วารสารเภสัชวิทยา ปีที่ 9, 2530
Thai J Pharmacol Vol 9, 1987

Cardiac and Arterial Baroreceptor Function in Heart Failure

Irving H. Zucker
Department of Physiology and Biophysics
University of Nebraska College of Medicine
Omaha. Nebraska 68105

Summary

Although the condition of heart failure can be defined in hemodynamic terms, it is an oversimplification to think that the systemic consequences of this disease entity is due solely to alterations in peripheral blood flow. Clearly, neurohumoral events can play a major role in the compensatory adjustments which take place in heart failure, albeit at the expense of a deterioration in organ function. Many of the normally occurring neurohumoral control mechanisms are abnormal in heart failure. These come about from changes in both efferent and afferent components of the reflex arcs.

The fact that sensory endings in the heart and blood vessels may play an important role in the abnormal reflex control of the circulation in heart failure has not been generally appreciated. There is a good deal of clinical and animal studies that suggest that mechanoreceptor function in the atria, ventricles, aorta and carotid sinus is abnormal in heart failure. In most cases these receptors function at a depressed sensitivity with the possible exception of left ventricular receptors. The mechanism (s) that are responsible for the observed receptor abnormalities in heart failure are not completely understood, however at this point it is reasonable to assume that both structural and compliance changes may be operative to cause the abnormalities observed for atrial receptors. The cause of the decrease in arterial baroreceptor discharge sensitivity is not known, however we do know that it is not due to a change in compliance of the carotid sinus or aortic arch.

Possibilities which need to be investigated include alterations in sympathetic control of baroreceptor discharge and changes in Na-K pump activity in the baroreceptors themselves. As far as ventricular receptors are concerned we do not currently have enough data to determine the mechanism of the enhanced reflex changes that are evoked from their stimulation in heart failure.

There is little doubt that a variety of neurohumoral abnormalities exist in heart failure which potentially influence cardiovascular regulation. These include increased secretion of vasoactive hormones such as catecholamines (1), vasopressin (2,3), renin-angiotensin (4), and prostaglandins (5). It has also been shown that alterations in autonomic function occur in heart failure, especially as regards the arterial baroreflex control of heart rate (6-8). It is generally assumed that the initial elevation in sympathetic tone that occurs in heart failure is mediated by

unloading of the arterial baroreceptors due in part to a falling cardiac output.

Although this idea fits with our current understanding of the reflex control of blood pressure, it is a simplification to think that the unloading of normally functioning reflexogenic areas of the circulation in a chronic disease state accounts for this observation. In fact, heart failure in man and experimental animals has been characterized as resulting in an increase in catecholamine excretion and in plasma catechols (1,9) while at the same time specific organs such as the heart are depleted of catecholamines (10). In addition, patients and experimental animals with heart failure are significantly hyporesponsive to administration of exogenous catecholamines (11-13). This apparent paradox may have important implications in determining the mechanism (s) of the alterations in cardiovascular reflex function in heart failure.

The reflex control of cardiovascular function relies on the input from a variety of sensory endings which are distributed throughout the cardiovascular system. As with most sensory endings, discharge characteristics depend upon the environment that surrounds the receptor. It has long been appreciated that arterial baroreceptors reset as a function of the ambient arterial pressure. Arterial baroreflex control of heart rate is markedly attenuated in patients and experimental animals with heart failure (6, 7). Cardiac receptor control of the circulation is similarly altered in heart failure (2, 14, 15). Undoubtedly much of the abnormal reflex control in heart failure is due to alterations in autonomic function in both the heart (6) and in the peripheral circulation (16). However, abnormalities in the sensory endings themselves cannot be ruled out as a contributory factor in the abnormal cardiovascular reflexes that have been observed in heart failure.

In the discussion that follows I will review the data that exists, albeit sparse, which strongly suggests that abnormalities in afferent mechanisms are responsible, in part, for some of the attenuation of cardiovascular reflexes seen in heart failure.

Cardiac Receptors

The discharge characteristics and reflex effects of stimulation of atrial receptors with medullated fibers have been extensively studied since the early work of Bainbridge (17). The experiments of Henry, Gauer and Reeves (18) initiated three decades of extensive investigation into the neural control of blood volume and the role of atrial receptors in its regulation. Although the influence of atrial receptors on mechanisms which control fluid balance in humans is currently under some doubt (19) it has been demonstrated that these receptors exert a profound influence on urine flow, vasopression secretion, heart rate and peripheral sympathetic nerve activity in the dog and in other species. Since patients with heart failure generally have chronically distended atria as well as ventricles it was of interest to determine if alterations in atrial receptor discharge could be observed after chronic elevations of left atrial pressure.

In a study by Greenberg et al. (14) it was shown that dogs with pulmonary artery stenosis and tricuspid avulsion had a reduced left atrial receptor discharge sensitivity compared to normal dogs. In a model of canine high output heart failure we subsequently showed similar results (15). Figure 1 shows the left atrial pressure-discharge curves for dogs with a chronic aorto-caval fistula (AVF) compared to a group of sham operated dogs. As can be seen the AVF dogs exhibited a lower discharge rate compared to sham dogs at most changes in left atrial pressure. The maximum slope in the dogs with chronic AVF 's was lower than the sham operated dogs. It is important to realize that the dogs with this model of congestive heart failure showed hemodynamic evidence of chronic congestive heart failure even though cardiac output was elevated. That is, they had left ventricular end diastolic pressures in the range of 25-30 mm Hg and heart rates in excess of 140 bpm. Heart weight/body weight ratios were significantly elevated in the dogs with volume overload. In addition, clinical signs of

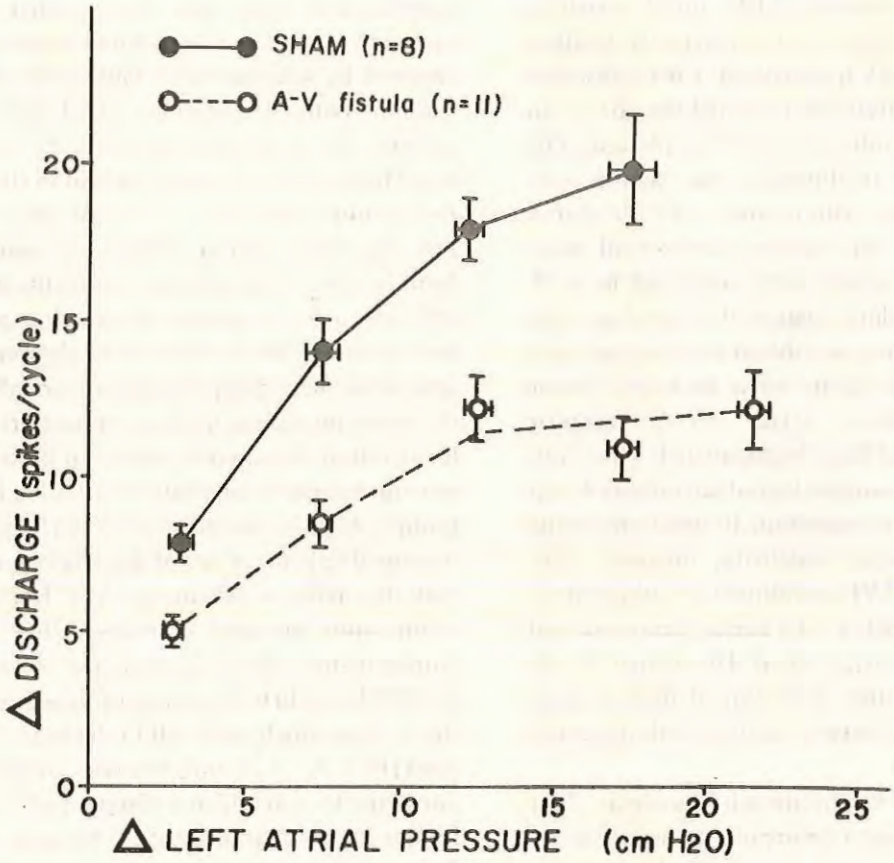

Figure 1. A plot of the change of left atrial receptor discharge versus the change in left atrial pressure (taken at the peak of the v wave) for sham operated dogs (closed circles) and for dogs with chronic AV fistulas (open circles). Vertical and horizontal bars are ± 1 SEM. The data was accumulated on 16 receptors from 11 AV fistula dogs and from 14 receptors from 8 sham dogs.

pulmonary and peripheral congestion were seen in all dogs. In these respects, this model is similar to that which is seen in low output failure.

The mechanism (s) responsible for the alteration in left atrial receptor discharge in heart failure is not completely understood, however there are several aspects of this abnormality which are clear. In an attempt to determine if chronic cardiac distension caused any morphological changes in left atrial receptor endings we examined these endings histologically (15). Interestingly, we found that in all of the dogs with chronic heart failure, the endings were either absent or grossly altered. In the sham dogs all endings that were examined were normal in appearance with clear myelinated fibers and unencapsulated endings. This finding had not been described before, however there have been observations made on arterial baroreceptor morphology in animals with long standing hypertension in which the endings appeared anatomically abnormal (20).

Another possible mechanism that was considered was a reduction in atrial compliance. If these dogs with chronically distended atria exhibit a reduction in atrial diastolic compliance then one would expect a decrease in atrial receptor discharge sensitivity simply because of

an increased stiffness. In a small number of animals we measured left atrial diastolic compliance using sonomicrometer techniques (2 sham and 2 AV fistula dogs). The relationship between left atrial diameter and the change in left atrial diastolic pressure was plotted. The slope of this relationship was significantly steeper for dogs with chronic AVF compared to sham dogs. In addition, the control atrial diameter was significantly increased in AVF dogs. This finding suggests that the dogs with chronic AVF have a reduced atrial compliance and are most likely at the top of the length-tension curve. Therefore, atrial stretch receptor discharge would likely be attenuated. This is not to say that the morphological alterations which were seen do not contribute in some way to the loss of discharge sensitivity, however after closing of the AVF and allowing a subgroup of dogs to recover for 8-10 weeks, heart size and discharge sensitivity returned to normal. It was found that in this subgroup of dogs a large number of the receptor endings still appeared abnormal (21).

In dogs with chronic mitral stenosis, Zehr et al. (22) showed a failure of vasopressin levels to rise in response to a non-hypotensive hemorrhage. Histological examination of the left atrium in these dogs indicated hypertrophy and fibrosis, thus making the atrium stiffer. Taken together, the data presented above indicate that the most likely explanation for the reduction in atrial receptor discharge sensitivity in heart failure is a reduction in atrial compliance.

Investigations into the reflex effects of left atrial receptor stimulation in heart failure have been conducted. These studies show a substantial attenuation if not a complete loss of atrial receptor mediated reflexes. Since atrial receptors have been implicated in the control of fluid balance, we hypothesized that the failure of patients or animals with heart failure to exhibit a diuresis in the face of markedly elevated left atrial pressure was due, in part, to the attenuation of left atrial reflex mechanisms (2). Left atrial pressure was elevated in anesthetized dogs that were either sham operated or were in heart failure. Pressure was elevated by inflation of a balloon in the left atrium. Balloon inflation raised left atrial pressure in the sham dogs from 11.7 $\pm$ 1.2 mm Hg to 23.5 $\pm$ 1.9 mm Hg and in the heart failure dogs from 17.5 $\pm$ 2.6 to 28.2 $\pm$ 3.0 mm Hg. There were no significant changes in heart rate or arterial pressure during the balloon inflation in either group. Although a prompt diuresis and increase in free water clearance was seen in the sham group during balloon inflation, there was no change in these parameters in the heart failure dogs. GFR and renal blood flow were unchanged during balloon inflation in both groups. Arginine vasopressin (AVP) levels were measured in both groups of dogs before, during and after balloon distension. AVP levels were significantly elevated in heart failure dogs. During balloon distension there was a reduction in AVP levels in both groups of dogs however, the level to which AVP fell in the heart failure dogs (10.2 $\pm$ 3.3 μU/ml) was still considerably above the level at which a diuresis and increase in free water clearance would be seen. These data are consistent with those of others who have seen elevated plasma vasopressin levels in patients and in animals with heart failure (3,22,23). Although these data are not conclusive they strongly suggest that abnormal atrial receptor mechanisms may contribute to the elevated plasma AVP in patients with heart failure and exacerbates and contributes to the elevation in extracellular fluid volume that occurs in these patients.

Atrial receptor modulation of renal sympathetic nerve activity (RSNA) has been demonstrated in dogs and non-human primates (24,25). Since changes in RSNA can potentially influence such renal parameters as renal blood flow, renin release and sodium reabsorption we investigated the extent to which this modulation was altered in dogs with heart failure (26). In normal dogs, left atrial balloon distension significantly reduced RSNA. In dogs with chronic AVF increases in left atrial pressure

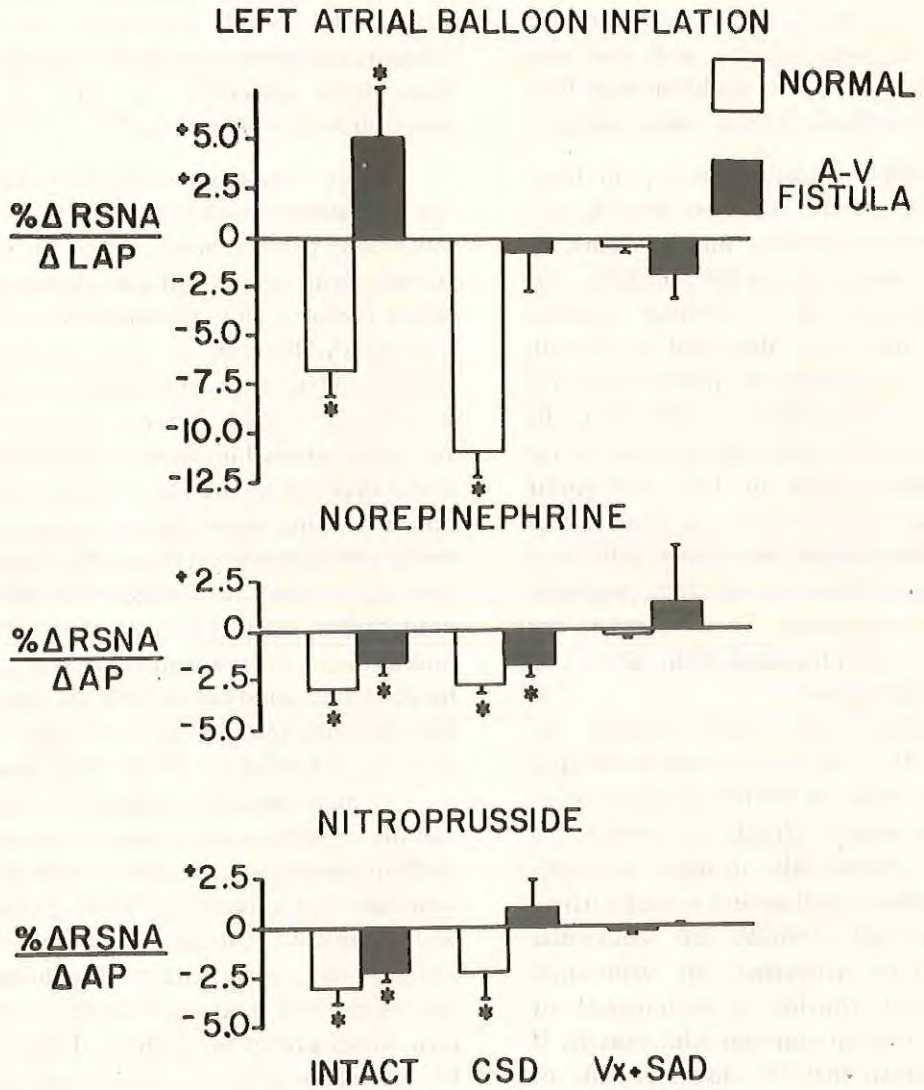

Figure 2. The mean data on renal sympathetic nerve activity changes derived from normal and AV fistula dogs in response to left atrial balloon inflation (top), norepinephrine injection (middle) and nitroprusside infusion (bottom). Open bars depict data from normal dogs. Closed bars show data from AV fistula dogs. * = significantly different from zero.

caused an increase in RSNA. This increase was due to a concomitant fall in arterial pressure and an unloading of the arterial baroreceptors.

As can be seen in Figure 2 the increase in RSNA per mm Hg change in left atrial pressure in dogs with AVF was completely abolished after carotid sinus denervation but was actually potentiated in the normal dogs. Vagotomy plus sinoaortic denervation abolished all reflex activity. The administration of norepinephrine and nitroprusside to elicit the arterial baroreflex showed that the dogs with chronic volume overload had a normal baroreflex control of renal nerve activity at the time that these studies were carried out. These data are consistent with the altered discharge characteristics of atrial receptors seen in heart failure and with the depressed diuretic reflex. In summary, atrial

receptor mediated reflex control of the circulation is likely to be substantially attenuated in heart failure and this may contribute to some of the problems with fluid balance that patients in heart failure exhibit.

Ventricular receptor function in heart failure has not been extensively investigated. Both chemically sensitive and mechanically sensitive receptors exist in the ventricles. The reflex effects of left ventricular receptor stimulation have been described in normal, conscious and anesthetized animals since the original work of von Bezold and Hirt (27). The so-called Bezold-Jarisch reflex is elicited by the chemical stimulation of left ventricular receptors with one of the veratrum alkaloids and results in hypotension and bradycardia as a result of vagal efferent activation and peripheral sympathetic withdrawal. These receptors can also be activated by mechanical stimuli such as ventricular distension.

In patients with aortic stenosis, leg exercise has been shown to result in forearm vasodilation while in normal patients or in patients with mitral stenosis vasoconstriction results (28). Presumably, increases in stroke volume which occurred against a fixed outflow resistance caused extensive left ventricular distension thus activating left ventricular receptors and causing a withdrawal of sympathetic tone to non-exercising muscle. It has been shown that the discharge rate of ventricular receptors will increase and evoke a bradycardia when severely unloaded as occurs during severe hemorrhage (29). A similar response was noted by LeWinter et al. (30) in conscious dogs with chronic AVF.

In this study, a progressive hemorrhage was performed while heart rate and blood pressure were continuously monitored. Before the AV fistula was produced, a tachycardia was observed in response to the decrease in blood volume. However, several weeks after the fistula, hemorrhage resulted in little change in heart rate (albeit from a higher resting level) until approximately 800 ml had been withdrawn at which time a bradycardia was seen. This bradycardia could be completely abolished by atropine but not by propranolol. Similar results have been observed in our laboratory (unpublished observations).

Figure 3 shows recordings from a dog that was instrumented with balloon occluders on the descending thoracic aorta and on the thoracic inferior vena cava in order to change arterial blood pressure. Note that in the top series of tracings the lowering of arterial pressure by inflation of the vena caval occluder resulted in a stimulus related increase in heart rate. Increasing arterial pressure by inflation of the aortic occluder resulted in a bradycardia. The bottom tracing shows similar occlusions two weeks after construction of an AVF. Notice that now every vena caval occlusion resulted in a bradycardia. As will be discussed below the arterial baroreflex is attenuated in heart failure, however this could not explain the reversal of the heart rate response seen in Figure 3 or in the study of LeWinter et al. described above (30).

A more plausible explanation might be that the sensitivity and/or activity of ventricular mechanoreceptors is altered in states in which heart size is chronically increased. In the dogs with chronic AVF, unloading of the ventricles by hemorrhage or by vena caval occlusion may have stimulated ventricular afferents which in turn caused a reflex bradycardia. This is similar to the observation of Oberg and Thoren following severe hemorrhage in the cat (29). The mechanism by which ventricular receptors inhibit the baroreflex and reverse the heart rate response is not completely understood, however it seems clear from the reflex and electrophysiological studies that, in heart failure, the ability of these receptors to increase their discharge is enhanced. A central mechanism is most likely responsible for suppressing the normal baroreflex (31,32).

Arterial Baroreceptors

Several studies have confirmed that the arterial baroreflex is depressed in humans and in animals with heart failure, at least as far as

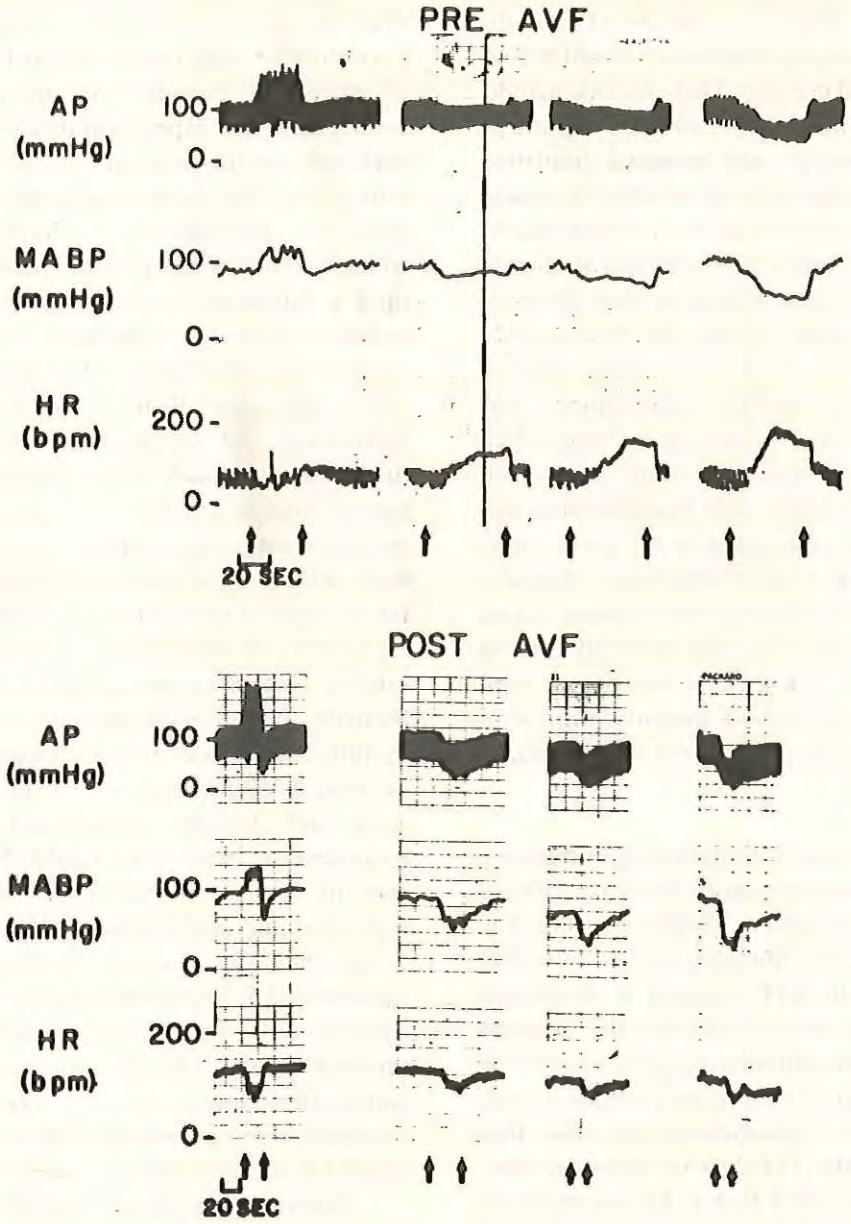

Figure 3. The heart rate response of a conscious dog to changes in arterial pressure (using vena caval and aortic hydraulic occluders) before (Pre-AVF) and 2 weeks following (Post-AVF) the construction of an infrarenal aorto-caval fistula. Note that in the post-AVF state a bradycardia is evoked in response to hypotension as well as to hypertension.

the control of heart rate is concerned (6-8). Most of the data suggests that a major mechanism which is involved in this attenuation of the baroreflex is a failure of the efferent vagus to modulate heart rate during increases in arterial pressure and to some degree poor sympathetic control of heart rate. Although efferent autonomic control of heart rate is certainly abnormal in heart failure, the possibility that afferent mechanisms may also contribute to the poor baroreflex sensitivity in heart failure has largely been ignored. One could predict that

because of several factors which take place in heart failure, there is a likelihood that the arterial baroreceptors themselves would behave in an abnormal manner. These factors include, expanded plasma volume, altered sympathetic tone, hyponatremia, and increased circulation of vasoactive substances, all of which have been shown to be operative in heart failure states.

We therefore undertook two studies to determine if we could uncover any effects of high output heart failure on baroreceptor afferent activity. In the first study afferent discharge from aortic baroreceptors was recorded in open chest anesthetized dogs which were either sham operated or had chronic AVF (33). Aortic diameter was also measured and wall strain was calculated at the point where aortic pressure was measured. Systolic baroreceptor discharge-systolic pressure curves were generated using appropriately placed vascular occluders. The curves were characterized by determining threshold pressure, saturation pressure, midpoint pressure and the normalized maximum gain.

The data from heart failure dogs indicated a reduced baroreceptor sensitivity and a resetting of the operating point to a higher pressure. The mechanism of this finding is unclear however, the dogs with AVF showed a significant elevation in the aortic diameter at the midpoint pressure and the saturation pressure whereas the mid-wall strain at these points was increased. The only aortic hemodynamic parameter that was altered in the AVF dogs was pulse pressure, being 45.7 $\pm$ 2.4 and 24.4 $\pm$ 2.0 mm Hg in the AVF and normal dogs, respectively ($p<0.001$). Systolic arterial pressure was elevated in the AVF dogs (136.6 $\pm$ 8.7 mm Hg) compared to the normal dogs (118.0 $\pm$ 5.5 mm Hg) but this difference failed to reach statistical significance. These data suggest that in this model of heart failure there is a decrease in baroreceptor discharge sensitivity which is unrelated to wall strain but which may by conditioned by the increased aortic pulse pressure seen in dog with AVF.

Since the experiment described above was done in a preparation in which it was difficult to control the input parameters such as the rate of change of pressure, etc. we decided to conduct a similar experiment using the isolated perfused carotid sinus in normal and heart failure dogs (34). In this study, the left carotid sinus was perfused with a Krebs-Henseleit solution at a constant pressure of 100 mm Hg until a baroreceptor discharge-carotid sinus pressure curve was generated. Piezoelectric crystals were placed across the carotid sinus so that an estimate of diameter could be recorded. Recording of single unit baroreceptor discharge were made from filaments of the carotid sinus nerve. Two types of curves were generated using this technique. Firstly, carotid sinus pressure was increased in discrete steps from a carotid sinus pressure of about 50 mm Hg to over 300 mm Hg. Steady-state discharge rate was plotted against carotid sinus pressure. Secondly, carotid sinus pressure was increased by ramps at rates of pressure change ranging between 2-200 mm Hg/sec. In this way both static and dynamic characteristics of the baroreceptor could be evaluated. Each curve was fit with a second order polynomial regression and characterized by determining : 1. the threshold pressure, 2. the saturation pressure and 3. the maximum gain. Dogs with chronic AVF had increased baroreceptor threshold pressures for the step pressure curve and the three lowest ramp rates, the saturation pressures were significantly higher in the AVF group for the step and the lowest ramp rate.

Figure 4 shows the data for the maximum baroreceptor gain in normal and AVF dogs. Note that a significantly lower gain was observed for the steps and for the lowest ramp rate (4.7 $\pm$ 0.22 mm Hg/sec) in the AVF group compared to the normal group. This decrease in static gain could not be attributed to differences in compliance of the carotid sinus or to differences in sodium, potassium or water content (using the contralateral, blood perfused sinus) of the carotid sinuses of the two groups of dogs. The results from the above two studies

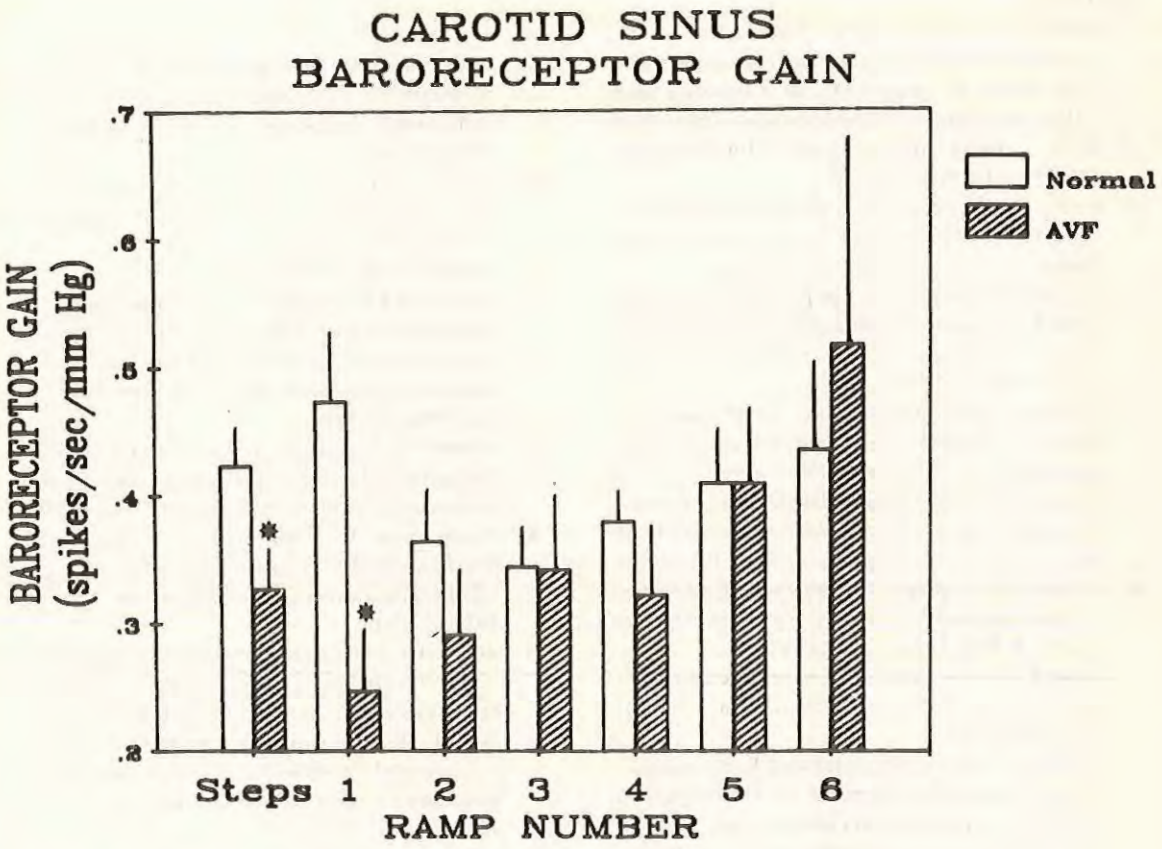

Figure 4. A comparison of the mean carotid sinus baroreceptor gain for normal and AV fistula dogs for step increases in carotid sinus pressure (Steps) and at progressively increasing carotid sinus pressure ramps. * = significantly different from the normal group.

suggest that the arterial baroreceptors become less sensitive in this model of heart failure. The mechanism for this abnormality remains to be elucidated however some possibilities may include alterations in sympathetic tone to the carotid sinus (35) or to changes in ionic flux across the receptor membrane. These possibilities need to be investigated. It is concluded from these data that part of the depressed baroreflex sensitivity that is seen in patients and animals with heart failure may be due to a depression at the afferent arm of the baroreflex. This could contribute to changes in systemic sympathetic tone which in turn may alter peripheral vascular resistance and organ function.

Finally, it is possible that some of the therapeutic benefits of the cardiac glycosides are related to their neuroexcitatory and neurosensitizing effects (36,37). Therapeutic doses of glycosides administered to experimental animals have clearly been shown to increase the discharge sensitivity of atrial (37), arterial (36), and ventricular receptors (38). In addition, cardiovascular reflexes have been shown to be potentiated in the presence of a variety of different glycosides (39,40). More extensive work in this area of heart failure therapy is needed to elucidate the mechanism (s) involved.

References

1. Rutenberg HL, Spann JF Jr. Alterations of cardiac sympathetic neurotransmitter activity in congestive heart failure. In : Mason DT, ed. Congestive heart failure : mechanisms, evaluation and treatment. New York : Yorke Medical Books. Dun-Donnelley Publishing Corp, 1976;85-95.
2. Zucker IH, Share L, Gilmore JP. Renal effects of left atrial distension in dogs with chronic congestive heart failure. Am J Physiol 1979;236:H554-60.
3. Goldsmith SR, Francis GS, Cowley AW Jr, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. J Am Coll Cardiol 1983;1:1385-90.
4. Watkins L, Burton JA, Haber E, Cant JR, Smith FW, Barger AC. Renin in the pathogenesis of congestive heart failure. J Clin Invest 1976;57:1606-17.
5. Newman WH, Frankis MB, Halashka PV. Increased myocardial release of prostacyclin in dogs with heart failure. J Cardiovasc Pharmacol 1983;5:194-201.
6. Eckberg DL. Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 1971;285:877-83.
7. White CW. Abnormalities in baroreflex control of heart rates in canine heart failure. Am J Physiol 1981;240:H793-9.
8. Vatner SF, Higgins CB, Braunwald E. Sympathetic and parasympathetic components of reflex tachycardia induced by hypotension in conscious dogs with and without heart failure. Cardiovasc Res 1974;8:153-61.
9. Chidsey CA. Harrison DC, Braunwald E. Augmentation of plasma norepinephrine response to exercise in patients with congestive heart failure. N Engl J Med 1962;267:650-4.
10. Pool PE, Covell JW, Levitt M, Gibb J, Braunwald E. Reduction of cardiac tyrosine hydroxylase activity in experimental heart failure : its role in depletion of cardiac norepinephrine stores. Circ Res 1967;20:249-353.
11. Newman WH. A depressed response of left ventricular contractile force to isoproterenol and norepinephrine in dogs with congestive heart failure. Am Heart J 1977;93:216-21.
12. Zucker IH, Waltke E, Gilmore JP. Cardiac responses to beta-adrenergic stimulation on anesthetized dogs with chronic congestive heart failure. Basic Res Cardiol 1980;75:697-711.
13. Goldstein RE, Beiser GD, Stampfer M, Epstein SE. Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction. Circ Res 1975;36:571-8.
14. Greenberg TT, Richmond WH, Stocking RA, Gupta PD, Meehan JP, Henry JP. Impaired atrial receptor responses in dogs with heart failure due to tricuspid insufficiency and pulmonary artery stenosis. Circ Res 1973;32:424-33.
15. Zucker IH, Earle AM, Gilmore JP. The mechanism of adaptation of left atrial stretch receptors in dogs with chronic congestive heart failure. J Clin Invest 1977;60:323-31.
16. Zelis R, Nellis SH, Longhurst J, Lee G, Mason DT. Abnormalities in the regional circulations accompanying congestive heart failure. Prog Cardiovasc Dis 1975;18:181-99.
17. Bainbridge FA. The influence of venous filling upon the rate of the heart. J Physiol (Lond) 1915;50:65-84.
18. Henry JP. Gauer OH, Reeves JS. Evidence of the atrial location of receptors in influencing urine flow. Circ Res 1956;4:85-90.
19. Gilmore JP. Neural control of extracellular volume in the human and nonhuman primate. In : Handbook of physiology-the cardiovascular system III. 1983;885-915.
20. Angell-James JE. Characteristics of single aortic and right subclavian baroreceptor fiber activity in rabbits with chronic renal hypertension. Circ Res 1973;32:149-61.
21. Zucker IH, Earle AM, Gilmore JP. Changes in the sensitivity of left atrial receptors following reversal of heart failure. Am J Physiol 1979;237:H555-9.
22. Zehr JE, Howe A, Tsakiris AG, Rastelli GC, McGoon DC, Segar WE. ADH levels following nonhypotensive hemorrhage in dogs with chronic mitral stenosis. Am J Physiol 1971;221:312-37.
23. Goldsmith SR, Dodge D. Response of plasma vasopressin to ethanol in congestive heart failure. Am J Cardiol 1985;55:1354-7.
24. Karim F, Kidd C, Malpus CM, Penna PE. The effects of stimulation of the left atrial receptors on sympathetic efferent nerve activity. J Physiol (Lond) 1972;227:243-60.
25. Echtenkamp SF, Zucker IH, Gilmore JP. Characterization of high and low pressure baroreceptor influences on renal nerve activity in the primate *Macaca fascicularis*. Circ Res 1980;46:726-30.
26. Zucker IH, Gorman AJ, Cornish KG, Lang M. Impaired atrial receptor modulation of renal nerve activity in dogs with chronic volume overload. Cardiovasc Res 1985;19:411-8.
27. Bezold A von, Hirt L. Uber die physiologischen wirkungen des essigauren Veratrins. Unters Physiol Lab Wurzburg 1867;1:75-156.
28. Mark AL, Kioschos JM, Abboud FM, Heistad DD, Schmid P. Abnormal vascular responses to exercise in patients with aortic stenosis. J Clin Invest 1973;52:1138-46.
29. Oberg B, Thoren P. Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat. A possible cause of vasovagal reaction. Acta Physiol Scand 1972;85:164-73.

30. LeWinter MM, Karliner JS, Covell JW. Alteration in heart rate response to hemorrhage in coscious dogs with volume overload. Am J Physiol 1978;235:H422-8.
31. Holmberg MJ, Gorman AJ, Cornish KG, Zucker IH. Attenuation of arterial baroreflex control of heart rate by ventricular receptor stimulation in the conscious dog. Circ Res 1983;52:597-607.
32. Holmberg MJ, Gorman AJ, Cornish KG, Zucker IH. Intracoronary epinephrine attenuates baroreflex control of heart rate in the conscious dog. Am J Physiol 1984;247:R237-45.
33. Zucker IH, Niebauer MJ, Holmberg MJ. Aortic baroreceptor characteristics in dogs with chronic volume overload. Basic Res Cardiol (in press).
34. Niebauer MJ, Zucker IH, Static and dynamic responses of carotid sinus baroreceptors in dogs with chronic volume overload. J Physiol (Lond) 1985;369:295-310.
35. Tomomatsu E, Nishi K. Increased activity of carotid sinus baroreceptors by sympathetic stimulation and norepinephrine. Am J Physiol 1981;240:H650-8.
36. Gillis RA, Quest JA. The role of the nervous system in the cardiovascular effects of digitalis. Pharmacol Rev 1980;31:19-97.
37. Zucker IH, Peterson TV, Gilmore JP. Ouabain increases left atrial stretch receptor discharge in the dog. J Pharmacol Exp Ther 1980;212:320-4.
38. Thames MD, Waickman L, Abboud F. Sensitization of cardiac receptor (vagal afferents) by intracoronary acetylstrophanthidin. Am J Physiol 1980;239:H628-35.
39. Sleight P, Lall A, Muers M. Reflex cardiovascular effects of epicardial stimulation by acetylstrophanthidin in dogs. Circ Res 1969;25:705-11.
40. Thames MD, Miller BD, Abboud FM. Sensitization of vagal cardiopulmonary baroreflex by chronic digoxin. Am J Physiol 1982;243:H815-8.