Neurohumoral regulation of arterial pressure in hemorrhage and heart failure

THOMAS E. LOHMEIER
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi 39216

HEMORRHAGE AND HEART FAILURE are conditions characterized by reduced cardiac output and arterial pressure. In both conditions, neurohormonal mechanisms are evoked in an attempt to restore arterial pressure to normal levels. However, the relative importance of the various neurohormonal mechanisms in arterial pressure control is quite different in these two states for several reasons, including the following. First, hemorrhage and heart failure are associated with diametrically opposite changes in cardiac pressures, which in turn lead to unique neurohormonal responses. Second, the duration of the cardiovascular insult is acute in hemorrhage but protracted in heart failure. Although it is well established that reflex mechanisms play a critical role in the acute regulation of arterial pressure, the importance of reflexes in long-term control of arterial pressure, such as in the pathophysiological state of heart failure, is unclear. As the kidneys are of preeminent importance in the long-term regulation of arterial pressure (17), the factors that alter renal excretory function would be expected to dominate in the regulation of arterial pressure in heart failure. Unfortunately, some of the factors that promote sodium retention and, therefore, restore cardiac output and arterial pressure toward control levels in the early stages of heart failure are the same factors that lead to unabated fluid retention and further cardiac dysfunction in the latter phase of this disease.

Hemorrhage. Progressive blood loss elicits a number of neurohormonal responses that impact the regulation of arterial pressure (32). During the initial phase of blood loss (normotensive hemorrhage), arterial pressure is maintained at normotensive levels in large part by peripheral vasoconstriction, initiated by activation of the sympathetic nervous system. The second phase (hypotensive hemorrhage) occurs rather abruptly with further blood loss and is associated with sympathoinhibition. The maintenance of arterial pressure during the initial phase is greatly dependent on the arterial baroreflex. An elegant study in chronically instrumented dogs subjected to differential denervation of carotid sinus and aortic baroreceptors demonstrated that the former play a somewhat greater role in delaying the transition from the normotensive to the hypotensive phase of hemorrhage (42). In rats, this transition to the hypotensive phase of hemorrhage was delayed by prior activation of the defense reaction by air jet stress (31). This is a significant observation, because, unlike in a laboratory setting, hemorrhage usually occurs in the presence of stressful stimuli. An interesting study in transgenic rats overexpressing neuropeptide Y indicated that this vasoconstrictor peptide, which is synthesized in the central and peripheral nervous systems and is coreleased with norepinephrine from sympathetic nerve terminals, contributes to the maintenance of arterial pressure during hemorrhage (26).

Although the mechanisms that account for sympathoinhibition in the hypotensive phase of hemorrhage remain to be completely defined, some progress has been made recently in elucidating the central component of this response. The notion that endogenous serotonin release within the central nervous system mediates the rapid onset of hypotension in response to hemorrhage appears to be refuted by a study in which selective serotonin antagonists and agonists were administered centrally in rats before the onset of hemorrhage (34). Other studies in rats have identified the ventrolateral midbrain periaqueductal gray region and the lateral parabrachial nucleus as important central sites that mediate hypotension and bradycardia in the hypotensive phase of hemorrhage (5, 7).

It is well established that the vasoconstrictor actions of angiotensin (ANG II) play an important role in the preservation of arterial pressure during hemorrhage. Decreased arterial pressure and concomitant activation of the sympathetic nervous system would be expected to be major stimuli for renin secretion during hemorrhage (8, 36). Recent studies suggest a novel stimulus as well. In addition to its actions during lactation and parturition, studies in conscious rats indicate that oxytocin also increases renin release (18, 58).
During hypovolemia and hypotension, the levels of oxytocin in the circulation are sufficiently elevated to achieve this effect. Although the specific mechanism has not been established, in some way oxytocin interacts with the sympathetic nervous system to stimulate renin release by activating β-adrenergic receptors. In addition to increasing renin release by a sympathetic mechanism, oxytocin also increases heart rate in hypovolemic and hypotensive states (19). In contrast, oxytocin acts centrally to restrain exercise-induced tachycardia (6).

Another way in which the renin-angiotensin system contributes to the regulation of arterial pressure during hypovolemia and hypotension is by stimulating thirst. Although ANG II is a potent dipsogen (28), the prevailing level of arterial pressure influences the central actions of ANG II, which stimulate drinking. Increased arterial pressure blunts and decreased arterial pressure enhances the dipsogenic response to ANG II (37, 43). The influence of arterial pressure on the drinking response to ANG II is mediated via cardiac and arterial baroreflexes. Consequently, electrolytic lesions of the nucleus of the solitary tract, which eliminate cardiac and arterial baroreceptor input into the central nervous system, enhance the effects of pressor infusion rates of ANG II on thirst (33). In contrast to the inhibitory influence of activating the baroreflex on the drinking response to exogenous ANG II, unloading baroreceptors during hemorrhage would be expected to promote, not oppose, the central dipsogenic effects of endogenous ANG II.

Similar to ANG II, the levels of vasopressin achieved in the circulation during hemorrhage contribute to arterial pressure homeostasis by increasing peripheral resistance. Accordingly, there has been and there still is considerable interest in the nonosmotic stimuli that influence vasopressin secretion (12, 41). Although both ANG II and oxytocin may promote vasopressin secretion during hypovolemia and hypotension (19, 33), over the years much attention has been given to the relative importance of atrial vs. arterial baroreceptors in mediating reflex increases in vasopressin secretion. In this regard, a recent study in conscious dogs subjected to both thoracic inferior vena caval constriction and hemorrhage to unload cardiac and arterial baroreceptors provided strong evidence that arterial baroreceptors, rather than atrial baroreceptors, play the more important role in stimulating vasopressin secretion in response to hemorrhage (41). In response to both stimuli, increments in plasma vasopressin concentration were highly correlated to reductions in systolic but not atrial pressure. Furthermore, the sensitivity of this relationship was markedly reduced by ablation of afferent input from sinoaortic baroreceptors but not cardiac receptors.

In contrast to the relative unimportance of unloading cardiac receptors on vasopressin secretion during hemorrhage, extracellular recordings from supraoptic magnocellular neurons in the rat clearly indicate that increased cardiac pressure inhibits vasopressinergic but not oxytocinergic neurons (15). Furthermore, considerable progress has been made in elucidating the central pathways responsible for inhibiting vasopressin release after activation of both cardiac and arterial baroreceptors (13, 14, 16). The apparent dichotomy between the effects of loading and unloading (during hemorrhage) cardiac receptors on vasopressin secretion may indicate that cardiac-reflex control of vasopressin secretion is more important in the defense of hyper- than hypovolemia.

Several studies focused on the preservation of organ function after resuscitation from severe hemorrhage. In one study, prior induction of heat shock proteins by heat stress protected cardiovascular and hepatocellular functions after hemorrhage, possibly by decreasing circulating levels of proinflammatory cytokines (27). Another study demonstrated that testosterone receptor blockade with flutamide in male rats attenuated the depressed adrenal function associated with hemorrhage (2). Finally, different forms of stroma-free polymerized hemoglobin have been used during resuscitation of hemorrhage shock. Of concern, one of the more popular forms, diaspirin cross-linked hemoglobin, was found to decrease tissue perfusion in normal dogs, possibly by scavenging nitric oxide. However, in dogs first subjected to hemorrhage, this cross-linked hemoglobin did not further reduce organ perfusion, leading the authors to conclude that nitric oxide inhibition does not impair hemodynamic recovery during hemorrhage (39).

Heart failure. Neurohumoral activation plays an important role in the progression of heart failure (9, 10, 24, 44). This activation varies considerably throughout the evolution of the disease. Unfortunately, there are few longitudinal studies that have determined the sequential neurohumoral changes that occur during the natural history of heart failure and how these changes impact hemodynamics and salt and water balance. Two recent studies, however, have been quite comprehensive and have addressed these issues (10, 24). In dogs subjected to rapid ventricular pacing and in rats with myocardial infarction secondary to coronary artery ligation, salt and water excretion fell dramatically after initiating the cardiac insult, but returned toward control levels thereafter despite marked impairment of cardiac function and persistently low blood pressure. In both studies, high plasma levels of atrial natriuretic peptide were sustained throughout the entire period of study, reflecting the importance of this peptide in restoring sodium excretion toward control levels in the face of reduced arterial pressure (23). Despite low arterial pressure and sustained activation of the sympathetic nervous system, stimuli expected to increase renin secretion, only modest activation of the renin-angiotensin system occurred in the early compensated phase of heart failure. The mechanisms that suppress renin secretion in the early phase of heart failure have not been completely elucidated but are of critical importance because even relatively small increments in plasma ANG II concentration have pronounced antinatriuretic effects in human and experimental heart failure (11, 24). Increments in plasma ANG II concentra-
tion to levels present in the advanced stages of heart failure cause marked and sustained sodium retention and can even initiate the transition from compensated to decompensated heart failure (24).

Most experimental studies have focused on a single time point in the evolution of heart failure and usually the advanced or decompensated phase of the disease has been emphasized. Although global activation of the sympathetic nervous system does not typically occur under physiological or pathophysiological conditions (29, 30), the pattern of sympathetic activation in heart failure does include the kidneys, at least in the decompensated phase of heart failure (9, 30). As increased renal sympathetic nerve activity (RSNA) contributes to the avid sodium retention characteristic of advanced heart failure, there has been considerable interest in identifying the mechanisms that lead to renal sympathoexcitation. Much attention has been given to the arterial baroreflex because several acute studies have reported increased RSNA in association with impaired baroreflex suppression of RSNA in overt heart failure (9, 10, 20). However, a causal relationship between baroreflex dysfunction and chronic increments in RSNA has not been established. Nonetheless, pertinent experiments have been conducted in dogs with hemibladders to allow 24-h urine collection from denervated and innervated kidneys (21, 22). As both kidneys are subjected to the same blood pressure and circulating hormones, this is a very sensitive technique for detecting neural influences on renal excretory function. During induction of chronic ANG II hypertension, sodium excretion from innervated kidneys increased relative to denervated kidneys, a response that was abolished by cardiopulmonary and arterial baroreceptor denervation. These findings suggest that cardiac and/or arterial baroreflexes chronically inhibit RSNA during ANG II hypertension. Moreover, these results indicate that the baroreflex does not totally reset in the face of long-term alterations in body fluid volumes and arterial pressure. Consequently, these findings lend credence to the hypothesis that baroreflex dysfunction could account for chronic increases in RSNA in heart failure.

A similar experimental approach has been taken to assess the influence of the renal nerves on the renal vasculature. Both RSNA and renal blood flow were monitored in denervated and innervated kidneys of individual rabbits during their daily activity (4). Whereas variations in RSNA did have transient effects on renal blood flow, daily mean values for renal blood flow were not significantly different between denervated and innervated kidneys. Use of this novel experimental model in rabbits subjected to heart failure would provide unique insight into the time-dependent changes in RSNA and their impact on renal blood flow throughout the progression of heart failure.

Increases in cardiac pressure in response to volume expansion reflexively inhibit RSNA and promote sodium excretion (9, 11). As the cardiorenal reflex is blunted in advanced heart failure, it has been suggested that impaired reflex suppression of RSNA might also contribute to volume overload and decompensation. To determine whether impairment of this reflex might be an early event in the progression of heart failure, the cardiorenal reflex was assessed in patients with compensated heart failure by employing thermoneutral water immersion, which increases central blood volume (11). In these patients, the natriuretic response to water immersion was intact but impaired in the presence of a twofold increase in plasma ANG II concentration. When plasma ANG II concentration was restored to normal levels after chronic administration of an angiotensin-converting enzyme inhibitor, the natriuretic response to water immersion increased to levels observed in control subjects. It was concluded that the cardiorenal reflex, although modulated by prevailing levels of ANG II, is preserved in the compensated phase of heart failure.

Other studies have attributed increments in RSNA in advanced heart failure to the central actions of hormonal or humoral factors. Rats with decompensated, high-output heart failure have increased RSNA (35). Microinjection of an ANG II-receptor antagonist into the nucleus of the solitary tract produced a substantially greater fall in RSNA in rats with an aortic-caval shunt than in controls. Although the specific mechanism was not addressed, the authors concluded that activation of the renin-angiotensin system within the nucleus of the solitary tract contributes to enhanced RSNA in this model of heart failure. Rats with advanced pacing-induced heart failure have increased RSNA associated with impaired baroreflex sensitivity (20). Chronic endothelin-1 (ET-1) blockade decreased both arterial pressure and RSNA in rabbits with heart failure; in comparison, the antagonist had no effect on either arterial pressure or RSNA in controls. Additionally, ET-1 blockade improved baroreflex sensitivity in the former but not in the latter. These results suggest that ET-1 contributes to renal sympathoexcitation in heart failure, possibly by decreasing baroreflex sensitivity.

On the basis of tissue levels of ET-1 and gene expression of prepro-ET-1, a study in dogs with pacing-induced heart failure identified atrial myocytes and pulmonary tissue as major contributors to the increased plasma levels of ET-1 in heart failure (25). Although there was no evidence for increased renal synthesis of ET-1, a relatively high concentration of ET-1 was present in the kidneys, suggesting a high rate of ET-1 uptake from the circulation. As the renal actions of ET-1 impair renal excretory function (1,3), the high tissue levels of ET-1 in the kidneys indicate that ET-1 is yet another factor that contributes to avid sodium retention in decompensated heart failure. Because high plasma levels of ANG II are typically observed in decompensated heart failure, the failure of canine kidneys to increase ET-1 synthesis in pacing-induced heart failure is noteworthy. This is because the hypertension induced by chronic infusion of ANG II in the rat is associated with increased renal ET-1 synthesis (1). Indeed, the generated ET-1 contributes significantly to the hypertension (1,3). Whether the differen-
tial effect of increased plasma levels of ANG II on renal synthesis of ET-1 in heart failure and hypertension reflects hypertension-induced renal endothelial dysfunction has not been established. Finally, some of the effects of ET-1 in heart failure may not be detrimental. Studies in cultured cardiomyocytes indicate that ET-1 may prevent cardiomyocyte toxicity by increasing the production of antioxidants (40).

REFERENCES


