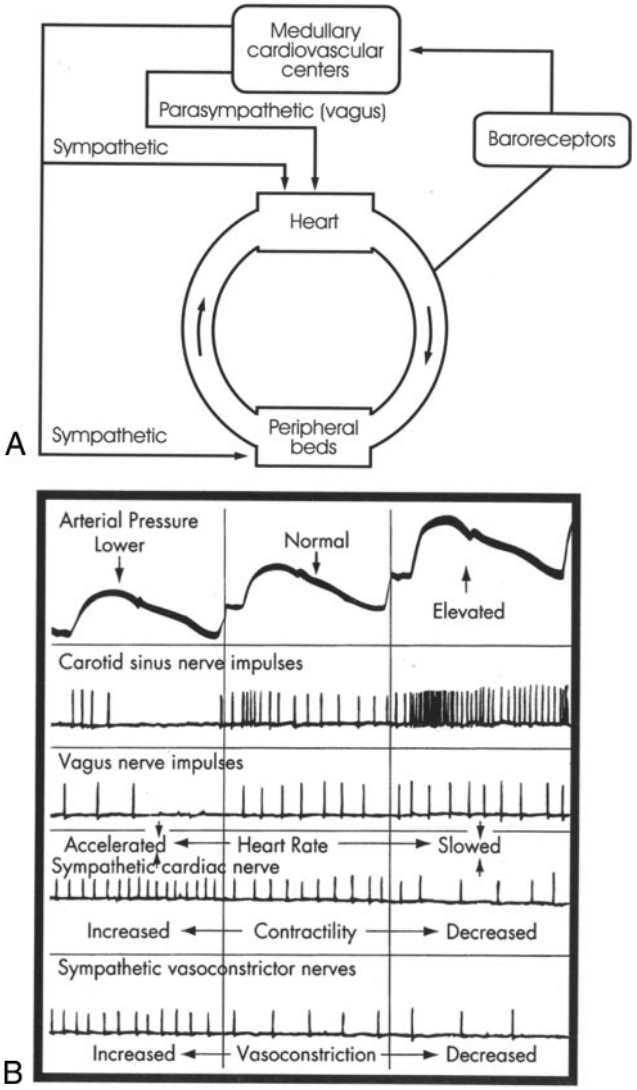

Figure 2. Arterial baroreceptor control of the circulation. A, The major components of the baroreceptor reflexes are (1) an afferent limb comprising the arterial baroreceptors in the carotid sinus and aortic arch and their respective sensory nerves, the glossopharyngeal and vagus nerves; (2) the cardiovascular centers in the medulla oblongata that receive and integrate the sensory information; and (3) an efferent limb comprising the sympathetic nerves to the heart and blood vessels and the parasympathetic (vagus) nerves to the heart. The baroreceptors are stimulated by stretch of the vessel wall, which results from an increase in transluminal pressure. Permission has been obtained from Wolters Kluwer Health/Lippincott Williams & Wilkins. B, Impulses originating in the baroreceptors tonically inhibit discharge of the sympathetic nerves to the heart and blood vessels, and tonically facilitate discharge of the vagus nerves to the heart. An increase in arterial blood pressure increases baroreceptor afferent activity, resulting in further inhibition of the sympathetic nerves and activation of the vagus nerves. This produces vasodilation, venodilation, and reductions in stroke volume, heart rate, and cardiac output, which tend to normalize arterial blood pressure. A decrease in arterial blood pressure has opposite effects (panel A from Rothe and Friedman[107] and panel B from Rushmer.[108] Permission has been obtained from Wolters Kluwer Health/Lippincott Williams & Wilkins.).

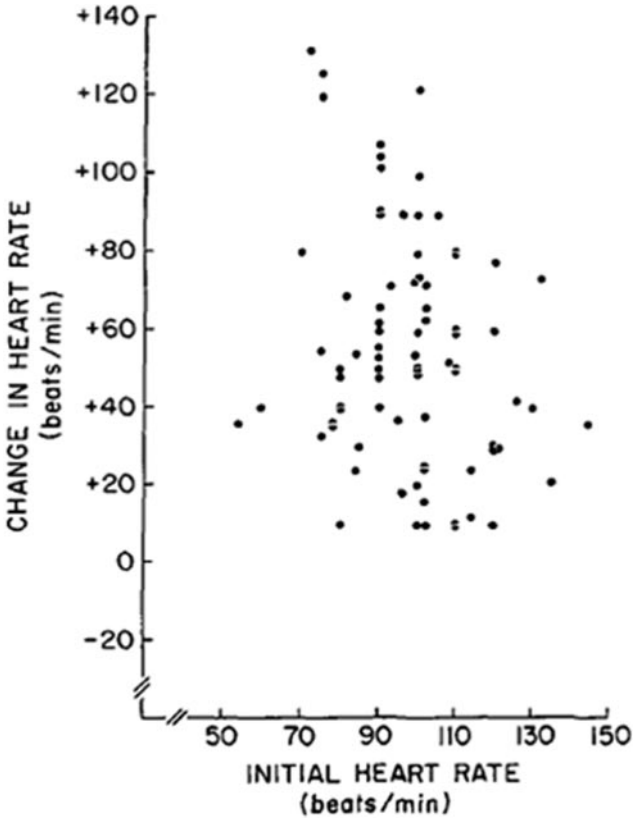

Figure 3. Increase in heart rate versus initial heart rate in 80 IV infusions in 31 conscious, resting dogs. The infusions were with Tyrode's solution given over 3 to 6 minutes; the total infused volume was 300 to 800 mL. The increase in heart rate was inversely proportional to the initial heart rate. From Horwitz and Bishop.[14] Permission has been obtained from Wolters Kluwer Health/Lippincott Williams & Wilkins.

stimulation of stretch receptors in the atria were found to play a prominent role in the initiation of the reflex, afferent nerve endings in the pulmonary and systemic veins were also implicated. Because no discrete reflexogenic area is likely entirely responsible for mediating the Bainbridge reflex, the term *cardiopulmonary receptors* will be used throughout this article in discussions pertaining to the afferent limb of the reflex.[18,19]

ROLE OF BAINBRIDGE REFLEX IN HUMANS

The many observations in animal models raised questions about the existence of the Bainbridge reflex in humans. In 1982, Boettcher et al.[20] assessed systematically the phylogenic development of the Bainbridge reflex from the dog, to the baboon, and to humans. Special attention was given to conducting the studies at low control heat rates and in the absence of general anesthesia. A volume of saline was administered by IV infusion over 3 to 15 minutes to increase left ventricular end diastolic pressure markedly (to approximately 30 mm Hg), and the changes in heart rate were evaluated. The findings indicated that intravascular volume loading caused a 106% increase in heart rate in conscious dogs but only 38% and 21% increases in heart rate in conscious baboons and conscious volunteers, respectively (Fig. 6). Thus, it was concluded that the extent of use of the Bainbridge reflex was species-dependent, i.e., dogs >baboons >humans. It was postulated that the reduced importance of the Bainbridge reflex with movement up the phylogenic scale was due to a more dominant arterial

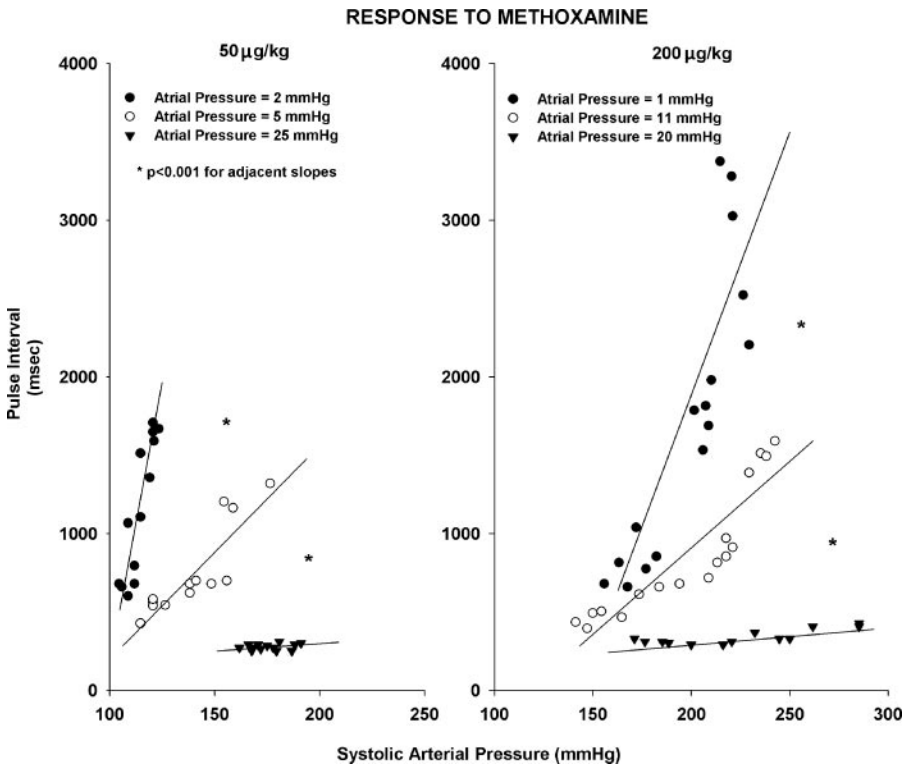

Figure 4. Comparison of pulse interval/systolic arterial blood pressure (PI/SAP) slope in response to 50 μg/kg of methoxamine in the same dog studied on 3 separate days (left) and in response to 200 μg/kg of methoxamine in another dog studied on 3 separate days (right). Slopes were determined when atrial pressure was low, i.e., no infusion (circles), and during moderate (triangles) and maximum intravascular volume loading (squares). Note that intravascular volume loading reduced the PI/SAP slope, indicating a reduced sensitivity of the baroreceptor reflex. During maximum volume loading, the PI/SAP slope was flat, indicating lack of a heart rate response to methoxamine-induced hypertension. From Vatner et al.[17] Permission has been obtained from Wolters Kluwer Health/Lippincott Williams & Wilkins.

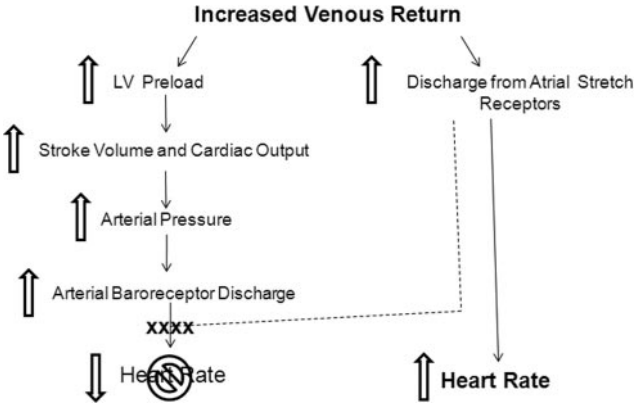

Figure 5. Interaction between the arterial baroreceptor and the Bainbridge reflexes in control of heart rate during an increase in venous return. Activation of the Bainbridge reflex, i.e., increased activity of cardiopulmonary volume receptors, results in an increase in heart rate. This can occur because of a simultaneous inhibition of arterial baroreceptor control of heart rate. The thick arrows indicate an increased or decreased activity; *xxxx* indicates inhibition of a particular step. In this case, the arterial baroreceptor control of heart rate was completely nullified, as indicated by the international *no* circle, so that the Bainbridge reflex–induced increase in heart rate was unopposed.

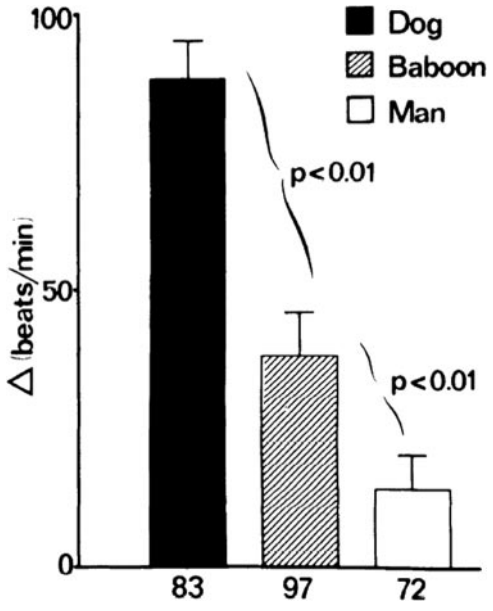

Figure 6. Species-related variation in the increases in heart rate produced by a standardized volume overload under conscious condition. Baseline values for heart rate are shown beneath the bars. The increases in heart rate varied as follows: dog >baboon >humans. From Boettcher et al.[20] Permission has been obtained from the American Physiological Society.

baroreceptor mechanism because of the need to compensate for the changes in the distribution in blood volume that accompany changes in posture (sitting, standing, etc.). The authors also proposed that a lower-baseline vagal tone in humans in comparison with dogs may also be involved. This would preclude appreciable increases in heart rate by withdrawal of vagal tone, which was the predominant mechanism by which the Bainbridge reflex produces tachycardia. Giuntini et al.[21] also observed modest increases in heart rate during acute intravascular volume loading in conscious humans. A limitation of the aforementioned human studies is that the imposed levels of left atrial pressure were very high and relevant only to cardiac disease states—such as severe heart failure, myocardial ischemia, or acute mitral regurgitation—or to massive volume overload.

Parasympathetic and sympathetic activity to the heart can be assessed by analysis of the power spectrum of heart rate oscillations.[22–24] In this technique, the surface electrocardiogram is recorded and used to determine the R-R interval, which is analyzed for its spectral components: low-frequency interval (0.04 to 0.15 Hz) and high-frequency interval 0.15 to 0.5 Hz). The area under the high-frequency oscillations is considered to represent parasympathetic (vagal) modulation, whereas the area under the low-frequency oscillations or the "low-frequency to high-frequency power ratio" is considered to reflect sympathetic modulation. Barbieri et al.[25] used multivariate spectral analysis to investigate the presence of the Bainbridge reflex in conscious supine humans from simultaneous measurements of R-R interval, respiration, and arterial blood pressure at several levels of increased central blood volume. Central blood volume was increased progressively across a physiological range (CVP increased from an average of 5 to 8 mm Hg), by passive leg raising alone and combined with a 500-mL infusion of normal saline. The investigators also analyzed the effect of an increase in central blood volume on the natural interaction between heart rate and respiratory activity, e.g., near synchrony between inspiration and increasing heart rate, known as the *respiratory sinus arrhythmia*. The study yielded 2 important findings. First, although vagal- and baroreflex-mediated decreases in heart rate dominated during the initial increases in central blood volume (heart rate decreased from an average of 63 to 60 beats per minute [bpm]), vagal activity became reduced when central blood volume was increased, further resulting in small increases in heart rate (to 65 bpm), consistent with the existence of a modest Bainbridge reflex. Second, the 2 systems most responsible for controlling short-term fluctuations of heart rate, the arterial baroreflex and the respiratory sinus arrhythmia, both appeared to be optimized (point of maximum gain) in a state of mild hypervolemia, which suggested that normovolemic conditions may be a state of mild cardiovascular stress to normal human subjects.

Increases in central blood volume occur in a variety of clinical scenarios involving IV infusions, changes in body positioning, modifications of ventilatory conditions, and use of constricting drugs that reduce venous capacitance. The expression of the Bainbridge reflex is difficult to predict, because it would be influenced by the strength of the arterial baroreceptor reflex and by the prevailing hemodynamic conditions, including intravascular volume status. Furthermore, various perioperative factors (hypoxemia, hypercapnia, positive end-expiratory pressure, laryngoscopy, intubation, and surgical stimulation) and nonperioperative factors (aging, obstructive sleep apnea and its comorbidities) can themselves cause activation of the sympathetic nervous system,[11] which may limit the influence of the cardiovascular reflexes on heart rate. The ability of aging to reduce the sensitivity of the Bainbridge and the arterial baroreceptor reflexes, as discussed below, would be a factor in some patients. Finally, in the surgical patient, the contribution of the Bainbridge reflex would also likely be affected by the anesthetic drugs. It has been demonstrated that the control of heart rate by the arterial baroreceptor reflex is impaired by volatile[26–32] and IV[33,34] anesthetics, but little information is available on the effect of these drugs on the cardiopulmonary reflexes. If the anesthetic drugs have less of a depressive effect on the cardiopulmonary reflexes than on the arterial baroreceptor reflex, it is conceivable that the Bainbridge reflex would be more prominent in the anesthetized patient than in the conscious patient.

"REVERSE" BAINBRIDGE REFLEX

Although Bainbridge himself did not describe a bradycardic response during a reduction in venous return, i.e., a reverse Bainbridge reflex, the reflex was eventually described as full cardiopulmonary reflex, encompassing both increases in heart rate during hypervolemia and decreases in heart rate during hypovolemia.[19,25] The existence of a reverse Bainbridge reflex would imply that the cardiopulmonary receptors are active under baseline conditions and that they impose a tonic stimulatory influence on the sinoatrial (SA) node firing rate. Accordingly, a reduction in venous return would cause an unloading (deactivation) of these receptors, and thus initiate a reflex-induced reduction in heart rate. In theory, a reverse Bainbridge reflex would constitute a break on the heart in situations of poor diastolic filling. Various clinical studies using different approaches to reduce venous return have provided insight into the role of a reverse Bainbridge reflex in humans. These studies are described below.

Role of Reverse Bainbridge Reflex in Spinal and Epidural Anesthesia

Spinal anesthesia produces preganglionic sympathetic denervation, which causes dilation of arterioles (resistance vessels) and veins (capacitance vessels).[35] Arteriolar dilation causes a reduction in systemic vascular resistance, whereas venous dilation causes venous pooling and reductions in venous return, stroke volume, and cardiac output. These changes combine to cause systemic hypotension. The cardiac sympathetic (accelerator) fibers come off the spinal cord at the level of T_1–T_4.[35] It is has been shown that blocks either above T_4 (high spinal anesthesia) or below T_4 (low spinal anesthesia) are associated with bradycardia or in no significant change in heart rate,[35–42] despite the tendency of the arterial baroreceptor reflex to increase heart rate in the face of arterial hypotension. The bradycardia during high spinal anesthesia has been classically attributed solely to a direct paralysis of the cardiac sympathetic nerves, thus leaving control of the SA node to the inhibitory vagal fibers.[35–38] However, this mechanism cannot explain the decrease in heart rate during low spinal anesthesia (Fig. 7), because the sympathetic innervation to the heart is intact. A role for a reverse Bainbridge reflex has been proposed.[35–38,41] This mechanism is supported by additional clinical observations. First, the extent of cardiac slowing of the heart during spinal anesthesia does not correlate with the level of anesthesia.[37,38,42] Instead, it correlates with the decrease in arterial blood pressure. The common factor linking heart rate and arterial blood pressure is venous return and thus right atrial pressure. Second, in a patient who is hypotensive and exhibits bradycardia during high spinal blockade, raising the legs or placing the patient in the head-down position will increase both arterial blood

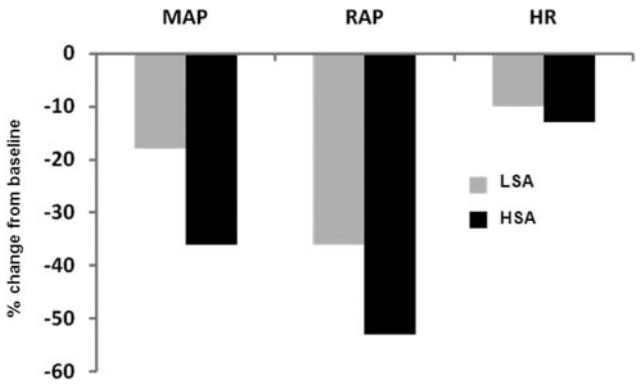

Figure 7. Hemodynamic changes in awake patients after induction of low and high spinal anesthesia. Of note is that mean arterial blood pressure (MAP), right atrial pressure (RAP), and heart rate (HR) decreased under both low and high spinal anesthesia (LSA and HSA, respectively). Data from Sancetta et al.[36]

pressure and heart rate.[35,37] If the decrease in heart rate were strictly due to the cardiac sympathetic block, such postural changes would not cause an increase in heart rate. These observations led Greene to suggest that the Bainbridge reflex is the most important determinant of heart rate during spinal anesthesia.[37]

Carpenter et al.[43] provided further evidence for a role for a reverse Bainbridge reflex in spinal anesthesia. In a study assessing the incidence of side effects in 936 patients receiving spinal anesthesia, they found that severe bradycardia (heart rate <50 bpm) occurred in 13% of the patients. Carpenter et al. suggested that the most important cause for this bradycardia was a reduction in venous return rather than an interruption of sympathetic flow to the heart because the decreases in heart rate that they observed were much in excess of the approximate 10% decreases that are achievable with complete cardiac sympathetic denervation in the presence of maintained venous return.[44]

Baron et al.[45] demonstrated that a reverse Bainbridge reflex may play a role in patients undergoing epidural anesthesia. These investigators performed a study on young unpremedicated patients to determine the effects of low-level epidural anesthesia with bupivacaine (T_8–T_{12}; too low to involve the cardiac sympathetic nerves) on arterial baroreceeptor control of heart rate, and to assess the role of variations in venous return in possible alterations of this control. Baroreflex testing was performed using graded IV bolus injections of phenylephrine and nitroglycerin (to increase or decrease systolic arterial blood pressure by 20 to 30 mm Hg) and thus to alter the level of activity of the reflex. The findings indicated that epidural anesthesia caused a decrease in systolic arterial and right atrial pressures but had no effect on heart rate; a reduction in sensitivity of the arterial baroreceptor reflex was also observed. In addition, the application of lower-body positive pressure during epidural anesthesia restored venous return and returned associated hemodynamic variables, including heart rate, and baroreflex sensitivity (BRS) to preepidural levels. This finding linked the hemodynamic changes during epidural anesthesia to a reduction in venous return and excluded the possibility that they were due to absorption of bupivacaine into the circulation.[46] The findings of Baron et al. indicated (1) that lumbar epidural anesthesia induced an enhancement of cardiac vagal activity sufficient to prevent the arterial baroreceptor-mediated increase in heart rate during arterial hypotension, and (2) that this response was due to a reduction in venous return and an unloading of the cardiopulmonary receptors. The lack of change in heart rate during epidural anesthesia in these studies reflected relative bradycardia because an increase in heart rate was expected secondary to the hypotension. The authors commented that an absolute bradycardia may occur during lumbar epidural anesthesia when the decrease in venous return is enhanced by acute blood loss[47] or head-up position.[48]

Role of Reverse Bainbridge Reflex During Controlled Hypotension

Nitroglycerin and sodium nitroprusside (SNP) are used for controlled hypotension for the purpose of reducing intraoperative blood loss.[49] The different vascular sites of action of these 2 drugs provide an opportunity to assess the influence of the reverse Bainbridge reflex in the anesthetized patient. Both nitroglycerin and SNP dilate blood vessels via their ability to donate nitric oxide (NO), which causes relaxation of vascular smooth muscle.[50] However, they differ in that nitroglycerin acts predominantly on venous (capacitance) vessels, whereas SNP has a balanced effect on arteriolar (resistance) vessels and venous vessels.[51,52] Fahmy[53] compared the circulatory effects of nitroglycerin and SNP in 2 groups of halothane-anesthetized patients (age range: 18 to 72 years; average of 46 years) undergoing hip replacement surgery. The groups were comparable with regard to age, sex distribution, and weight. Drug infusion was adjusted to decrease systolic blood pressure to a comparable level (approximately 75 mm Hg). Nitroglycerin had no effect on heart rate, whereas SNP produced a 24% increase in heart rate, presumably mediated by the arterial baroreceptor reflex. The intraoperative blood loss was 578 ± 82 mL with nitroglycerin in comparison with 762 ± 93 mL with SNP. The lack of change in heart rate during nitroglycerin was associated with a more marked decrease in right atrial pressure in comparison with that during SNP (−67% vs −30%). Fahmy's findings are consistent with the presence of a reverse Bainbridge reflex during nitroglycerin that was sufficient to nullify the arterial baroreceptor-mediated increase in heart rate. Additional evidence for this reflex was provided by Guggiari et al.,[54] who demonstrated no change in heart rate during nitroglycerin-induced hypotension in anesthetized (phenoperidine and droperidol) adults undergoing intracranial aneurysm surgery. However, Yaster et al.[55] found that hypotensive infusions of either SNP or nitroglycerin were associated with tachycardia (requiring treatment with a β-receptor blocking drug) in anesthetized (morphine and thiopental) children (age range: 9 to 14 years) undergoing scoliosis, craniofacial, or hepatic surgery. The difference in findings for Fahmy and Yaster et al. could be age related, but differences in the anesthetic technique cannot be discounted. Although suggestive, caution should be exercised in assessing the presence of a reverse Bainbridge reflex from the comparative changes in heart rate caused by the hypotensive infusions of SNP and nitroglycerin in Fahmy's

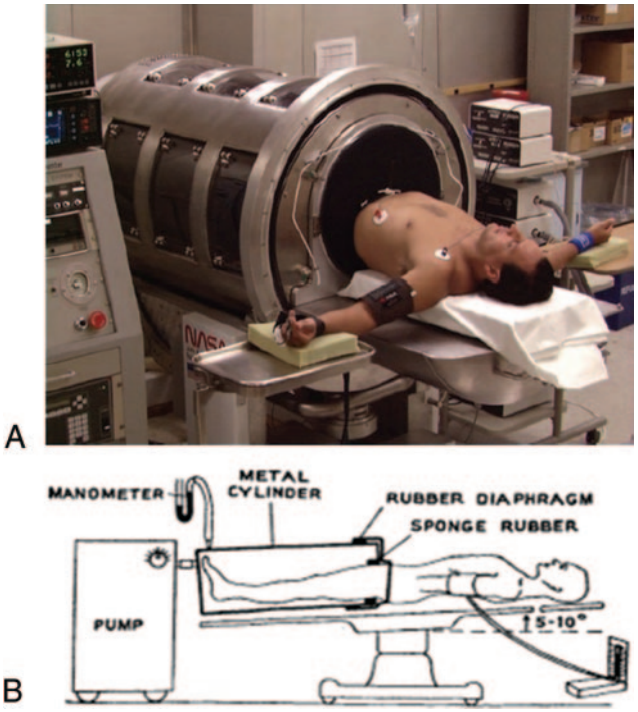

Figure 8. A, Subject placed in the lower-body negative pressure (LBNP) device. From Cooke et al.[62] Photo courtesy of the American Physiological Society. B, Diagram of early negative pressure device showing application of a cylinder to legs of patient. From Saunders.[65] Permission has been obtained from Elsevier Limited.

study. Evidence has emerged suggesting that NO has extravascular actions, which themselves may influence SA node firing rate.[56–60] There is no way of assessing the role of these extravascular actions of NO during the IV infusions of SNP and nitroglycerin in Fahmy's study. Thus, it cannot be considered conclusive evidence for the existence of a reverse Bainbridge reflex in the anesthetized patient.

Studies of Reverse Bainbridge Reflex Using Lower-Body Negative Pressure

The most direct approach to investigating the reverse Bainbridge reflex is to do the opposite of what Bainbridge did, and to reduce venous return by removal of blood from the circulation. However, in humans this is impractical and ethically unacceptable. An alternative approach is to use lower-body negative pressure (LBNP). This maneuver redistributes blood from the upper body to the lower extremities, thus reducing CVP and venous return.[61,62]

Application of LBNP has been used since the mid-1960s to simulate the cardiovascular effects of hemorrhage and orthostatic stress in humans.[19,61–64] It has also been used effectively to augment the decrease in arterial blood pressure during drug-induced controlled hypotension.[65] LBNP has the following advantages: the degree of central hypovolemia can be easily controlled by the level of negative pressure applied to the lower body, and the procedure is noninvasive and rapidly reversed. The technique involves the placement of the subject in a cylindrical metal tank, which is sealed at the level of the iliac crests (Fig. 8). Suction is produced by a vacuum pump and is controlled with calibrated regulator. Typically, LBNP is increased in steps, e.g., −5, −10, −20, and −40 mm Hg, and steady-state cardiovascular responses are assessed.[62,66–71] When LBNP is increased maximally, i.e., −40 mm Hg, the decreases in CVP, right atrial pressure, stroke volume, and cardiac output are accompanied by decreases in mean arterial blood pressure, implying an unloading of both the cardiopulmonary receptors and the arterial baroreceptors. An increase in heart rate is typically observed during severe LBNP, which is attributable to engagement of the arterial baroreceptor reflex. When LBNP is increased moderately, i.e., ≤ −20 mm Hg, an increase in systemic vascular resistance compensates for the decrease in cardiac output, and mean arterial blood pressure is usually unchanged. Thus, it has been traditionally assumed that during moderate LBNP, the cardiopulmonary receptors, but not the arterial baroreceptors, are unloaded and that this maneuver can be used to selectively investigate the cardiopulmonary reflexes. During moderate decreases in LBNP, several studies[64,67,69,70] demonstrated no significant change in heart rate (Fig. 9), and another study[72] demonstrated a minimal decrease in heart rate of 2 bpm, although this effect was abolished by halothane anesthesia. These findings were interpreted as evidence against the existence of a reverse Bainbridge reflex in humans. However, this conclusion has been brought into question by multiple lines of evidence suggesting that low levels of nonhypotensive LBNP unload the arterial baroreceptors as well as the cardiopulmonary receptors. These findings include the following: (1) In anesthetized dogs, aortic baroreceptor nerve discharge decreased even though mean arterial blood pressure remained constant during hemorrhage.[73] (2) Arterial baroreceptors respond to very small (1 to 2 mm Hg) changes in blood pressure.[74] (3) Removal of a small volume of blood caused a significant decrease in mean arterial blood pressure in sinoaortic-denervated conscious primates, but had no effect on mean arterial blood pressure in intact animals.[75] 4) Nonhypotensive hypovolemia induced by mild LBNP reduced carotid artery and ascending aortic dimensions in humans, which could alter arterial baroreceptor discharge properties.[76] (5) Recording of beat-to-beat cardiovascular responses to low-level LBPN revealed transient reductions in mean arterial blood pressure even though steady-state values were unchanged.[77–79] (6) An LBNP level, as low as −5 mm Hg, decreased CVP and had no effect on stroke volume or systolic arterial blood pressure, although power spectral analysis indicated a reduction in vagal heart rate variability, implying excitation of arterial baroreceptor pathways.[80] Moreover, during LBNP the subatmospheric pressure is applied to vessels and viscera in the pelvis and abdomen, as well as to the lower extremeties. Thus, the possibility that reflexes originating in sensory receptors in these regions, and in the cardiopulmonary area, may contribute to circulatory adjustments during LBNP cannot be excluded.

The inability to selectively and unambiguously deactivate the cardiopulmonary receptors in the LBNP studies has made it difficult to draw definitive conclusions concerning the importance and strength of a reverse Bainbridge reflex in humans. However, the lack of change in heart rate during moderate LBNP suggests that if a reverse Bainbridge reflex is present in humans, it is not very

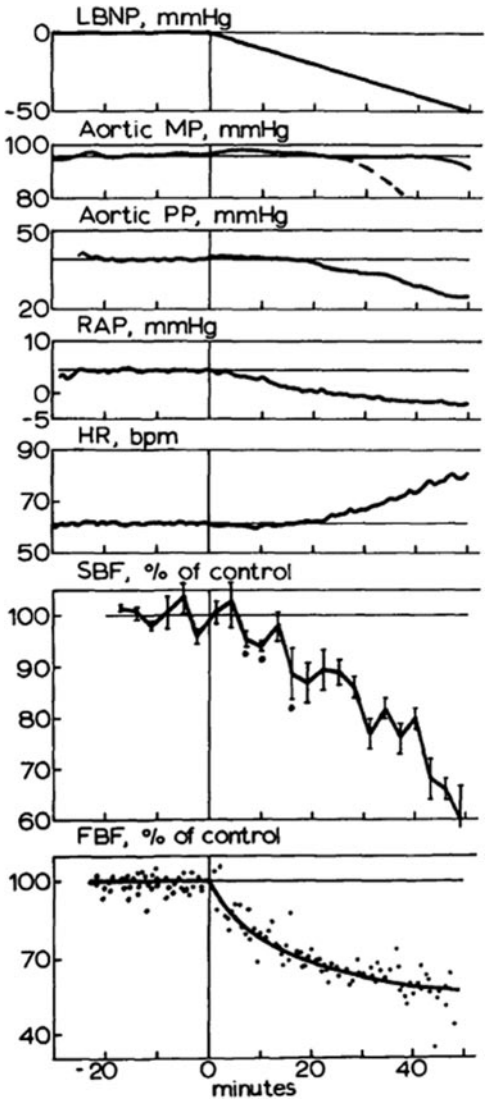

Figure 9. Average responses to a ramp of lower-body negative pressure (LBNP) in 6 normal healthy men. The dashed line for aortic mean pressure shows the response of 2 subjects who had a marked decrease at LBNP of −35 mm Hg; the solid line thereafter shows the average mean pressure for the remaining four subjects. Of note is that moderate decreases in LBNP caused decreases in right atrial pressure (implying an unloading of the cardiopulmonary volume receptors), but had no effect on aortic pressure (implying no change in activity of arterial baroreceptor receptors). The lack of change in heart rate was interpreted as evidence that the cardiopulmonary volume receptors, including the atrial receptors, had no influence on the rate of sinoatrial (SA) node discharge. MP = mean pressure; PP = pulse pressure; RAP = right atrial pressure; HR = heart rate; SBF = splancnic bloodflow; and FBF = forearm bloodflow. From Johnson et al.[67] Permission has been obtained from Wolters Kluwer Health/Lippincott Williams & Wilkins.

powerful because it can be completely nullified by what is likely a moderate arterial baroreceptor-mediated tachycardic effect.

Roles of the Reverse Bainbridge Reflex and the Bezold–Jarisch Reflex in the Paradoxical Bradycardia During Severe Hemorrhage

The Bezold–Jarisch reflex is an eponym for a triad of responses (bradycardia, hypotension, and apnea) after IV injection of veratrum alkaloids in animal models.[81,82] Veratrum alkaloids are plant extracts that were used clinically for the treatment of systemic hypertension but were discarded during the 1960s because of the narrow safety margin between the depressor dose and the dose causing medullary side effects such as vomiting and gastrointestinal activity.[81] Their effects during IV injection were initially reported in 1867 by von Bezold and Hirt.[83] Seventy years later, Jarisch and Richter conducted a series of studies[84,85] that confirmed the existence of the reflex and demonstrated that the receptor area was in the heart (not the great vessels), the afferent pathway was in the vagus nerve, and the efferent pathway involved an inhibition of sympathetic outflow to the peripheral vessels and an increased activity in the vagus nerve to the heart. The ventricular receptors underlying the Bezold–Jarisch reflex are the nonencapsulated terminals of the nonmyelinated vagal C-fiber afferents located in the walls of the ventricles.[86] Although veratrum alkaloids are not normally present in animals, it has become apparent that physiological factors, including mechanical stimulation, can trigger the Bezold–Jarisch reflex.[87]

The literature contains reports of bradycardia during severe hemorrhage in humans.[88–90] During mild hemorrhage, the response to unloading of the arterial baroreceptors dominates. The decrease in arterial blood pressure produces a reduction in arterial baroreceptor discharge rate, which reduces the restraint to the vasomotor center, resulting in an increase in sympathetic output to the heart (increasing heart rate and myocardial contractility) and peripheral blood vessels (increasing arteriolar tone and vascular resistance). These responses tend to normalize blood pressure in the face of a moderate decrease in blood volume. During severe hemorrhage (a decrease in cardiac output of 40%–50%, equivalent to loss of approximately 30% of blood volume), a paradoxical decrease in heart rate, as well as decreases in total peripheral resistance and arterial blood pressure, may occur, which can result in fainting and circulatory collapse (Fig. 10).[91] On theoretical grounds, one can propose that both the reverse Bainbridge reflex and the Bezold–Jarisch reflex may contribute to the bradycardia associated with significant blood loss. However, the work of Oberg et al. suggests that this may not be the case.[92,93] These investigators found that severe hemorrhage in anesthetized cats produced reflex bradycardia, which was abolished by cooling of the cervical vagi, by treatment with atropine, or by cutting the cardiac vagal nerves. Others have demonstrated similar findings in conscious rabbits.[94] Oberg's group also observed that surgical interruption of these afferent pathways from these cardiac receptors under baseline conditions did not itself produce bradycardia, which implied that the reflex response during severe hemorrhage was caused by an activation of some type of reflex and not by an unloading of tonically active receptors. Moreover, they also showed that the slowing of the heart was correlated to, and preceded by, an increased firing of receptors located in the left ventricle and in signaling in nonmyelinated afferent fibers. Taken together, the findings from Oberg et al. would exclude a role for a reverse Bainbridge reflex during severe hemorrhage.

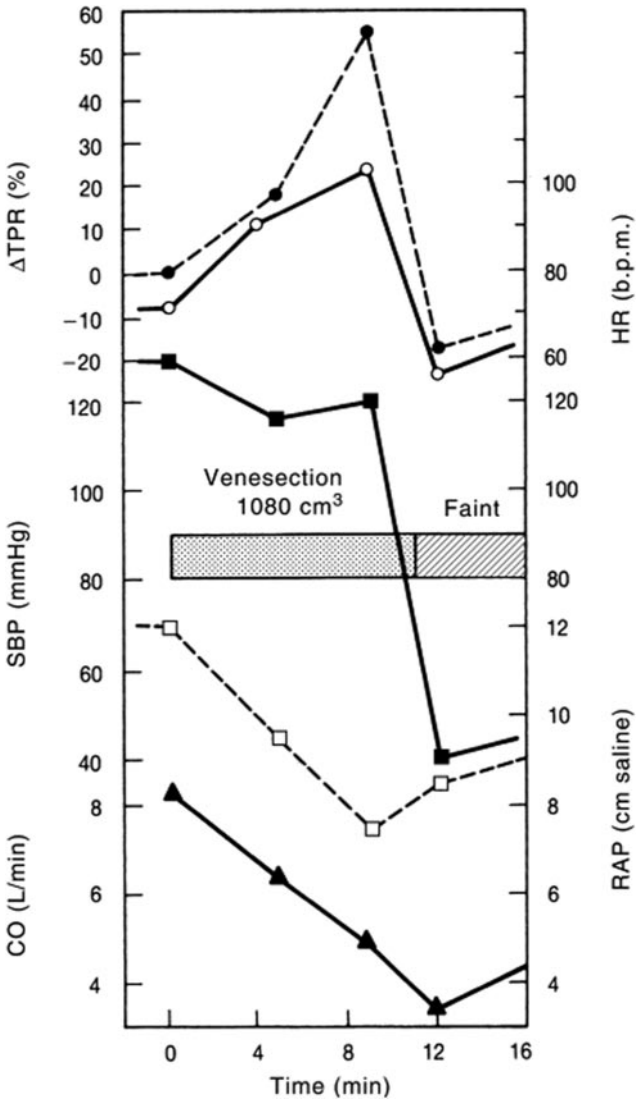

Figure 10. Hemodynamic responses to venesection in human volunteer, illustrating the 2 phases of the acute response to hypovolemia. In phase I, arterial blood pressure is maintained in the face of progressive reductions in cardiac output (CO;▲), by increases in total peripheral resistance (TPR; ●). The onset of phase II occurs abruptly once CO has reached a critical level and is characterized by dramatic decreases in TPR, arterial blood pressure, and heart rate, and the subject faints. (○), heart rate (HR); (■), systolic blood pressure (SBP); (□), right atrial pressure (RAP). Modified from Barcroft et al.[91] Permission has been obtained from Elsevier Limited.

Oberg's group also demonstrated that ventricular receptors were activated by obstructing the aorta and mechanical stimulation of the heart, and thus that they seemed to function as mechanoreceptors, which were stimulated by "distortion" of the myocardium. Oberg et al. theorized that during severe hemorrhage, the ventricular receptors were excited by an abnormal squeezing of the myocardium when the ventricles contract vigorously around a nearly empty chamber, leading to reflex bradycardia. Their findings suggest that the bradycardia during severe blood loss is mediated exclusively by the ventricular receptors and by the Bezold–Jarisch reflex.

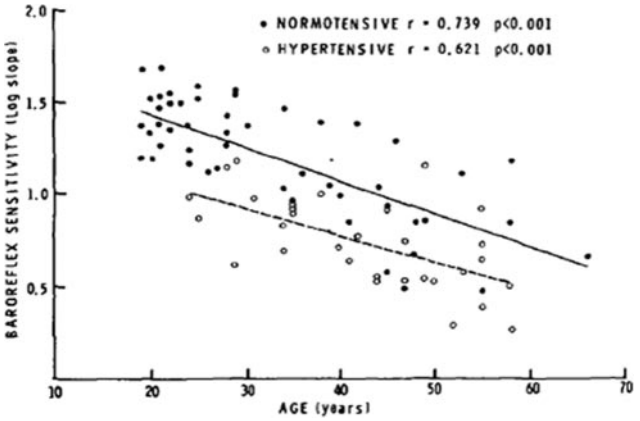

Figure 11. Effect of age on arterial baroreceptor reflex sensitivity. Each symbol represents 1 subject's results. The solid and dashed lines are regression lines for age on log sensitivity for normotensive and hypertensive subjects, respectively. Note that baroflex sensitivity was inversely correlated to age. From Gribbin et al.[98] Permission has been obtained from Wolters Kluwer Health/Lippincott Williams & Wilkins.

EFFECT OF AGING ON THE ARTERIAL BARORECEPTOR AND CARDIOPULMONARY REFLEXES—IMPLICATIONS TO THE BAINBRIDGE REFLEX

Circulatory lability and orthostatic hypotension are common in the elderly.[95–97] Cardiovascular autonomic dysfunction in the elderly contributes to impaired compensatory capability of the circulation to stress, including changes in central blood volume. In 1971, Gribbin et al.[98] were the first investigators to investigate the relationship between age and arterial baroreceptor control of heart rate. The study was performed in awake healthy subjects over a wide age range (19 to 66 years). Cardiovagal baroreflex sensitivity (BRS) was evaluated by measuring heart rate reductions, i.e., increases in R-R interval, during stepwise increases in arterial blood pressure by phenylephrine infusion. This technique is based on the finding that when the R-R interval is assessed over a range of blood pressures, a sigmoid relationship between R-R interval and blood pressure is generated.[99] The linear portion of this curve is used to quantify BRS. The slope of this curve is compared to assess differences in BRS under different conditions or for different populations. Gribbin et al.[98] found that aging was associated with a decreased BRS, i.e., blunted reflex adjustments in R-R interval in response to an invoked change in arterial blood pressure (Fig. 11), a finding that has been subsequently confirmed by others.[100–102] Several mechanisms have been proposed to explain the age-related reduction in arterial baroreflex regulation of heart rate: (1) arterial stiffening within the segments containing the baroreceptors, which would reduce the stimulus (arterial stretch) applied to the baroreceptors during a given change in blood pressure, (2) altered afferent signals from the baroreceptors, (3) altered central integration of barosensory information (afferent–efferent coupling), and (4) impaired cardiac vagal function.[99,100] This age-related decrease in baroreflex responsiveness must be considered when assessing the effect of aging on the cardiopulmonary reflexes, including the Bainbridge reflex.

Cleroux et al.[103] evaluated the effect of aging on the cardiopulmonary reflexes. The awake subjects were divided into the following groups: young (16 to 30 years), middle aged (37 to 49 years), and elderly (61 to 73 years). Increases in central blood volume were obtained using leg raising, and decreases in central blood volume were obtained using graded LBNP (−7 and −15 mm Hg). Measurements of mean arterial blood pressure, heart rate, forearm vascular resistance, plasma norepinephrine concentration, and plasma renin activity were obtained. Leg raising caused no significant change in mean arterial blood pressure or heart rate in any of the groups; however, the leg-raising-induced decreases in forearm vascular resistance, norepinephrine concentration, and plasma renin activity were less in the elderly. LBNP had no effect on mean arterial blood pressure or heart rate in any age group, but it caused increases in forearm vascular resistance, plasma norepinephrine, and plasma renin, which were much less pronounced in the elderly. The findings from Cleroux et al. suggested (1) absence of a Bainbridge (or a reverse Bainbridge) reflex in all age groups and (2) that the peripheral component of the volume-sensitive cardiopulmonary reflex is impaired in the elderly. However, these findings must remain inconclusive because of the possibility of activation of the arterial baroreceptor pathway during nonhypotensive LBNP, and the likelihood that the responsiveness of this pathway could be reduced with aging (as described above). Clèroux et al. proposed several potential mechanisms to explain the apparent adverse effect of aging on the cardiopulmonary reflexes. These include (1) an impairment of central integration of the cardiopulmonary reflex (cell degeneration, altered release of neurotransmitters, etc.) (2) a reduced ability of cardiac volume receptors to sense changes in volume because of cardiac hypertrophy and reduced wall distensibility, and (3) a reduction in the number of cardiopulmonary receptors or their reactivity to physiological stimuli. The authors excluded age-related changes to the efferent limb of the reflex because the blood pressure, heart rate, and forearm vascular resistance responses during the cold pressor test were the same in young, middle-aged, and elderly individuals.

In contrast, Salem[104] presented findings during controlled hypotention suggesting an increase in responsiveness of cardiopulmonary reflexes—i.e., a more pronounced reverse Bainbridge reflex—in the elderly. It was reported that controlled hypotension with the ganglionic blocking drug pentolinium combined with head-up tilt was associated with increases in heart rate in healthy adults anesthetized with halothane (which could be treated effectively with a β-receptor blocking drug) but with decreases in heart rate that were directly related to the decreases in CVP in similarly treated elderly patients.[104,105] These findings suggest that a cardiopulmonary receptor-mediated bradycardiac effect is weak and easily overridden by baroreceptor pathways in young adults, but that it may become more prominent and can dominate with aging. The vast difference in the conditions of the studies of Clèroux et al. and Salem make it difficult to provide a definitive explanation for their divergent conclusions. However, it is possible that the high sympathetic tone in elderly patients may have predisposed them to the bradycardic effect of ganglionic blockade in Salem's study.

Rooke et al.[106] evaluated the hemodynamic changes during high (range T_1–T_{10}) spinal anesthesia in elderly men, 59 to 80 years, with a history of cardiac disease. The findings indicated that spinal anesthesia caused decreases in mean arterial blood pressure, which were secondary to decreases in both systemic vascular resistance and cardiac output. The decreases in cardiac output were due to decreases in stroke volume, which resulted from reductions in venous return, as reflected in decreased left ventricular end diastolic pressure; heart rate remained constant. The lack of a baroreflex-mediated tachycardia during hypotension in these elderly men with cardiac disease may be explained by the counterveiling influence of a reverse Bainbridge reflex. However, this interpretation is complicated by the potential for an impairment to the arterial baroreceptor reflex, a blunted sympathetic tachycardic response because of the subjects' chronic medications, e.g., β blockers, and the sympathetic blockade afforded by high spinal anesthesia.

CONCLUSION

The Bainbridge reflex is present in conscious humans, although it is less prominent than in the dog, the species in which the reflex was originally observed. This difference may be related to a more dominant arterial baroreceptor reflex in humans. The influence of the Bainbridge reflex in an individual surgical patient cannot be readily predicted because of perioperative factors that may alter the responsiveness of the cardiac sympathetic nerves, e.g., surgical manipulation and anesthetics, and nonperioperative factors associated with disease and aging. The complicated interactions among the various reflex pathways and the difficulty in anatomically or physiologically separating their contribution pose a challenge to clinical researchers attempting to precisely characterize the role of the Bainbridge reflex under the various scenarios associated with increased central blood volume.

Observations obtained in some patients undergoing spinal anesthesia, epidural anesthesia, and controlled hypotension have suggested the presence of a reverse Bainbridge reflex in humans. However, the findings during LBNP, which is a more direct means of evaluating this reflex, have not been compelling. The decreases in heart rate observed during severe hemorrhage appear to be mediated by the Bezold–Jarisch reflex rather than by a reverse Bainbridge reflex.

DISCLOSURES

Name: George J. Crystal, PhD, FAHA.
Contribution: This author helped write the manuscript.
Attestation: George J. Crystal approved the final manuscript.
Name: M. Ramez Salem, MD.
Contribution: This author helped write the manuscript.
Attestation: M. Ramez Salem approved the final manuscript.
This manuscript was handled by: Martin J. London, MD.

REFERENCES

1. Bainbridge FA. The influence of venous filling upon the rate of the heart. J Physiol 1915;50:65–84

2. Hainsworth R. Reflexes from the heart. Physiol Rev 1991;71:617–58
3. Hakumaki MO. Seventy years of the Bainbridge reflex. Acta Physiol Scand 1987;130:177–85
4. Frank O. Zur dynamic des herzmuskels. Z Biol 1895; 32:370–437
5. Patterson SW, Piper H, Starling EH. The regulation of the heart beat. J Physiol 1914;48:465–513
6. Marey EJ. Physiologie Medicale de la Circulation due Sang. Paris: Adrien Delahaye, 1863:202–26
7. Hering HE. Der Karotisdruckversuch. Munch Med Wochschr 1923;70:1287–90
8. Heymans C, Ladon A. Sur le mecanisme de la bradycardie hypertensive et adrenalinique. Compt Rend Soc Biol 1924;90:996
9. Sagawa K. Baroreflex control of systemic arterial pressure and vascular bed. In: Shepherd JT, Abboud FM, eds. Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow. Bethesda, MD: American Physiological Society, 1983:453–96
10. Dampney RA. Functional organization of central pathways regulating the cardiovascular system. Physiol Rev 1994;74:323–64
11. Neukirchen M, Kienbaum P. Sympathetic nervous system: evaluation and importance for clinical general anesthesia. Anesthesiology 2008;109:1113–31
12. Nonidez J. Identification of the receptor areas in the venae cavae and the pulmonary veins which initiate cardiac acceleration (Bainbridge's reflex). Am J Anat 1937;61:203–31
13. Coleridge JC, Linden RJ. The effect of intravenous infusions upon the heart rate of the anaesthetized dog. J Physiol 1955;128:310–9
14. Horwitz LD, Bishop VS. Effect of acute volume loading on heart rate in the conscious dog. Circ Res 1972;30:316–21
15. Goetz KL. Effect of increased pressure within a right heart cul-de-sac on heart rate in dogs. Am J Physiol 1965;209:507–12
16. Ledsome JR, Linden RJ. The effect of distending a pouch of the left atrium on the heart rate. J Physiol 1967;193:121–9
17. Vatner SF, Boettcher DH, Heyndrickx GR, McRitchie RJ. Reduced baroreflex sensitivity with volume loading in conscious dogs. Circ Res 1975;37:236–42
18. Heymans C, Neil E. Reflexogenic Areas of the Cardiovascular System. London: Churchill, 1958
19. Mark AL, Mancia G. Cardiopulmonary baroreflexes in humans. In: Shepherd JT, Abboud FM, eds. Handbook of Physiology. The Cardiovascular System. Peripheral Circulation and Organ Blood Flow. Bethesda, MD: American Physiological Society, 1983:795–831
20. Boettcher DH, Zimpfer M, Vatner SF. Phylogenesis of the Bainbridge reflex. Am J Physiol 1982;242:R244–6
21. Giuntini C, Maseri A, Bianchi R. Pulmonary vascular distensibility and lung compliance as modified by dextran infusion and subsequent atropine injection in normal subjects. J Clin Invest 1966;45:1770–89
22. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho–vagal interaction in man and conscious dog. Circ Res 1986;59:178–93
23. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. Cardiovasc Res 1996;32:208–16
24. Barbieri R, Waldmann RA, Di Virgilio V, Triedman JK, Bianchi AM, Cerutti S, Saul JP. Continuous quantification of baroreflex and respiratory control of heart rate by use of bivariate autoregressive techniques. Ann Noninvasive Electrocardiol 1996;1:264–77
25. Barbieri R, Triedman JK, Saul JP. Heart rate control and mechanical cardiopulmonary coupling to assess central volume: a systems analysis. Am J Physiol Regul Integr Comp Physiol 2002;283:R1210–20
26. Umehara S, Tanaka M, Nishikawa T. Effects of sevoflurane anesthesia on carotid-cardiac baroreflex responses in humans. Anesth Analg 2006;102:38–44
27. Muzi M, Ebert TJ. A comparison of baroreflex sensitivity during isoflurane and desflurane anesthesia in humans. Anesthesiology 1995;82:919–25
28. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173–9
29. Duke PC, Fownes D, Wade JG. Halothane depresses baroreflex control of heart rate in man. Anesthesiology 1977;46:184–7
30. Tanaka M, Nishikawa T. Arterial baroreflex function in humans anaesthetized with sevoflurane. Br J Anaesth 1999;82:350–4
31. Morton M, Duke PC, Ong B. Baroreflex control of heart rate in man awake and during enflurane and enflurane-nitrous oxide anesthesia. Anesthesiology 1980;52:221–3
32. Ebert TJ, Harkin CP, Muzi M. Cardiovascular responses to sevoflurane: a review. Anesth Analg 1995;81:S11–22
33. Kotrly KJ, Ebert TJ, Vucins EJ, Roerig DL, Stadnicka A, Kampine JP. Effects of fentanyl-diazepam-nitrous oxide anaesthesia on arterial baroreflex control of heart rate in man. Br J Anaesth 1986;58:406–14
34. Sato M, Tanaka M, Umehara S, Nishikawa T. Baroreflex control of heart rate during and after propofol infusion in humans. Br J Anaesth 2005;94:577–81
35. Greene NM. Preganglionic sympathetic blockade in man: a study of spinal anesthesia. The Torsten Gordh Lecture, 1980. Acta Anaesthesiol Scand 1981;25:463–9
36. Sancetta SM, Lynn RB, Simeone FA, Scott RW. Studies of hemodynamic changes in humans following induction of low and high spinal anesthesia: I. General considerations of the problem. The changes in cardiac output, brachial artery pressure, peripheral and pulmonary oxygen contents and peripheral blood flows induced by spinal anesthesia in humans not undergoing surgery. Circulation 1952;6:550–71
37. Greene NM. Physiology of Spinal Anesthesia. Baltimore: Williams and Wilkins, 1958
38. Greene NM. Physiology of sympathetic denervation. Annu Rev Med 1962;13:87–104
39. Ward RJ, Bonica JJ, Freund FG, Akamatsu T, Danziger F, Englesson S. Epidural and subarachnoid anesthesia. Cardiovascular and respiratory effects. JAMA 1965;191:275–8
40. Salinas F. Spinal anesthesia. In: Benzon HT, Raja SN, Molloy RE, Liu SS, Fishman SM, eds. Essentials of Pain Medicine and Regional Anesthesia. Philadelphia: Elsevier, 2005:560–74
41. Dobson PM, Caldicott LD, Gerrish SP, Cole JR, Channer KS. Changes in haemodynamic variables during transurethral resection of the prostate: comparison of general and spinal anaesthesia. Br J Anaesth 1994;72:267–71
42. Brooker RF, Butterworth JF, Kitzman DW, Berman JM, Kashtan HI, McKinley AC. Treatment of hypotension after hyperbaric tetracaine spinal anesthesia. A randomized, double-blind, cross-over comparison of phenylephrine and epinephrine. Anesthesiology 1997;86:797–805
43. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology 1992;76:906–16
44. O'Rourke GW, Greene NM. Autonomic blockade and the resting heart rate in man. Am Heart J 1970;80:469–74
45. Baron JF, Decaux-Jacolot A, Edouard A, Berdeaux A, Samii K. Influence of venous return on baroreflex control of heart rate during lumbar epidural anesthesia in humans. Anesthesiology 1986;64:188–93
46. Chang KS, Morrow DR, Kuzume K, Andresen MC. Bupivacaine inhibits baroreflex control of heart rate in conscious rats. Anesthesiology 2000;92:197–207
47. Bonica JJ, Kennedy WF, Akamatsu TJ, Gerbershagen HU. Circulatory effects of peridural block: 3. Effects of acute blood loss. Anesthesiology 1972;36:219–27
48. Ecoffey C, Edouard A, Pruszczynski W, Taly E, Samii K. Effects of epidural anesthesia on catecholamines, renin activity, and vasopressin changes induced by tilt in elderly men. Anesthesiology 1985;62:294–7

49. Greene DW, Verner IR, Fahmy NR Techniques for deliberate hypotension. In: Enderby GEH, ed. Hypotensive Anaesthesia. Edinburgh: Churchill Livingstone, 1985:109–83
50. Crystal GJ, Gurevicius J. Nitric oxide does not modulate myocardial contractility acutely in in situ canine hearts. Am J Physiol 1996;270:H1568–76
51. Mason DT, Zelis R, Amsterdam EA. Actions of the nitrites on the peripheral circulation and myocardial oxygen consumption: significance in the relief of angina pectoris. Chest 1971;59:296–305
52. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45:340–54
53. Fahmy NR. Nitroglycerin as a hypotensive drug during general anesthesia. Anesthesiology 1978;49:17–20
54. Guggiari M, Dagreou F, Lienhart A, Gallais S, Mottet P, Philippon J, Viars P. Use of nitroglycerine to produce controlled decreases in mean arterial pressure to less than 50 mm Hg. Br J Anaesth 1985;57:142–7
55. Yaster M, Simmons RS, Tolo VT, Pepple JM, Wetzel RC, Rogers MC. A comparison of nitroglycerin and nitroprusside for inducing hypotension in children: a double-blind study. Anesthesiology 1986;65:175–9
56. Schwarz P, Diem R, Dun NJ, Forstermann U. Endogenous and exogenous nitric oxide inhibits norepinephrine release from rat heart sympathetic nerves. Circ Res 1995;77:841–8
57. Matsuda T, Bates JN, Lewis SJ, Abboud FM, Chapleau MW. Modulation of baroreceptor activity by nitric oxide and S-nitrosocysteine. Circ Res 1995;76:426–33
58. Sears CE, Choate JK, Paterson DJ. NO-cGMP pathway accentuates the decrease in heart rate caused by cardiac vagal nerve stimulation. J Appl Physiol 1999;86:510–6
59. Zanzinger J. Role of nitric oxide in the neural control of cardiovascular function. Cardiovasc Res 1999;43:639–49
60. Musialek P, Casadei B. Nitrovasodilators and heart rate: more than the arterial baroreflex. Cardiovasc Res 2000;47:404–5
61. Wolthuis RA, Bergman SA, Nicogossian AE. Physiological effects of locally applied reduced pressure in man. Physiol Rev 1974;54:566–95
62. Cooke WH, Ryan KL, Convertino VA. Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. J Appl Physiol 2004;96:1249–61
63. Stevens PM, Lamb LE. Effects of lower body negative pressure on the cardiovascular system. Am J Cardiol 1965;16:506–15
64. Brown E, Goei JS, Greenfield AD, Plassaras GC. Circulatory responses to simulated gravitational shifts of blood in man induced by exposure of the body below the iliac crests to sub-atmospheric pressure. J Physiol 1966;183:607–27
65. Saunders JW. Negative-pressure device for controlled hypotension during surgical operations. Lancet 1952;259:1286–7
66. Zoller RP, Mark AL, Abboud FM, Schmid PG, Heistad DD. The role of low pressure baroreceptors in reflex vasoconstrictor responses in man. J Clin Invest 1972;51:2967–72
67. Johnson JM, Rowell LB, Niederberger M, Eisman MM. Human splanchnic and forearm vasoconstrictor responses to reductions of right atrial and aortic pressures. Circ Res 1974;34:515–24
68. Frey MA, Hoffler GW. Association of sex and age with responses to lower-body negative pressure. J Appl Physiol 1988;65:1752–6
69. Pawelczyk JA, Raven PB. Reductions in central venous pressure improve carotid baroreflex responses in conscious men. Am J Physiol 1989;257:H1389–95
70. Jacobsen TN, Morgan BJ, Scherrer U, Vissing SF, Lange RA, Johnson N, Ring WS, Rahko PS, Hanson P, Victor RG. Relative contributions of cardiopulmonary and sinoaortic baroreflexes in causing sympathetic activation in the human skeletal muscle circulation during orthostatic stress. Circ Res 1993;73:367–78
71. Levine BD, Giller CA, Lane LD, Buckey JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. Circulation 1994;90:298–306
72. Ebert TJ, Kotrly KJ, Vucins EJ, Pattison CZ, Kampine JP. Halothane anesthesia attenuates cardiopulmonary baroreflex control of peripheral resistance in humans. Anesthesiology 1985;63:668–74
73. Hakumaki MO, Wang BC, Sundet WD, Goetz KL. Aortic baroreceptor discharge during nonhypotensive hemorrhage in anesthetized dogs. Am J Physiol 1985;249:H393–403
74. Eckberg DL. Baroreflexes and the failing human heart. Circulation 1997;96:4133–7
75. Cornish KG, Gilmore JP, McCulloch T. Central blood volume and blood pressure in conscious primates. Am J Physiol 1988;254:H693–701
76. Taylor JA, Halliwill JR, Brown TE, Hayano J, Eckberg DL. 'Non-hypotensive' hypovolaemia reduces ascending aortic dimensions in humans. J Physiol 1995;483(Pt 1):289–98
77. Hisdal J, Toska K, Walloe L. Beat-to-beat cardiovascular responses to rapid, low-level LBNP in humans. Am J Physiol Regul Integr Comp Physiol 2001;281:R213–21
78. Hisdal J, Toska K, Flatebo T, Walloe L. Onset of mild lower body negative pressure induces transient change in mean arterial pressure in humans. Eur J Appl Physiol 2002;87:251–6
79. Fu Q, Shibata S, Hastings JL, Prasad A, Palmer MD, Levine BD. Evidence for unloading arterial baroreceptors during low levels of lower body negative pressure in humans. Am J Physiol Heart Circ Physiol 2009;296:H480–8
80. Floras JS, Butler GC, Ando SI, Brooks SC, Pollard MJ, Picton P. Differential sympathetic nerve and heart rate spectral effects of nonhypotensive lower body negative pressure. Am J Physiol Regul Integr Comp Physiol 2001;281:R468–75
81. Aviado DM, Guevara Aviado D. The Bezold–Jarisch reflex. A historical perspective of cardiopulmonary reflexes. Ann N Y Acad Sci 2001;940:48–58
82. Campagna JA, Carter C. Clinical relevance of the Bezold–Jarisch reflex. Anesthesiology 2003;98:1250–60
83. Bezold AV, Hirt L. Uber die physiologischen wirkungen des essigsauren veratrins. Unters Physiol Lab. Wurzburg 1867;1:75–156
84. Jarisch A, Richter H. Die afferenten bahnen des veratrineeffektes in den herznerven. Arch Exp Pathol Pharmacol 1939;193:355–71
85. Jarisch A, Richter H. Die kreislauf des veratrins. Arch Exp Pathol Pharmacol 1939;193:347–54
86. Thoren PN. Characteristics of left ventricular receptors with nonmedullated vagal afferents in cats. Circ Res 1977;40:415–21
87. Mark AL. The Bezold–Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1:90–102
88. Secher NH, Sander Jensen K, Werner C, Warberg J, Bie P. Bradycardia during severe but reversible hypovolemic shock in man. Circ Shock 1984;14:267–74
89. Secher NH, Jacobsen J, Friedman DB, Matzen S. Bradycardia during reversible hypovolaemic shock: associated neural reflex mechanisms and clinical implications. Clin Exp Pharmacol Physiol 1992;19:733–43
90. Schadt JC, Ludbrook J. Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. Am J Physiol 1991;260:H305–18
91. Barcroft H, McMichael J, Edholm OG, Sharpey-Schafer EP. Posthaemorrhagic fainting. Study by cardiac output and forearm flow. Lancet 1944;243:489–91
92. Oberg B, White S. The role of vagal cardiac nerves and arterial baroreceptors in the circulatory adjustments to hemorrhage in the cat. Acta Physiol Scand 1970;80:395–403
93. Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat. A possible cause of the vaso-vagal reaction. Acta Physiol Scand 1972;85:164–73
94. Evans RG, Ludbrook J, Ventura S. Role of vagal afferents in the haemodynamic response to acute central hypovolaemia in unanaesthetized rabbits. J Auton Nerv Syst 1994;46:251–60
95. Lipsitz LA. Orthostatic hypotension in the elderly. N Engl J Med 1989;321:952–7

96. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research group. Hypertension 1992;19:508–19
97. Laitinen T, Niskanen L, Geelen G, Lansimies E, Hartikainen J. Age dependency of cardiovascular autonomic responses to head-up tilt in healthy subjects. J Appl Physiol 2004;96:2333–40
98. Gribbin B, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 1971;29:424–31
99. Monahan KD. Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol 2007;293:R3–12
100. Monahan KD, Dinenno FA, Seals DR, Clevenger CM, Desouza CA, Tanaka H. Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance. Am J Physiol Heart Circ Physiol 2001;281:H284–9
101. Laitinen T, Hartikainen J, Vanninen E, Niskanen L, Geelen G, Lansimies E. Age and gender dependency of baroreflex sensitivity in healthy subjects. J Appl Physiol 1998;84:576–83
102. Rudas L, Crossman AA, Morillo CA, Halliwill JR, Tahvanainen KU, Kuusela TA, Eckberg DL. Human sympathetic and vagal baroreflex responses to sequential nitroprusside and phenylephrine. Am J Physiol 1999;276:H1691–8
103. Clèroux J, Giannattasio C, Bolla G, Cuspidi C, Grassi G, Mazzola C, Sampieri L, Seravalle G, Valsecchi M, Mancia G. Decreased cardiopulmonary reflexes with aging in normotensive humans. Am J Physiol 1989;257:H961–8
104. Salem MR. Pulse-rate changes in elderly patients during deliberate hypotension. Anesthesiology 1969;30:328–30
105. Salem MR, Ivankovic AD. The place of beta-adrenergic blocking drugs in the deliberate induction of hypotension. Anesth Analg 1970;49:427–34
106. Rooke GA, Freund PR, Jacobson AF. Hemodynamic response and change in organ blood volume during spinal anesthesia in elderly men with cardiac disease. Anesth Analg 1997;85:99–105
107. Rothe CF, Friedman JJ. Control of the Cardiovascular System. In: Selkurt EE, ed. Physiology. 3rd ed. Boston: Little, Brown and Company, 1971:372
108. Rushmer RF. Cardiovascular Dynamics. 3rd ed. Philadelphia: WB Saunders, 1970:165