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THE EFFECTS OF EXPERIMENTAL HEART FAILURE ON ARTERIAL BAROREFLEX CONTROL OF THE CIRCULATION IN CONSCIOUS DOGS

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THE EFFECTS OF EXPERIMENTAL HEART FAILURE ON ARTERIAL BAROREFLEX CONTROL OF THE CIRCULATION IN CONSCIOUS DOGS

By

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ABSTRACT

THE EFFECTS OF HEART FAILURE ON ARTERIAL BAROREFLEX CONTROL OF THE CIRCULATION IN CONSCIOUS DOGS

By

Nicholas Bari Olivier

Aortic denervated dogs were prepared for reversible carotid sinus isolation and the induction of heart failure by rapid ventricular pacing to determine if heart failure impairs baroreflex control of blood pressure in conscious subjects. Complete open-loop stimulus-response relationships were determined in quietly resting, conscious dogs before (Phase I), during (Phase II) and after the resolution (Phase III) of heart failure. Reflex range and gain were determined for baroreflex control of mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), and total peripheral resistance (TPR). Ventricular pacing at rates of 255 bpm for 21 days resulted in bi-ventricular, low-output congestive heart failure characterized by a 45% reduction in resting cardiac output (3.51 ± .6 to 1.91 ± .6 L/min), an increase in right atrial pressure from 1 ± 2 to 12 ± 3 mmHg, and an increase in left atrial pressure from 3 ± 2 to 21 ± 21 mmHg. A dramatic impairment in carotid sinus baroreflex control of both MAP and HR was associated with the development of heart failure. The range of reflex control of MAP was reduced by 52% while the average reflex gain decreased by 59 percent. These changes in

baroreflex control of MAP were due entirely to a similar impairment in the range (75%) and average gain (66%) for reflex control of cardiac output since reflex control of TPR was unaffected by heart failure. This selective impairment in CO responses while TPR control remained intact is suggestive of an efferent neuro-effector site for the overall reflex impairment. Pacing was then discontinued and recovery from heart failure was evident as early as day 7 of Phase III. During this recovery, reflex control of blood pressure was largely restored. Near complete recovery in the range (76% recovery) and average gain (75% recovery) were evident during this first week. These data suggest a rapidly adapting mechanism for the impairments in the carotid baroreflex caused by pacing-induced experimental heart failure.

The efforts and any benefits associated with the information summarized within are dedicated to my wife, and closest friend ...

Amanda Marie Jumonville

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INTRODUCTION

Homeostatic Cardiovascular Reflexes are Impaired in Congestive Heart Failure

Reflex adjustments in cardiac output and vascular resistance are necessary to maintain a stable blood pressure during periods of hemodynamic stress. Postural changes, such as assuming a standing position, elicit venous pooling of blood and a reduction in venous return. The resulting drop in cardiac filling pressure, cardiac output and arterial blood pressure are normally sensed by baroreceptors located in the heart and lungs (cardiopulmonary receptors) and the aortic arch and carotid artery bifurcation (arterial receptors). A change in the activity of these stretch receptors during orthostasis initiates neuro-endocrine excitation including an increase in circulating plasma concentrations of norepinephrine, renin, angiotensin, and vasopressin (Campese, 1980). The result is a compensatory increase in heart rate and vascular smooth muscle contraction which collectively prevent a postural drop in systemic blood pressure.

Subjects with advanced heart failure, however, do not respond normally to orthostatic stress. Several studies have shown that plasma levels of norepinephrine, renin activity, and vasopressin do not rise during passive head-up tilt in symptomatic heart failure patients. (Cody, 1921; Levine, 1983; Goldsmith, 1983) Wood and Zelis and others have shown though, that venous compliance is reduced in heart failure

such that postural venous pooling may not be as profound. (Wood, 1956; Zelis, 1974) The question then arises whether passive tilt represents an adequate baroreceptor stimulus under these circumstances. More recent studies by Kassis (1987), and Ferguson (1984), substantiated the adequacy of baroreceptor unloading by documenting a significant fall in both cardiac filling pressure and systemic arterial pressure during either head-up tilt or lower body negative pressure. Mohanty et al. (1989) measured ventricular dimensions during lower body negative pressure in patients with heart failure and also confirmed that such a stimulus invokes a significant reduction in end-diastolic ventricular diameter and left atrial diameter. Thus, even in the face of decreased venous compliance, these provocative maneuvers are capable of unloading baroreceptors. Nevertheless, the patients with heart failure in these studies did not experience the normal increase in heart rate, forearm vascular resistance or plasma catecholamines expected from the reduction in baroreceptor load. Nonspecific impairments in vascular responsiveness to adrenergic stimuli were ruled out by the demonstration of a normal pressor response to cold water hand immersion.

These findings clearly demonstrate that heart failure is associated with significant alterations in cardiovascular reflex mechanisms. Despite general agreement for this conclusion, uncertainty remained regarding which baroreceptor field, cardiopulmonary or arterial, is specifically impaired by heart failure. Since postural changes tend to unload both baroreceptor fields simultaneously, it is difficult to ascribe observed impairments to one reflex or the other. Rowell (1986) pointed out that the fall in cardiac filling pressure following passive tilt or lower body negative pressure usually occurs before the drop in arterial blood pressure. Most of the reflex changes in forearm vascular resistance also occur before the fall in arterial pressure while heart rate changes tend to follow the hypotension. As a result, it has been suggested that the forearm responses reflect the cardiopulmonary reflex while the heart rate response is

dependent on the arterial baroreceptors. This distinction however, is probably incomplete, making it difficult to differentiate the two reflex responses when both are activated and potentially interacting.

Potential Mechanisms for Impairment in the Arterial Baroreflex

Advanced congestive heart failure is typically accompanied by several neuro-endocrine changes as well as varying morphologic changes in several components of the baroreflex arc. For example, adrenergic tone is increased, parasympathetic stimulation is reduced and resting plasma levels of renin, angiotensin, atrial natriuretic peptides, and vasopressin are increased in naturally occurring and experimental models of heart failure. (Francis, 1988) Many of these changes have been studied in relative isolation, each being capable of modifying overall baroreflex characteristics. As a result, each could be important as a possible cause for alterations in baroreflex properties in heart failure.

For clarity, the effects of these neuro-endocrine and morphologic changes will be considered separately and categorized according to the location of their effect as afferent, central or efferent modifiers. It should be remembered however, that many of these effectors can influence baroreflex properties at multiple sites and also that many potentially interactive effectors can exist concurrently in patients with heart failure.

Afferent Mechanisms -- The assertion that baroreflex properties are altered by the existence of heart failure has led to an almost universal assumption that the major site of impairment was the arterial baroreceptors themselves. Surprisingly, very little experimental evidence exists to support this reasonable, but unproven assumption. In addition, most of the available evidence is only indirect, supporting the possibility that receptor function is altered secondary to the neural, endocrine, and morphologic changes that accompany heart failure. For example, Zelis (1971) reported that arterial

wall sodium content is increased in dogs with pacing-induced heart failure. He speculated that high sodium and water content reduces the compliance of arteries. If so, then the pressure-volume relationship of the carotid sinuses might be altered in a fashion compatible with a reduction in their sensitivity. Bagshaw (1972) reported contrasting results when he perfused the isolated carotid sinuses of anesthetized dogs with norepinephrine. He discovered that norepinephrine also reduces the compliance of the vessel but can actually enhance the sensitivity of baroreceptors. A similar finding was observed if postganglionic cervical sympathetic nerves were stimulated at relatively high frequencies of 10-20 Hertz. (Peveler, 1980) This somewhat unexpected finding was tentatively explained by a series relationship between the adventitial receptors and the smooth muscle contractile elements. Despite the agreement of these findings, the effects of adrenergic stimulation (endocrine or neural) on receptor function, appears to be complex; with either enhancement (Tomomatsu, 1981; Sampson, 1970) or depression (Bolter, 1980; Keith, 1974)) of receptor activity and sensitivity noted in different studies. Munch (1987) has attempted to explain these differences by suggesting a bimodal, "dose-dependent" effect. Mild adrenergic stimulation appears to increase the resting activity of the receptors but reduces their strain sensitivity. This "low-dose" effect is thought to reflect significant changes in the vessel wall properties of the carotid sinuses since it is mimicked by other vasoconstrictors and can be abolished by alpha blockade. Greater degrees of adrenergic stimulation apparently enhance baroreceptor sensitivity through a direct action on the receptor endings themselves.

Baroreceptor sensitization could also potentially occur as a result of increased plasma levels of vasopressin. Schmid (1985) studied anesthetized, vagotomized and aortic denervated rabbits in which the carotid sinus regions had been surgically isolated. The isolated sinuses were then selectively pressurized with fluids containing either a vehicle or vasopressin. Baroreflex strength was determined by measuring the

degree to which baroreceptor loading reduced lumbar sympathetic nerve activity. Intrasinus vasopressin augmented the magnitude of baroreflex restraint on sympathetic nerve activity. Since exposure to vasopressin was limited to the carotid sinus region, he concluded that vasopressin has a sensitizing effect on the carotid baroreceptors themselves. No such sensitization was observed when the carotid sinuses were perfused with angiotensin II.

Each of these studies presents evidence that baroreceptor function could be altered in heart failure. Only one brief report by Zucker (1983) describes the changes in arterial baroreceptor sensitivity actually associated with cardiac disease. He reported that high-output heart failure caused by an aorto-caval fistula reduced the sensitivity of the pressoreceptors in the aortic arch by approximately 50 percent. Fragmentation and degeneration of the receptor endings reported for other forms of cardiovascular disease (Abraham, 1967) may be responsible for such findings.

Central Mechanisms -- Alterations in baroreflex properties could also conceivably arise secondary to changes in the central processing of baroreceptor afferent information and/or the coordination of the efferent neural responses. Again, the available evidence can only support a potential role for neuro-endocrine factors in mediating such a central effect during heart failure. In a companion experiment to the one noted above, Schmid isolated the carotid sinuses in anesthetized rabbits but administered vasopressin systemically. Enhanced baroreflex restraint of sympathetic nerve activity was again observed and was abolished after complete sino-aortic denervation. (Guo, 1982) Schmid implicated a central mechanism since the arterial baroreceptors were isolated and therefore not exposed to the systemically administered vasopressin. This conclusion is also supported by the work of Undesser (1984), who demonstrated that destruction of the area postrema region of the brainstem prevents the enhancement of baroreflex control of sympathetic nerve activity by vasopressin.

Central enhancement of the baroreflex has also been reported following angiotensin II administration. Hull (1985) infused AII in the lateral cerebral ventricles of conscious dogs prepared for reversible carotid sinus isolation. The open-loop gain of arterial baroreflex control of blood pressure was enhanced during these central infusions. Whether CNS levels of angiotensin increase in parallel with plasma levels in heart failure remains uncertain. When AII was administered in the systemic veins, an upward resetting of the reflex was noted without a change in gain. Characterization of this response as either a peripheral action or a different central action due to different sites of central exposure could not be made from his data. (Hull, 1985) It should be noted, however, that the central effects of angiotensin II on baroreflex function may be species dependent since Schmid has reported that peripheral infusions of AII can actually slightly depress reflex control of sympathetic nerve activity. (1985) He attributed this to a central depressant effect since AII had no effect when confined to the carotid sinuses themselves (i.e. no effect on the receptors) although he provided no evidence to exclude some peripheral effect on efferent reflex components.

Cardiac ventricular receptor activity is likely to be increased, at least transiently, during heart failure as a result of diastolic chamber enlargement and increased sympathetic stimulation. (Thoren, 1977) The cardiac ventricular receptor reflex can have a profound depressant effect on arterial baroreflex function (Denison, 1985). Although the mechanism for this reflex interaction is not well understood, there is data implicating a central site based on evidence that both reflex receptor fields send afferent projections that converge in the nucleus tractus solitarius of the medulla. (Cottle, 1964; Lam, 1952) Sensitization of ventricular receptors and enhancement of their inhibitory effect on the arterial baroreflex may also be the means by which atrial natriuretic peptides depress the reflex tachycardic response to baroreceptor unloading. (Ebert, 1988)

Although much less potent, atrial cardiac receptors can also influence arterial baroreflex function. Experimental activation of atrial receptors augments carotid baroreflex control of heart rate. (Teo, 1985) Atrial receptor activity is naturally increased by stretch of the atrial wall and is thought to be increased during the early stages of heart failure. Interestingly, Greenberg (1973) has shown that chronic heart failure causes an adaptation or desensitization of these atrial receptors. This desensitization involves a reduction in their tonic resting activity as well as a decrease in their strain sensitivity. This chronic decrease in atrial receptor activity could potentially inhibit baroreflex function.

Efferent Mechanisms -- Abnormalities in efferent baroreflex mechanisms could involve altered efferent autonomic nerve activity or transmission, or abnormal end-organ responsiveness to this efferent activity. Most of the available studies investigating efferent mechanisms in heart failure have focused on changes in end-organ sensitivity. As might be expected, heart failure is associated with a depression in cardiac responsiveness to autonomic stimuli. White created right heart failure in dogs by inducing tricuspid insufficiency and pulmonic stenosis. Approximately 4 weeks later, after clinical signs and hemodynamic evidence of heart failure were evident, he cut the vagus nerve and stimulated the distal end at frequencies ranging from .1 to 3 Hz. (White, 1981a) Dogs in heart failure had less of a bradycardic response to vagal stimulation than control dogs. White then perfused the sinoatrial node artery with different concentrations of acetylcholine and recorded the resulting change in heart rate. Again, the bradycardic response was depressed by over 50% in affected dogs compared to normal controls. That this was a specific insensitivity to cholinergic stimuli was confirmed by demonstrating equivalent bradycardic responses to hypertonic saline infusions in both groups of dogs.

Covell et al. (1966) reported a similar cardiac desensitization to adrenergic nerve stimulation. Using the same model of heart failure in anesthetized dogs, they stimulated the right and left post-ganglionic sympathetic cardio-accelerator nerves and recorded the changes in heart rate and peak contractile force. Control animals received right atrial stimulations only, in order to control for any positive inotropic effects resulting from an increase in contraction frequency. Dogs with heart failure had a significantly blunted response to the sympathetic nerve stimulations (from 1 to 9 Hz) in terms of both contractile force and heart rate. A two minute intravenous infusion of norepinephrine elicited essentially equivalent increases in peak contractile force in the two groups suggesting that the source of the desensitization may have resided in nerve terminal release of norepinephrine. White's study (see above) also reported a normal tachycardic response to sinoatrial artery infusions of norepinephrine. This is a somewhat surprising finding considering the well described reduction in beta-adrenergic receptors in failing hearts. (Vatner, 1985; Bristow, 1982) Newman, however, did document such a depression in inotropic responses to both norepinephrine and isoproterenol infusions in dogs with experimental heart failure. (Newman, 1977 & 1978)

The effects of cardiac end-organ insensitivity on reflex function are obvious. Without a comparable increase in cardiac stimulation intensity, and/or compensation by the vascular component of the baroreflex, blood pressure control by the arterial baroreflex would be impaired.

The evidence regarding vascular responsiveness in heart failure is conflicting. Forster (1989) presented a study in which a dorsal pedal artery and saphenous vein were harvested before and after congestive heart failure was induced by rapid ventricular pacing. Vascular rings were studied in-vitro in the presence of propranolol, indomethacin, and desipramine (to antagonize beta receptors, prostanoid production and neuronal catecholamine re-uptake respectively). Dose response relationships for

force generation in response to norepinephrine and phenylephrine were determined. Vessels from heart failure dogs actually exhibited an increase in maximal tension and a reduction in EC_{50} suggesting an enhanced adrenergic sensitivity in the failure state. Different results have been reported when vascular sensitivity is assessed in-vivo. Wilson, for example, using the same model of heart failure, stimulated the lumbar sympathetic chain and recorded the changes in regional vascular resistance. (Wilson, 1988) A high spinal block was performed to eliminate potentially varying background sympathetic activity, and atropine was administered to abolish sympathetic cholinergic vasodilation. The absolute increase in vascular resistance to nerve stimulation was not different between heart failure and normal dogs. However, since resting resistance was greater in heart failure, the fact that the change in resistance was not greater for failure dogs is suggestive of a moderate insensitivity of the vasculature to nerve stimulations. Since the responses to regional intra-arterial infusions of norepinephrine were not different for the two groups, Wilson, like White, concluded that the apparent deficit was due to decreased neuronal release of norepinephrine. Admittedly, other potential considerations would include changes in ganglionic transmission or the concomitant neuronal release of a noncholinergic vasodilator substance. Kaiser (1989) also used pacing-induced heart failure to examine the in-vivo vascular responses to topically applied norepinephrine and nitroglycerin. No differences were noted for these agonists between control and heart failure dogs although the endothelial dependent vasodilator response to acetylcholine was significantly impaired for the latter.

Although studies on individual neural or hormonal factors suggest that congestive heart failure would be associated with altered arterial baroreflex characteristics, the net effect on the baroreflex from these multiple neural and hormonal changes during heart failure is difficult to predict.

Previous Studies Investigating Baroreflex Characteristics in Heart Failure

Only a few studies have attempted a specific examination of arterial baroreflex characteristics in subjects with heart failure. Each of these studies however, was potentially flawed by the technical limitations described below.

Studies Based on Heart Interval-Blood Pressure Relationships -- Most of the studies done in subjects with heart failure have employed modifications of a technique originally described by Smyth (1969) where systolic arterial pressure (SAP) and the R-R electrocardiographic interval (HI) are recorded during a transient change in blood pressure induced by injections of vasoactive substances. A linear regression is performed between the change in systolic pressure for each cardiac cycle and the change in the next heart interval. The slope of this regression has been used as an index of baroreflex sensitivity. However, interpretation of the resulting data is potentially misleading for several reasons. For example, the relationship between heart rate and heart interval is nonlinear. As a result, a decrease in heart interval slope could occur with no change or even a slight *increase* in the slope for heart rate control. This would be particularly evident when resting heart rates are different (higher); a condition typical for heart failure. Moreover, the applied stimulus to the baroreceptors is constantly changing with this technique so the analysis is sensitive mainly to fast acting responses. While parasympathetic inputs to the heart can change quickly, the sympathetic responses are considerably slower (Scher, 1970). Such a limitation might create a bias toward detection of parasympathetic responses, which is suggested by the consistent observation that slopes for hypertensive stimuli are greater than for hypotensive stimuli (White, 1981). This could produce misleading results, particularly since the relative importance of sympathetic and parasympathetic influences on heart

rate appear to change with heart failure. (Vatner, 1974) Despite these technical limitations, this form of reflex analysis is widely used, and provides fairly consistent results.

Higgins (1972) studied the HI-SAP relationship in conscious dogs before and after induction of low output heart failure using a tricuspid avulsion-pulmonic stenosis model. Bolus phenylephrine injections were used to manipulate arterial pressure and vary the stimulus to the arterial baroreceptors. The slopes for HI control were depressed by 80% during heart failure. White reported similar findings for dogs, with the additional finding that HI slopes were also depressed when blood pressure was decreased by glyceryl trinitrate. Similar findings have been reported for humans with naturally occurring heart failure. (Ellenbogen, 1989; Olivari, 1983)

Despite the consistency of these results, it remains difficult to conclude how baroreflex regulation of blood pressure is affected by heart failure since several recent studies have shown that reflex heart rate responses can be qualitatively different than the responses for the other components of the reflex (total peripheral resistance for example) and for the overall baroreflex regulation of blood pressure. (Hull, 1985; Cowley, 1984; Angell-James, 1980; and Guo, 1983)

Studies of Reflex Control of Blood Pressure -- Since the regulated variable of the arterial baroreflex is arterial pressure, an analysis of baroreflex characteristics should at least include some measure of this capacity. Only two studies have attempted to quantitate baroreflex control of blood pressure in experimental subjects with heart failure. Higgins, in 1972, observed that bilateral carotid occlusion produced less of an increase in blood pressure in dogs with right heart failure when compared to normal dogs. He concluded that baroreflex control of blood pressure is impaired by heart failure. However, data such as this does not provide enough information to evaluate the "strength" of the baroreflex, which is more rigorously quantified by the range and gain of the complete reflex stimulus-response relationship. The response to bilateral

carotid occlusion alone cannot reliably distinguish between a reflex that is simply reset and one with an altered range and/or gain. White, in 1981, provided additional evidence to support Higgen's conclusion in a study of anesthetized dogs with right heart failure. He reported that the range of blood pressures resulting from changes in isolated right carotid sinus pressure was reduced by heart failure. Unfortunately, this potentially important finding was confounded by the use of general anesthesia. Several studies have now shown that anesthesia can augment, impair, or reset baroreflex function (Ebert, 1985; Cox, 1979; Stephenson, 1980) The dramatic effects of anesthesia on reflex function are actually evident in White's study as the effect of vagotomy on baroreflex function. In White's study, vagotomy in normal dogs caused a negative ordinal shift and a decrease in the range of baroreflex control. This is directionally opposite to the observations for the identical experiment in conscious dogs. In the absence of anesthesia, vagotomy causes a shift up in the baroreflex curve with an increase in range. (Stephenson, 1980) If anesthesia can depress the response to vagotomy, might it similarly induce an artifactual depression in baroreflex responses in heart failure?

Formulation of the Experimental Questions

Although abnormal baroreflex control of heart rate appears to be a consistent finding in conscious subjects with heart failure, there is still no convincing evidence to answer the question of whether reflex regulation of blood pressure is impaired. The primary aim of this dissertation, therefore, is to answer this question. Does experimentally induced congestive heart failure impair baroreflex regulation of blood pressure and control of the circulation in conscious subjects? Baroreflex integrity will be determined by analyzing the range and gain of the open-loop baroreflex stimulus response

relations using the reversible carotid isolation model described by Stephenson. (1980) The hypothesis to be tested is that heart failure produces a significant impairment in both the range and gain of baroreflex control of heart rate and blood pressure.

As pointed out, many potential mechanisms could contribute to impairment of the baroreflex in heart failure. Detecting a dominant mechanism would be difficult in conscious animals because of the invasive nerve stimulation and recording experiments that would be required. An additional experimental aim is to provide a preliminary search for the major site(s) of reflex impairment. This search is based on the premise that abnormalities in the afferent and central components of the reflex would be expected to produce a generalized effect on the efferent reflex components (cardiac and vascular responses) whereas differential cardiac or vascular abnormalities would suggest an efferent site of impairment, perhaps at the end-organ level. I hypothesize that heart failure impairs reflex function through a selective cardiac efferent mechanism rather than the generalized pattern predicted from an afferent defect. This hypothesis will be tested by quantifying and comparing the range and gain of baroreflex control of both cardiac output and total peripheral resistance (TPR) in conscious dogs, before and during experimentally induced congestive heart failure.

Finally, I propose a third hypothesis, that CHF-induced impairments in the arterial baroreflex are quickly reversible (within 2 weeks) after resolution of the heart failure state. In addition to the clinical importance of determining the reversibility of reflex abnormalities, a study of the time course for the development and resolution of observed changes may provide important clues about the mechanism of these changes. Anatomic mechanisms, such as decreased vascular (baroreceptor) compliance, would be expected to develop and resolve more slowly than changes induced by neural or hormonal stimuli. Zelis, for example, has shown that the increased vascular stiffness seen in humans with heart failure persists for at least 18 days after heart failure is resolved by cardiac transplantation. (Sinoway, 1988) The

evidence to date regarding the reversibility of CHF induced depressions in heart interval control are conflicting. Dogs with *high*-output failure induced by an aorto-caval fistula continued to show a depression in the HI-SAP relationship for as long as 8 months following surgical closure of the fistula. (White, 1981) In contrast, the depressed HI-SAP slopes seen in humans with *low*-output heart failure are normalized as early as two weeks after orthotopic cardiac transplantation and resolution of the heart failure state. (Ellenbogen, 1989) Use of a reversible model of heart failure will allow a test of this hypothesis through quantification of baroreflex responses before, during, and at selective time intervals after the reversal of failure.

Selection and Characterization of the Heart Failure Model

The hypotheses to be tested in this dissertation impose certain demands on the selection of an experimental model of heart failure.

1) The model should produce low-output, congestive, biventricular failure to accurately represent the conditions of most naturally occurring forms of heart failure.

2) The severity of heart failure should be relatively stable throughout the three week period of study. Preparations based on myocardial damage with toxins or ischemia are therefore undesirable since they frequently produce either too little damage with rapid recovery, or cause premature death from fulminating cardiac failure.

3) Previous experience has shown that open-loop baroreflex characteristics remain relatively stable for an individual normal dog from day to day. In contrast, the coefficients of variation between dogs can be as high as 25-35%. A repeated measures design is therefore required to allow each dog to provide their own normal control data. Since the functional lifespan of

the isolated carotid sinus preparation is typically 6 weeks or less, the induction of heart failure cannot involve extensive interventions or surgical manipulations requiring prolonged recovery times.

4) The model of heart failure must be reversible.

Only one established model of heart failure satisfies all these requirements, the rapid cardiac pacing model originally described by Whipple (1962) and Coleman (1971). Continuous ventricular pacing at rates between 240 and 280 bpm consistently produces a significant reduction in resting cardiac output and increases in atrial pressures within 3-7 days of initiation. Plasma levels of norepinephrine, renin, vasopressin, and atrial natriuretic peptide are all increased. (Riegger, 1981; 1984; 1988). The mechanism of cardiac impairment has not been elucidated although an increase in afterload (wall stress) and a reduction in cardiac contractility have been suggested from echocardiographic evaluations. (Wilson, 1987) Despite a 5-fold increase in myocardial oxygen consumption, ischemia does not appear to be a major pathophysiologic mechanism since neither the myocardial A-V oxygen difference or coronary sinus lactate concentrations are significantly increased. (Wilson, 1987) Partial recovery of the reduced ejection fraction occurs within 48 hours of cessation of pacing while diastolic cardiac dimensions and systolic wall stress remain elevated. This improvement in systolic function in the absence of notable changes in cardiac loads again implicates some fundamental deficit in contractility. That structural cardiac changes are also present is suggested by the persistence of cardiomegaly despite restoration of cardiac output and atrial pressures during recovery.

METHODS

Thirty-five male and female adult mongrel dogs, weighing 20-30 kg, were used in this study. Completion of the general experimental protocol was accomplished in 8 of these dogs. Two additional dogs were used in a separate control experiment. The results presented in this dissertation are from these dogs. Of the dogs not completing the study, 1 was excluded because of refractory ventricular arrhythmias, 3 died prematurely in congestive heart failure, 4 died as a result of thoracic surgical complications, and 4 died from acute aortic rupture secondary to flow-probe pressure necrosis. Thirteen more dogs were not successfully studied because of premature deterioration of the carotid sinus preparation and/or the implanted recording instruments.

Surgical Preparations

Two aseptic surgical procedures were required to prepare the dogs for study. The first surgery was a thoracotomy for implantation of recording devices. The second surgery, performed approximately 10-14 days later, involved a cervical procedure to prepare the carotid sinuses for reversible isolation. It was necessary to perform the thoracotomy first to maximize the use of the limited lifespan of the carotid sinus preparation and to allow maturation time for the aorta-electromagnetic flow probe transducer system.

Thoracotomy -- Dogs were premedicated with intramuscular acepromazine malate (.1 mg/kg) and atropine (.05 mg/kg) and general anesthesia induced by a bolus intravenous injection of thiamylal sodium (4-8 mg/kg). Anesthesia was maintained by inhalation of a mixture of halothane (1-2%) in oxygen. A left 4th intercostal thoracotomy was then performed. A Tygon catheter (1.25 mm i.d.) was inserted into the descending aorta through a stab wound for measurement of arterial pressure. Similar catheters were also secured within the right and left atrial appendages. The adipose and connective tissues surrounding the ascending aorta were removed to facilitate placement of an electromagnetic flow probe around the vessel. Dacron velour was placed between the aorta and flow probe in 6 of the 31 dogs instrumented. Two platinum-tipped pacing electrodes were embedded and sutured to the myocardium of the left ventricular apex. Care was taken to avoid trauma to surrounding coronary vessels. The pericardium was closed around the cardiac implants. After the catheters and leads were exteriorized at the midscapular region, the chest was closed, evacuated and the dogs were allowed to recover. Each dog wore a protective canvas vest to protect the exteriorized ends of the implants. Following surgery, the dogs were acclimatized to the experimental setting on a daily basis while the catheters were irrigated with a heparinized penicillin-dextran (70,000 IU/ml) solution, and the surgical wounds were cleansed.

Cervical Isolated Carotid Sinus Preparation -- Each dog was allowed 10-14 days to recover from the thoracotomy before the second surgical procedure. Anesthesia was induced and maintained as described above. Reversible carotid sinus isolation was accomplished using the method of Stephenson and Donald (1980). All vessels surrounding the carotid sinuses were ligated except for the common and external

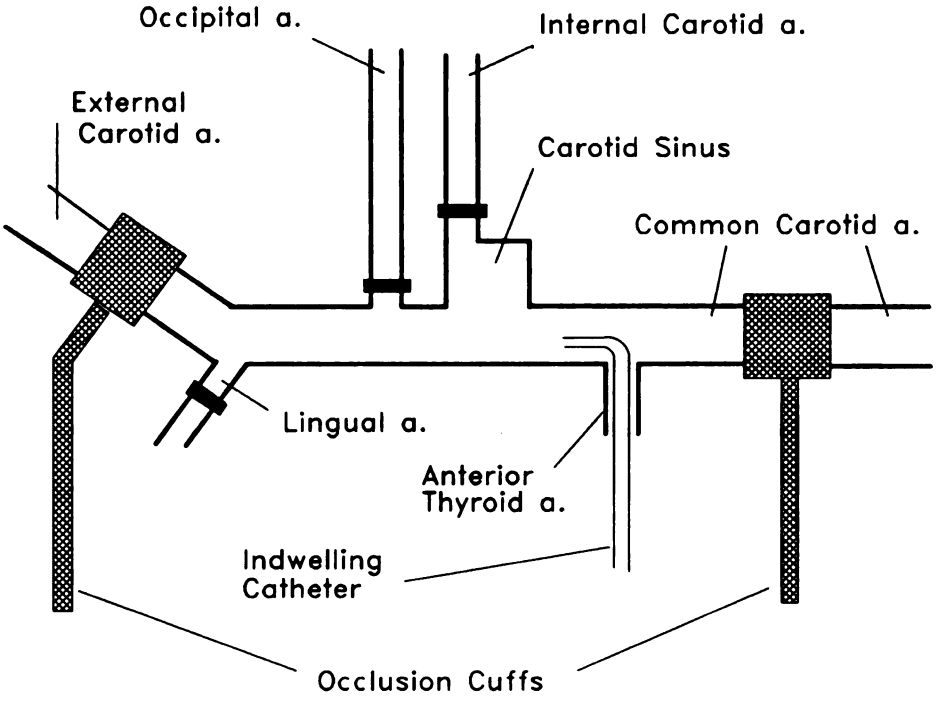


Figure 1. Schematic diagram depicting the surgical preparation of the carotid sinus regions for reversible vascular isolation. Heavy bars indicate ligation of vessels. Stippled structures represent pneumatic occluder cuffs.

carotid arteries which remained as the only entrance to, and exit from, the sinus region (Figure 1). Pneumatic occluder cuffs were placed around the common and external carotid arteries. Inflation of the occluder cuffs completely isolated the carotid sinuses from the rest of the systemic circulation. Tygon catheters (1.02 mm i.d.) were inserted into the common carotid artery between the occluders through the stump of the anterior thyroid artery. These catheters allowed independent control of carotid sinus pressure when the occluders were inflated and the sinuses temporarily isolated. Aortic denervation was accomplished by identifying (and transecting) the aortic depressor nerves as a small nerve bundle that exited the cervical vagosympathetic trunk. Verification of their identity was accomplished by intraoperative whole nerve recordings demonstrating the characteristic pulse-synchronous activity of aortic baroreceptors. The dogs were allowed 5-7 days to recover before experiments were initiated. Calibration of the aortic flow signal was accomplished at the end of this recovery period using a standard dye-dilution (indocyanin green) reference.

Confirmation of Aortic Denervation

Effective aortic denervation was verified in each dog by comparing the bradycardic response to a bolus injection of phenylephrine (200-400 ug) or methoxamine (2-4 mg) with the carotid sinus alternatively open and isolated. Pre-injection mean arterial blood pressure was not significantly different for the two respective states (129 vs. 124 mm Hg). Injection of the pressor agent in the closed-loop state caused an average increase in mean blood pressure of 55 mm Hg with a corresponding drop in heart rate of 45 bpm. In contrast, during carotid sinus isolation, pressor injections induced an 83 mm Hg rise in blood pressure yet only a 1 bpm average drop in heart rate. The slope

or "gain" of this measure of baroreflex activity was significantly reduced (-.855 bpm/mm Hg to .008 bpm/mm Hg) by sinus isolation for an average loss of 91% (range 79-100%) of the aortic baroreceptor heart rate buffering capacity.

Determination of Baroreflex Stimulus-Response Relationships

All experiments were conducted with conscious, quietly resting and unrestrained dogs in lateral recumbency. The experiment environment was shielded from extraneous visual or auditory stimuli. Heparin (5000 IU) was administered intravenously and the following variables were continuously recorded on an 8 channel Grass physiograph: phasic and mean aortic pressure, mean left and right atrial pressure, phasic and mean (cardiac output) aortic flow, carotid sinus pressure, and a surface lead electrocardiogram. Heart rate was determined manually from the EKG recording. Total peripheral resistance was calculated as the quotient of systemic perfusion pressure and cardiac output. At the time of study the dogs were allowed 10-15 minutes to adjust to the environment at which time resting hemodynamic values were recorded. The carotid sinuses were then temporarily isolated by inflation of the occluders and subjected to a static pressure of 50 mm Hg through a connection between the carotid catheters and an external reservoir of heparinized, lactated Ringers equilibrated with a gas mixture of 95% oxygen and 5% carbon dioxide. The steady state systemic reflex responses in heart rate, cardiac output, mean arterial pressure, and total peripheral resistance were then derived. These steady state responses were typically evident within 30-45 seconds of a change in static sinus pressure. The sinus pressure was then increased in a step fashion to 70 mm Hg and steady state responses again determined. This procedure was repeated throughout the range of carotid sinus reflex activity, typically from 50-200 mm Hg, in 20 mm Hg

steps. Total sinus isolation time averaged 12 minutes for the dogs of this study. Thereafter, the carotid occluders were deflated and communication between the carotid sinuses and the systemic circulation was re-established.

The resting closed-loop data, and the steady-state open-loop values for each hemodynamic variable at each carotid sinus pressure (CSP) were entered into an MS-DOS, 80286 based microcomputer. A best-fit (least squares) asymmetrical sigmoidal curve was approximated for the raw, steady-state data using a 5-parameter logistic equation (Ishikawa, 1984) and an iterative curve fitting algorithm (Wilkinson, 1988). In each case, the hemodynamic variable of interest served as the dependent variable with isolated carotid sinus pressure, the independent variable. The equation for fitting the reflex stimulus-response relationship for blood pressure, for example, is:

$$MAP = \frac{P_1}{1 + e^{[P_2(csp - P_3)]^{P_4}}} + P_5$$

Where: P_1 = range of dependent response

P_2 = slope coefficient

P_3 = domain centering coefficient

P_4 = asymmetry parameter

P_5 = minimum dependent response

Although most of the steady state reflex data assumed an obvious sigmoidal relationship, some of the cardiac output data sets during heart failure (both with and without pacing) were extremely flat (negligible range and slope). Forcing a sigmoidal fit to such data occasionally resulted in an abrupt and artifactual inflection in the fitted curve. Reflex gains calculated under such circumstances become artificially high. To eliminate this, linear fits were made for these data sets. In every case, the alternate

use of the linear fit was defended by comparing the goodness of fit of the two curve types. Since a higher number of parameters almost always leads to a lower sum of squares (SS), the comparison was standardized for the degrees of freedom available with each curve type according to the following *F* test. (Motulsky, 1987)

$$F = \frac{\left(\frac{SS_1 - SS_2}{df_1 - df_2}\right)}{\frac{SS_2}{df_2}}$$

Where: SS_1 = sum of squares, linear

SS_2 = sum of squares, sigmoidal

df_1 = degrees of freedom, linear

df_2 = degrees of freedom, sigmoidal

A linear fit was not used if the probability of the observed *F* value was less than 0.1.

Several physiologically relevant parameters of the baroreflex were derived from the fitted curves (Figure 2). These parameters included the maximum value of the dependent variable (MAX), the minimum dependent value (MIN), the range (RNG) of the reflex (MAX - MIN), and two reflex gain measurements. The maximum slope of the fitted curve represented the maximum gain (MAX GN) while the average slope between threshold and saturation values of CSP represented the average gain (AVG GN). Threshold and saturation are defined as the values of CSP bounding the upper and lower 5% of the range of the dependent variable respectively (threshold and saturation were undefined for those data fit with a linear model).

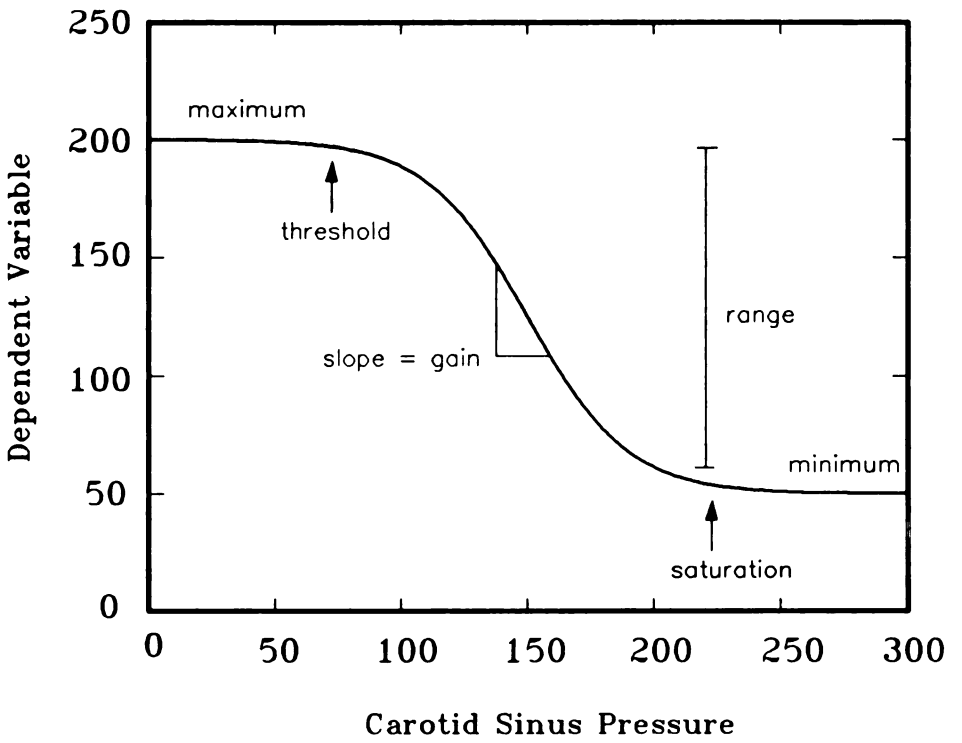


Figure 2. Hypothetical baroreflex stimulus-response curve depicting the physiologically relevant curve parameters.

Induction of Heart Failure

Heart failure was induced by continuous left ventricular pacing at constant rates between 240 and 280 bpm. The group average for the pacing rate employed in this study was 255 bpm. Pacing stimuli were supplied by a portable pulse generator (Medtronics, #5320) carried by each dog in their protective canvas vests. For each dog, the pulse current provided was 25% more than the minimum needed for complete electrical capture of the ventricles. Typically, this would range between 5 and 7 mA although there was a distinct tendency for this requirement to increase during the 3 week period of pacing. Although rarely needed, the pacing rate could be adjusted to modify the severity of heart failure. For the purposes of this study, heart failure was arbitrarily defined as a 25% or greater reduction in resting cardiac output and a left atrial pressure greater than 12 mm Hg. Characterization of the failure state was also accomplished using M-mode echocardiographic measurements of cardiac dimensions (Electronics For Medicine, Mark V; 2.5 MHz non-focused transducer). Left ventricular end-diastolic and end-systolic minor axis dimensions were determined as well as left atrial and aortic root diameter. Left ventricular wall thickness and left ventricular fractional shortening were also recorded.

Experimental Protocols

Baroreflex stimulus-response relationships and the derived curve parameters were determined during three phases of study. Phase I served as the control period to allow characterization of the normal reflex for each dog before the induction of heart failure. Phase II comprised the heart failure portion of the study and began with the initiation of chronic ventricular pacing and extended for 3 weeks. Phase III provided information regarding recovery from heart failure. It began at the end of the 3 weeks of Phase II

when continuous pacing was discontinued, and extended as long as the experimental models remained operative (approximately 2 weeks). Each dog was studied at selected times during the first two phases of study including: Phase I, day 1 (I-1), II-3, II-7, II-14, and II-21. An attempt was made to study each dog through two additional phase III days, III-7 and III-14 although only 3 dogs successfully completed this Phase.

Control Experiments -- It was important to be able to distinguish the effects of heart failure *per se* on baroreflex function from any potential effects of chronic, repetitive, current-pulse administration (pacing). Since heart failure could not be totally dissociated from pacing, a truly rigorous test of this hypothesis could not be made. However, two control experiments were designed to address this issue. The first experiment involved rapid pacing (240-260 bpm) for brief periods (30 minutes) during Phase I. Preliminary experience suggested that such a short pacing duration was not sufficient to cause overt heart failure in dogs. No-pace curves were generated immediately before and 10 minutes after this transient Phase I pacing period. Baroreflex characteristics for these pre-pace and post-pace curves were compared to identify any effects of pacing on reflex function that would be independent of heart failure itself. For example, if pacing alone had some depressant effect on reflex function, the gain and/or range of the baroreflex might be depressed in the post-pace curve relative to the pre-pace curve. This experiment was performed on each of the 8 dogs in the principal study.

It could be argued though, that any effect of exogenous current administration might be time dependent and therefore might not be evident within the short 30 minute period of Phase I pacing described above. In two additional dogs, pacing was continued for 7 days. Dissociation of pacing from heart failure in this longer control experiment required that the pacing rate be reduced to 170 bpm which also avoided overt evidence of circulatory failure. No-pace baroreflex characteristics were then determined before initiation of low-frequency pacing (LFP) and then again after 7 days

of continuous LFP pacing. Using the same argument, if pacing had some direct effect on reflex function, the 7 day LFP curves should be different than those determined before LFP.

Hypothesis 1 -- Heart failure produces a significant impairment in both the range and gain of baroreflex control of heart rate and blood pressure. The test of this hypothesis was made using a comparison of open-loop baroreflex characteristics for control of heart rate and mean arterial blood pressure between phase I, and the 4 days of Phase II. In order for natural reflex control of heart rate to be included in the analysis, rapid ventricular pacing was temporarily discontinued for approximately 20 minutes in the Phase II experiments to allow collection of the open-loop raw data (no-pace curves). Although the primary focus was on these data, reflex characteristics were also determined during a brief period of pacing in phase I and with the pacer on in Phase II (pace-curves). Since pacing could be expected to attenuate the cardiac output contributions to overall reflex control of blood pressure, this protocol might enable an assessment of the dependency of the reflex on the cardiac component (and conversely the vascular component, see below).

Hypothesis 2 -- Heart failure impairs reflex function through a selective cardiac efferent mechanism rather than a generalized depression of both efferent limbs. If heart failure associated abnormalities in the baroreflex reside in the afferent arm or the central processing sites, evidence of impairment in both efferent limbs (cardiac and vascular) would be expected. As an initial search for the major site of impairment, separate comparisons were made of baroreflex control of the two principle effectors, cardiac output and TPR. Baroreflex characteristics for both variables were determined on all Phase I and II experimental days, and for all available Phase III data. If, as hypothesized, baroreflex control of cardiac output is selectively impaired while TPR control remains intact, an efferent site of impairment would be suggested. In contrast, if reflex control of both cardiac output and TPR are similarly affected, a generalized

depression of the reflex would exist. Assuming a single "lesion", such a result would implicate a deficit in those parts of the reflex arc common to both efferent limbs; namely the afferent and/or central sites. Admittedly, this distinction is a simple one, and more easily defended if selective impairment is identified. Nevertheless, this analysis may provide important clues as to the mechanism of reflex impairment in heart failure.

Hypothesis 3 -- Impairments in the baroreflex induced by heart failure are quickly reversible after resolution of the failure state. In order to determine if observed baroreflex impairments are quickly reversible, chronic rapid ventricular pacing was discontinued at the end of the 3rd Phase II week, and the dogs allowed to recover from heart failure. Baroreflex characteristics were again determined on day III-7 and III-14 for comparisons with Phase I and II results. Normalization of any changes in the arterial baroreflex observed during Phase II would indicate rapid reversal of baroreflex impairment.

Statistical Analysis

Statistical analysis involved comparisons between control and heart failure for resting hemodynamic data, echocardiographic data, and the derived physiologic baroreflex parameters. When 2 treatment conditions were compared, as with the Phase I pre-pace and post-pace reflex characteristics, a paired *t* test was used. When comparisons involved several days, such as the repeated measures comparisons across the 5 experimental days of Phase I and II, a randomized block, model III analysis of variance was used. The exception to this involved the comparisons for the pace-curves in Phase I and II. Missing data unavoidably occurred for one dog on two days, and one dog on one day for a total of 3 out of the total 30 data cells of this series. Rather than estimate these missing cells, a one way unbalanced analysis of

variance was performed. Post hoc tests for the blocked ANOVA were performed if the overall F ratio reached the stated level of statistical significance. These post hoc comparisons were limited to contrasting each Phase II day with the Phase I data. This maintained the number of comparisons at or below the number of degrees of freedom for the ANOVA, and thereby sustained the nominal alpha statistical value of the overall comparison. (Bernhardson, 1975) Post hoc comparisons for the one-way ANOVA were performed using the Tukey-Kramer method for unbalanced designs. Statistical power (1-*beta*) calculations performed on the comparison between Phase I-1 and Phase II-21 no-pace curves were based on the non-central *F* distribution for paired *t* tests defined by Kendall and Stuart (1973) and implemented by Dallal (1988).

Analysis of the recovery data in Phase III presented a statistical challenge in the sense that only 3 dogs successfully completed this phase. Moreover, only two of these dogs had functional aortic flow probes for Phase III experimental days. Clear directional trends were evident in most parameters as the dogs were allowed to recover from heart failure. Use of the common *alpha* level of .05, however, could potentially result in an inordinate bias toward type I error protection with high vulnerability to type II errors. Since no physiologic basis could be advanced to justify such a bias, a more balanced degree of protection was sought. To achieve this, statistical power (1-*beta*) values were calculated for each of the recovery phase comparisons using the method described above. For interpretive reasons, an *alpha* level of .30 was chosen for the level of statistical significance instead of the traditional, but arbitrary, value of .05. This assignment provided what was considered a minimum degree of confidence in protecting against both type I and type II errors, with a *beta* level of approximately .60. Statistical significance (*alpha*) for all other tests, including the major comparisons between Phase I and Phase II, was assigned at the .05 level.

RESULTS

Throughout this chapter, results will be presented in customary units unless otherwise specified. Hence, units of pressure are mmHg, heart rates are beats per minute (bpm), cardiac output is liters/min and total peripheral resistance (TPR) as mmHg*min/liters. Units of gain are the quotient of the dependent variable unit and the independent units (mmHg). Tabulated values are presented as group means and standard deviations.

Stimulus-response figures provide a visual summary of the results and were generated by averaging representative points from the individual dogs' fitted curves. A best-fit sigmoidal curve was then applied to these averaged data points to provide a composite group curve. Because of the two-stage averaging procedure used for these composite curves, the apparent range and gains for these graphic figures may not coincide precisely with the average of the individual curve parameters for each dog. All comparisons and interpretations were derived from the latter, a group average of the individual values for each dog. The group composite curves are provided only for general visual comparisons.

Effects of Pacing Alone on Resting Hemodynamics and Reflex Function

The effects of short periods of rapid ventricular pacing (RVP) are summarized in Table 1. It was not possible to completely prevent hemodynamic changes associated with RVP in this Phase I control experiment; even when limited to short 30 minute periods. Brief pacing at 255 bpm resulted in an increase in resting mean arterial pressure from 95±12 to 107±12. Left atrial pressure (2±2 to 8±2) and TPR (27±5 to 31±5) were also increased. In contrast, right atrial pressure was not significantly affected by pacing (1±2 vs 2±1). Despite these modest changes in resting hemodynamics, pacing had very little effect on baroreflex function as illustrated in Figure 3. The stimulus-response curves for MAP and HR before and after brief RVP are nearly superimposable. Although not statistically significant, a modest reduction in both the range ($p = .07$, power = .54) and average gain ($p = .37$, power = .54) for cardiac output is evident after brief RVP. The increase in left, but not right atrial pressure suggests that even brief RVP can have deleterious effects on left ventricular function which could have contributed to a reduction in the cardiac output reflex responses. No significant changes were evident in reflex control of TPR after brief RVP.

Since it was not possible to completely dissociate RVP from hemodynamic changes that could potentially induce impairment in the arterial baroreflex, two dogs were paced at lower rates (LFP) continuously for seven days. The duration of 7 days was chosen since a reduction in the range and gain of baroreflex control of mean arterial pressure was evident in all 8 dogs of the principal study by day 3 and 7 of continuous RVP. The results of this control experiment are shown in Table 1 and Figure 4. Since only two dogs were studied, and only one of these had a functional aortic flow probe, statistical analyses were not performed on these data. As evident in Figure 4, though, LFP for 7 days had either no visible effect, or an effect opposite in

Table 1. Control Experiment: Effects of Brief Periods of Rapid Ventricular Pacing and Chronic Low Frequency Pacing on Resting Hemodynamics and Baroreflex Parameters. (* $p<.05$, NS = not significant for comparisons with control data).

	Brief RVP			7 days of LFP	
	Control	Pacing		Control	Pacing
Resting Values					
MAP	96±12	107±12	*	110±4	95±29
HR	99±13	255		110±14	170
CO	3.5±.6	3.4±.8	NS	5.9	7.4
TPR	27±5	32±5	*	17	11
LAP	2±2	8±2	*	2±0	3±2
Reflex Parameters	PrePace	PostPace		PrePace	PostPace
MAP					
Rng	151±23	162±20	NS	132±50	129±7
MxGn	-5.2±2.5	-4.6±3.0	NS	-1.70±.8	-1.7±.8
AvGn	-3.3 1.5	-2.7±1.0	NS	-1.0±.5	-1.1±.4
HR					
Rng	122±33	120±24	NS	48±18	61±25
MxGn	-4.0±1.6	-3.4±1.1	NS	-1.12±.9	-.732±.03
AvGn	-2.5±.9	-2.1±.6	NS	-.679±.5	-.466±.05
CO					
Rng	2.27±.9	1.59±.7	NS	1.3	3.3
MxGn	-.13±.08	-.09±.05	NS	-.012	-.041
AvGn	-.07±.05	-.05±.03	NS	-.008	-.028
TPR					
Rng	24±7	33±12	NS	13	11
MxGn	-.86±.4	-.79±.7	NS	-.130	-.091
AvGn	-.51±.2	-.44±.2	NS	-.086	-.073

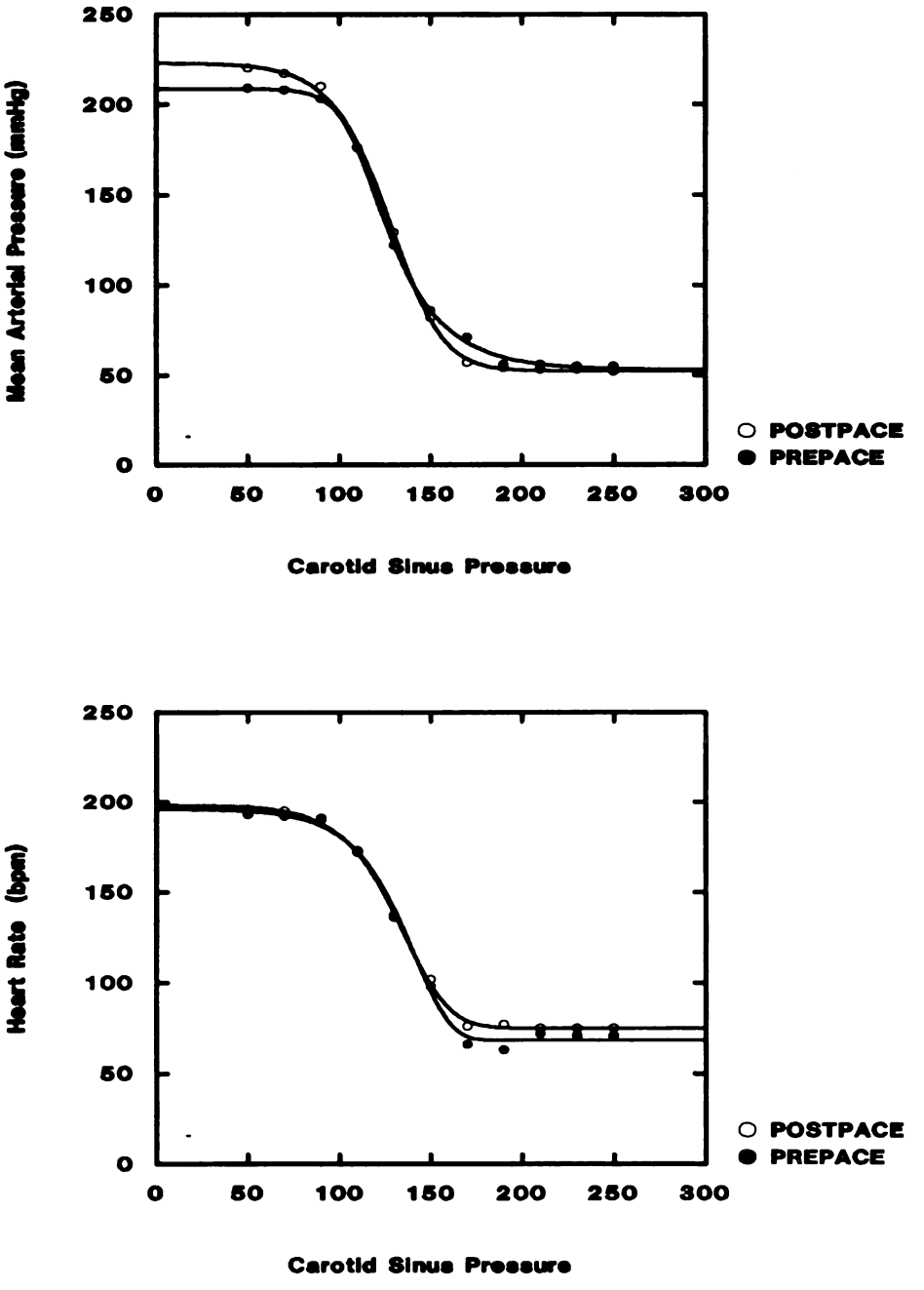
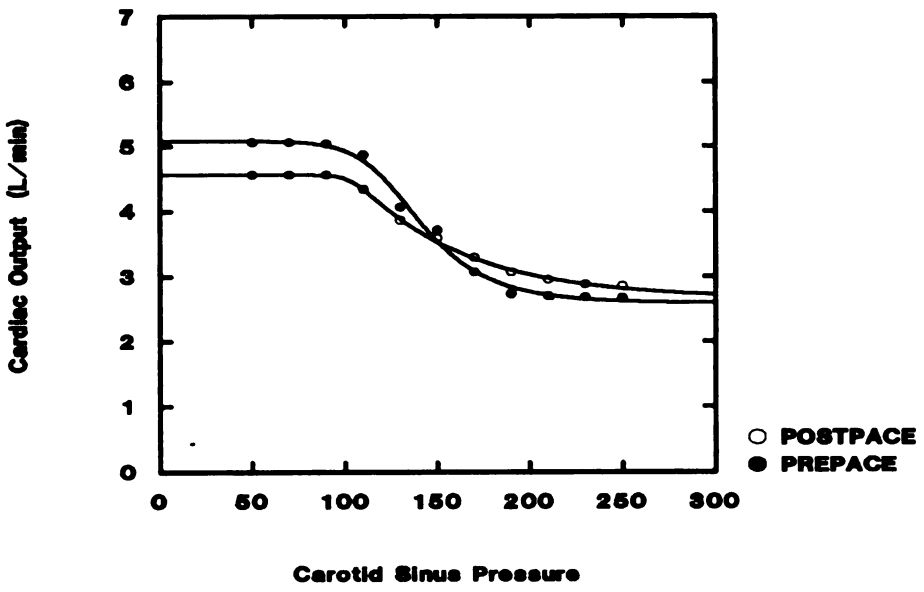


Figure 3. Reflex stimulus response curves before and after short periods (30 minutes) of rapid ventricular pacing. The ranges and gains of baroreflex control of mean arterial pressure, heart rate, cardiac output and total peripheral resistance were not significantly affected by this short duration of pacing.



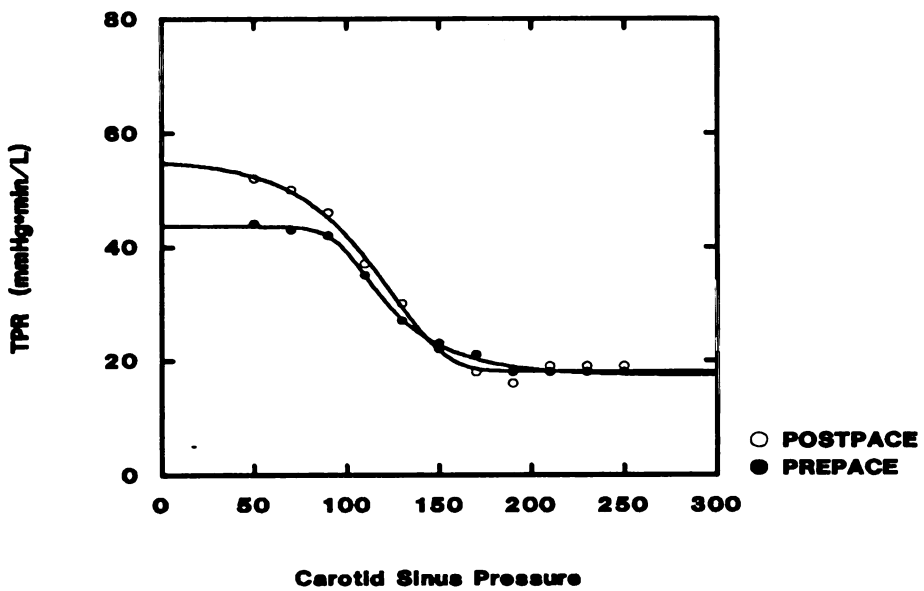


Figure 3. (cont'd.)

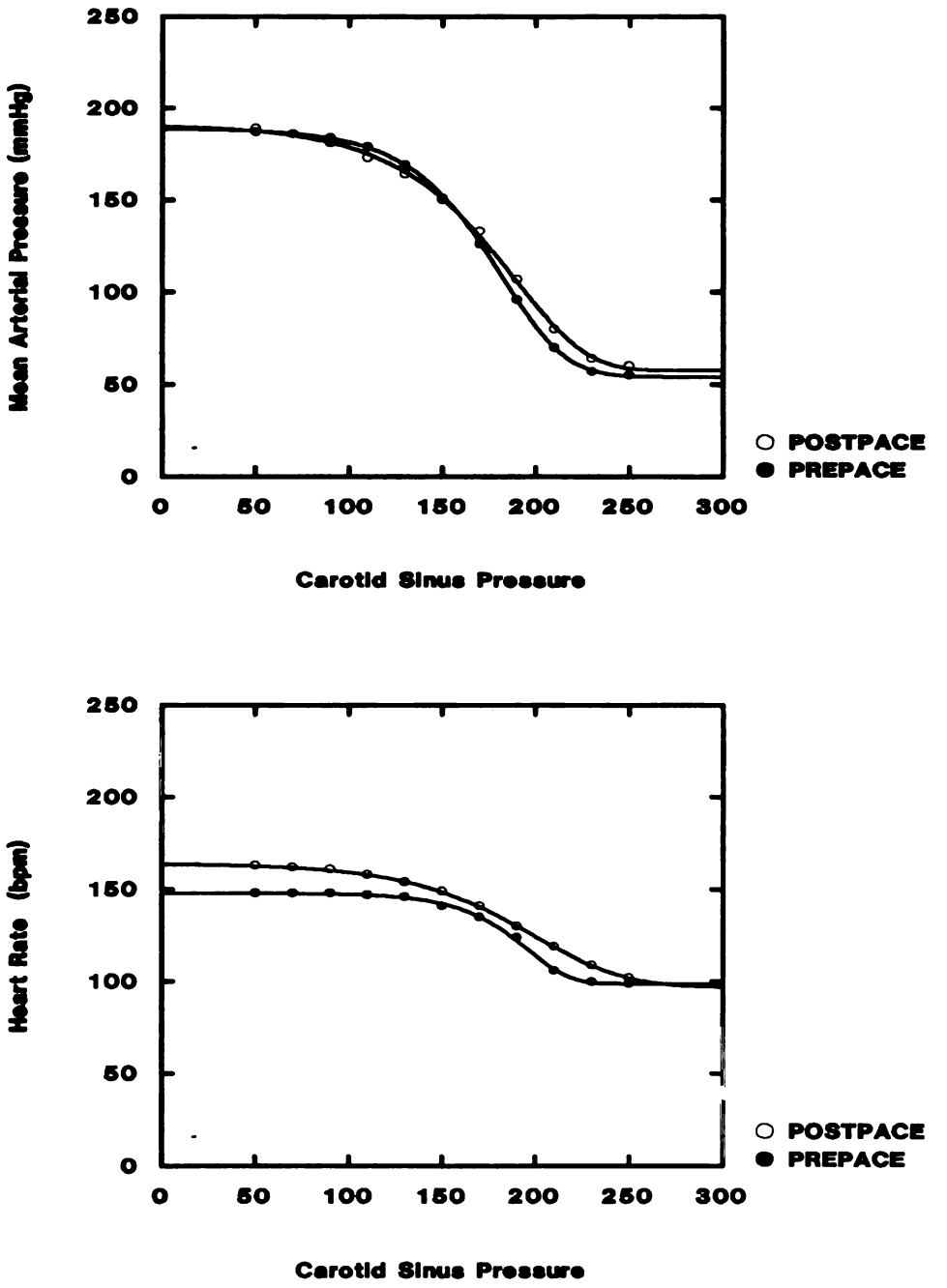
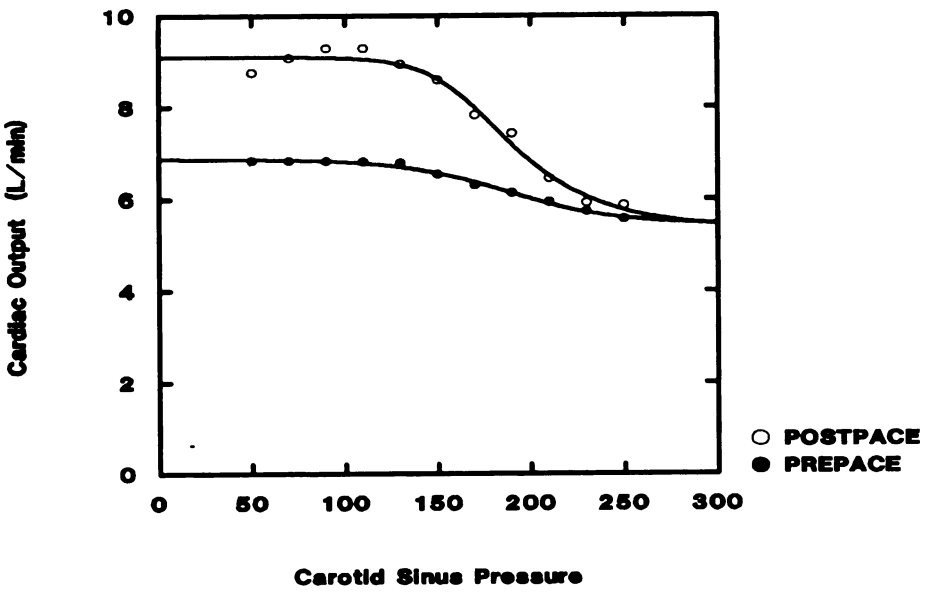


Figure 4. Reflex stimulus response curves before and after 7 days of low frequency ventricular pacing (LFP, 170 bpm) illustrating an absence of effect of pacing alone on baroreflex control of blood pressure, and heart rate. The effects of LFP on reflex control of cardiac output and total peripheral resistance are opposite in direction to those seen with chronic RVP and heart failure.



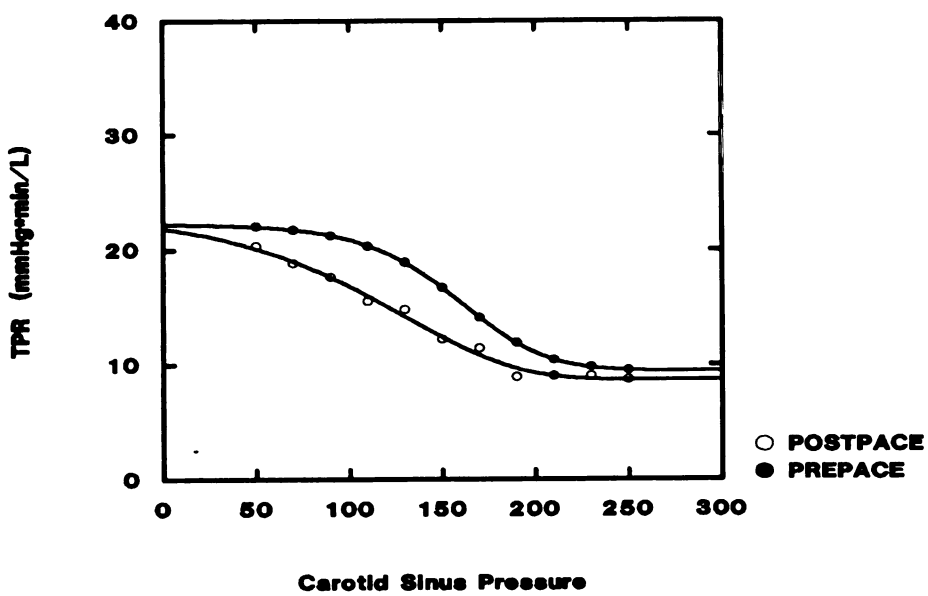


Figure 4. (cont'd.)

direction to that seen with congestive heart failure associated with chronic RVP. These results suggest that pacing alone, independent of heart failure, does not significantly impair baroreflex function.

Development of Congestive Heart Failure by Chronic Rapid Ventricular Pacing

Phase II of this study was initiated by programming a portable pulse generator to pace the left ventricle at rates between 240 and 280 bpm (group mean, 255 bpm). The effects of this pacing on resting hemodynamics are shown in Table 2. After three days, resting cardiac output was diminished by 31% and left atrial pressure increased from 3±2 to 12±4 mmHg. Cardiac output remained depressed by approximately 25-35% throughout phase II while left and right atrial pressure increased throughout the pacing period. As previously reported for this model of heart failure, mean arterial pressure decreases by approximately 15 mmHg, while unpaced heart rate and total peripheral resistance generally increase. All of these changes were statistically significant by day 21 of Phase II. These findings confirm the ability of this experimental model to consistently produce low-output, bi-ventricular failure in dogs.

Wilson (1987) reported that as much as a 4-fold increase in coronary blood flow occurs after 3 weeks of rapid ventricular pacing. Since the aortic flow probes were placed distal to the coronary arteries in these dogs, total cardiac output was underestimated by the magnitude of this coronary flow. Because coronary flow increases substantially in this model of heart failure, the severity of the reduction in cardiac output might be overestimated. For example, if coronary blood flow normally represents approximately 5% of total left ventricular flow (total cardiac output), and

Table 2. Effect of chronic rapid ventricular pacing on resting hemodynamics illustrating the rapid development of congestive, low-output heart failure. MAP = mean arterial pressure, HR = unpaced heart rate, CO = cardiac output, TPR = total peripheral resistance, LAP = left atrial pressure, RAP = right atrial pressure. (* $p < .05$ for comparisons with control data)

	Control	Heart Failure							
	I-1	II-3		II-7		II-14		II-21	
Resting Hemodynamics									
MAP	95±12	77±8	*	80±11	*	81±16	*	79±11	*
HR (unpaced)	97±22	92±12	NS	100±16	NS	104±14	NS	123±22	*
CO	3.51±.6	2.39±.6	*	2.39±.5	*	2.51±.7	*	1.91±.6	*
TPR	27±5	33±9	NS	30±6	NS	28±12	NS	36±9	*
LAP	3±2	12±4	*	15±5	*	18±4	*	21±4	*
RAP	1±2	5±1	*	8±1	*	9±3	*	12±3	*

Table 3. Echocardiographic data illustrating cardiac enlargement and systolic dysfunction resulting from chronic ventricular pacing. (n=5, * $p < .05$ compared to control values)

	Control	Heart Failure							
	I-1	II-3		II-7		II-14		II-21	
Echocardiographic Data									
LV End Dias Diam (mm)	41±3	42±3	NS	43±4	*	46±5	*	52±4	*
LV End Sys Diam. (mm)	31±2	33±4	NS	34±4	*	38±5	*	42±4	*
Frx Shortening (%)	25±2	21±3	*	22±3	NS	16±3	*	19±3	*
Left Atrial Diam. (mm)	21±3	24±3	NS	24±3	*	27±3	*	28±5	*
Aortic Root Diam. (mm)	24±2	23±2	NS	23±2	NS	22±3	NS	21±2	NS
Septal Thickness (mm)	7±1	8±1	NS	7±3	NS	8±3	NS	8±3	NS
LV Wall Thickness (mm)	8±1	8±1	NS	7±1	NS	7±1	NS	7±1	NS

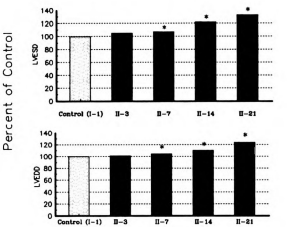
then increases 4-fold by day 21, total cardiac output would have been estimated at 3.69 L/min in Phase I and approximately 2.64 L/min on day 21 of Phase II; still a significant (28%) reduction.

The echocardiographic data presented in Table 3 and Figure 5 also show typical findings of congestive heart failure such as an increase in end-diastolic left ventricular and left atrial diameters. Although a definitive characterization of the cause of heart failure cannot be made from such data, a deficit in contractility is suggested by the decrease in fractional shortening (25±2 to 16±3 percent ($p<.05$) by day 21). End-systolic diameter was also significantly increased, a change usually induced by either a decrease in contractility and/or an increase in cardiac afterload. Crude estimations of left ventricular circumferential wall stress by the equation:

$$Stress\ \ (afterload) = \frac{(MAP)\ \ (Avg.\ \ LV\ \ Radius)}{LV\ \ wall\ \ Thick.}$$

suggest that afterload was not changed in this model (231±23 vs 235±9 mmHg) providing more support for a contractile deficit interpretation.

Subjective signs of heart failure were also evident. Dogs experienced moderate decreases in muscle mass and a mild decrease in body weight despite significant ascitic fluid accumulations. The dogs were generally not distressed at rest but developed a muffled cough with moderate activity. Appetites remained normal. Systolic cardiac murmurs suggestive of mitral regurgitation developed during Phase II in 3 of the 8 dogs.



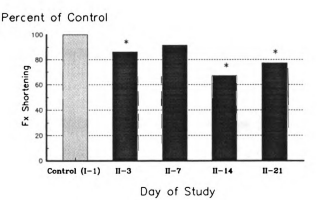


Figure 5. Time course for the development of echocardiographic changes associated with congestive heart failure. (n=5, * p<.05 compared to control, day I-1)

Heart Failure Persists During Brief Periods When Pacing is Discontinued

To allow reflex control of heart rate to participate in baroreflex control of arterial pressure, RVP was temporarily discontinued in Phase II. Figure 6 compares the changes in resting hemodynamics induced by RVP and the stability of these changes during the 20 minute period when pacing was discontinued for stimulus-response determinations. Brief discontinuation of pacing resulted in mild recovery of the cardiac output changes induced by RVP. On day 21 of pacing, cardiac output recovered immediately from 1.91 ± .6 to 2.40 ± .7 and finally to 2.62 ± .8 at the end of the 20 minute no-pace period. In contrast, left atrial pressure did not change immediately after turning the pacer off (21 ± 4) and actually increased to 24 ± 6 during the ensuing no-pace period. This increase might be related to the modest increase in venous return during the no-pace period.

Statistical notations in Figure 6 are for comparisons between the no-pace values and the Phase I, control data. All hemodynamic changes remained statistically different from control and fulfilled the definition of heart failure for this study.

Baroreflex Control of Blood Pressure and Heart Rate are Impaired in Congestive Heart Failure

The effects of pacing-induced congestive heart failure on baroreflex function are summarized in Table 4 and Figure 7. The results of this study confirm the findings of others, that heart failure impairs reflex control of heart rate. This was evident at all days of Phase II as a reduction in the range of reflex heart rate changes (decreased by 28%), the maximum heart rate attained during carotid sinus unloading (decreased by 20%), and the average gain for reflex control of heart rate (25% reduction). Maximum

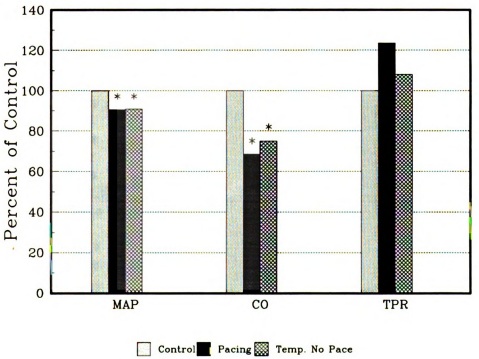


Figure 6. Comparison of resting hemodynamics in the control (Phase I) period, during pacing of Phase II, and during a brief no-pace period in Phase II. Congestive, low-output heart failure is maintained during transient Phase II periods when pacing is turned off. (* $p < .05$ for comparisons with control)

Table 4. Effects of congestive heart failure on arterial baroreflex characteristics. (* $p<.05$ compared to control, NS = not significant)

	Control	Heart Failure			
	I-1	II-3	II-7	II-14	II-21
Reflex Param.					
MAP					
MAX	220±20	157±24 *	149±21 *	134±16 *	126±21 *
MIN	57±5	56±4 NS	51±6 *	48±9 *	48±3 *
RNG	161±18	99±24 *	98±24 *	86±13 *	76±21 *
THRESH	95±15	75±13 *	78±20 *	83±11 *	81±15 *
SAT	153±16	135±17 NS	145±28 NS	154±23 NS	157±39 NS
MAX GAIN	-4.60±2.8	-2.42±.8 *	-2.43±1.2 *	-1.87±.8 *	-1.73±.8 *
AVG GAIN	-2.7±.9	-1.5±.4 *	-1.6±.7 *	-1.2±.4 *	-1.1±.5 *
HR					
MAX	198±21	156±18 *	156±19 *	165±16 *	159±20 *
MIN	73±21	78±21 NS	76±7 NS	65±16 NS	74±19 NS
RNG	125±28	78±32 *	79±19 *	99±20 *	89±23 *
THRESH	95±12	73±16 *	79±22 *	85±19 NS	91±17 NS
SAT	154±15	144±23 *	137±32 *	156±23 *	163±36 *
MAX GAIN	-3.25±1.0	-1.68±.9 NS	-2.93±1.9 NS	-2.26±1.1 NS	-2.57±1.6 NS
AVG GAIN	-2.05±.6	-1.16±.6 *	-1.60±.7 NS	-1.47±.7 *	-1.53 ±.9 *
CO					
MAX	4.56±.9	3.30±.8 *	3.09±1.2 *	2.98±1.0 *	2.59±.7 *
MIN	2.98±.5	2.73±.9 NS	2.37±.8 *	1.79±.5 *	1.94±.6 *
RNG	1.74±.4	.46±.4 *	.71±.4 *	1.18±.5 *	.52±.5 *
MAX GAIN	-.116±.05	-.040±.03 *	-.041±.03 *	-.076±.04 *	-.046±.04 *
AVG GAIN	-.081±.05	-.027±.02 *	-.032±.03 *	-.047±.03 *	-.027±.02 *
TPR					
MAX	53±12	57±23 NS	56±19 NS	49±24 NS	55±21 NS
MIN	19±3	22±10 NS	23±11 NS	21±8 NS	21±9 NS
RNG	33±11	35±13 NS	33±11 NS	28±17 NS	35±14 NS
THRESH	76±12	68±13 NS	71±17 NS	81±15 NS	63±5 NS
SAT	153±21	142±18 NS	153±24 NS	150±23 NS	170±55 NS
MAX GAIN	-.67±.4	-.67±.3 NS	-.82±.7 NS	-.73±.7 NS	-.53±.4 NS
AVG GAIN	-.38±.1	-.44±.2 NS	-.45±.3 NS	-.46±.5 NS	-.37±.3 NS

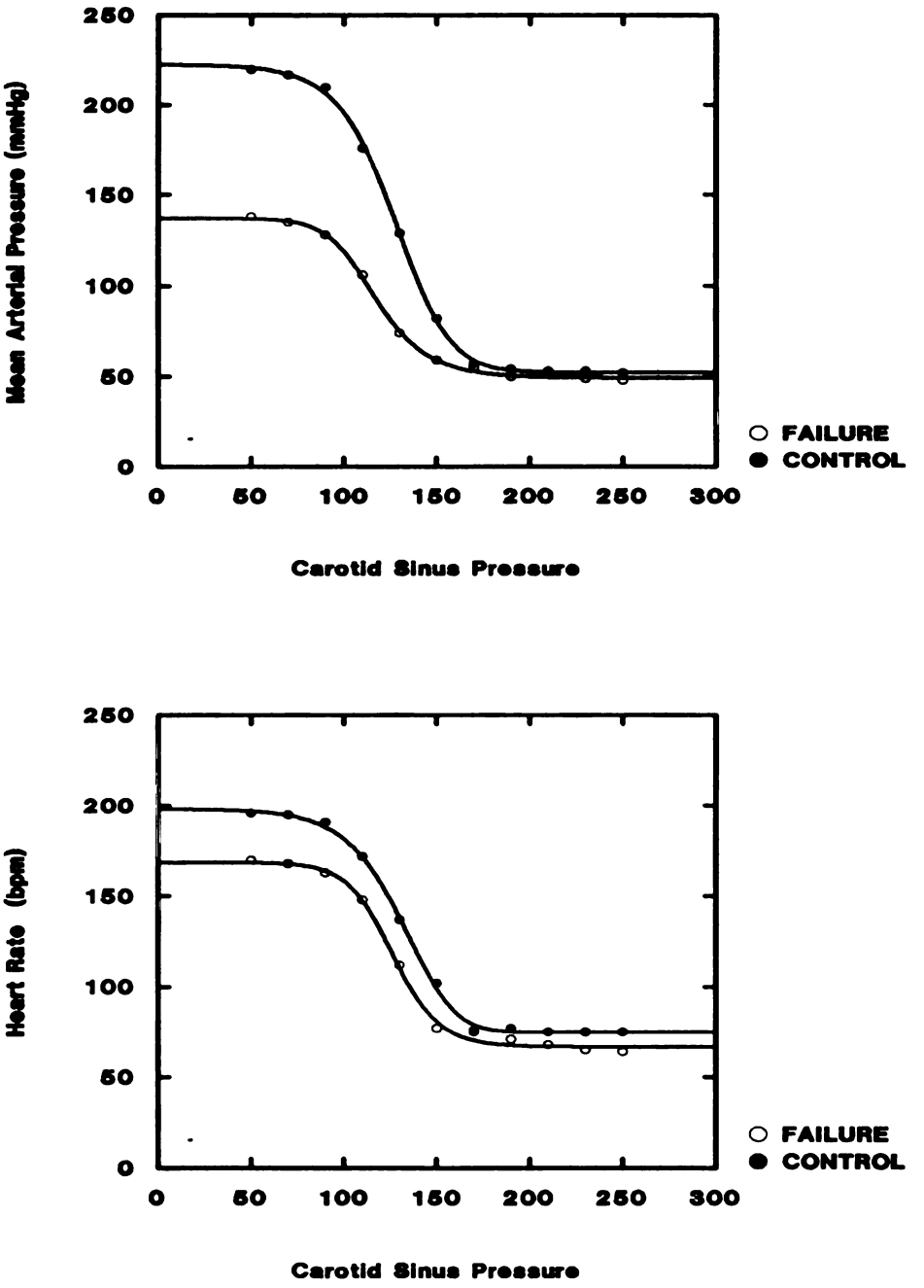


Figure 7. Heart failure reduces the range and average gain of baroreflex control of both mean arterial pressure and heart rate.

gain for heart rate control was decreased (-3.25±1 to -2.57±1.6) by heart failure although this difference was not statistically significant (control vs day 21, p=.277; power=.529). The minimum heart rate that could be achieved during isolated carotid sinus hypertension was not changed by heart failure. Interestingly, the bradycardic response to baroreceptor loading appeared to remain largely intact.

Reflex control of mean arterial pressure was also significantly impaired as early as 3 days after the initiation of RVP and low-output failure, and continued to be depressed throughout the 21 days of Phase II. MAP range decreased by 52%, primarily the result of a decrease in the maximum blood pressure attained during carotid sinus hypotension (220±20 vs 126±16). Average and maximal gain of reflex control of MAP were similarly decreased by 59% (-2.7±.9 to -1.1±.5) and 62% (-4.6±2.8 to -1.7±.8) respectfully. All of these changes were statistically significant ($p < .05$). These results confirm the first hypothesis of this study, that congestive heart failure impairs baroreflex control of blood pressure in conscious subjects.

Impairment in Reflex Control of Blood Pressure is Due to a Selective Impairment in Reflex Control of Cardiac Output

The mechanism for impaired reflex control of blood pressure in this model of heart failure was due primarily, if not entirely, to impairment in baroreflex control of cardiac output (Table 4 and Figure 8) since TPR control was not affected by heart failure (range p=.88, power=.88; max gain p=.59, power=.64; avg gain p=.91, power=.90).

As for MAP and HR, reflex control of cardiac output was depressed as early as 3 days after induction of heart failure and persisted throughout Phase II. A negative ordinal shift in cardiac output (approximately 1 L/min) was evident as a significant reduction in both the maximum (4.56±.9 to 2.5±.7) and minimum (2.98±.5 to 1.94±.6) reflex changes in cardiac output. Heart failure was also associated with a

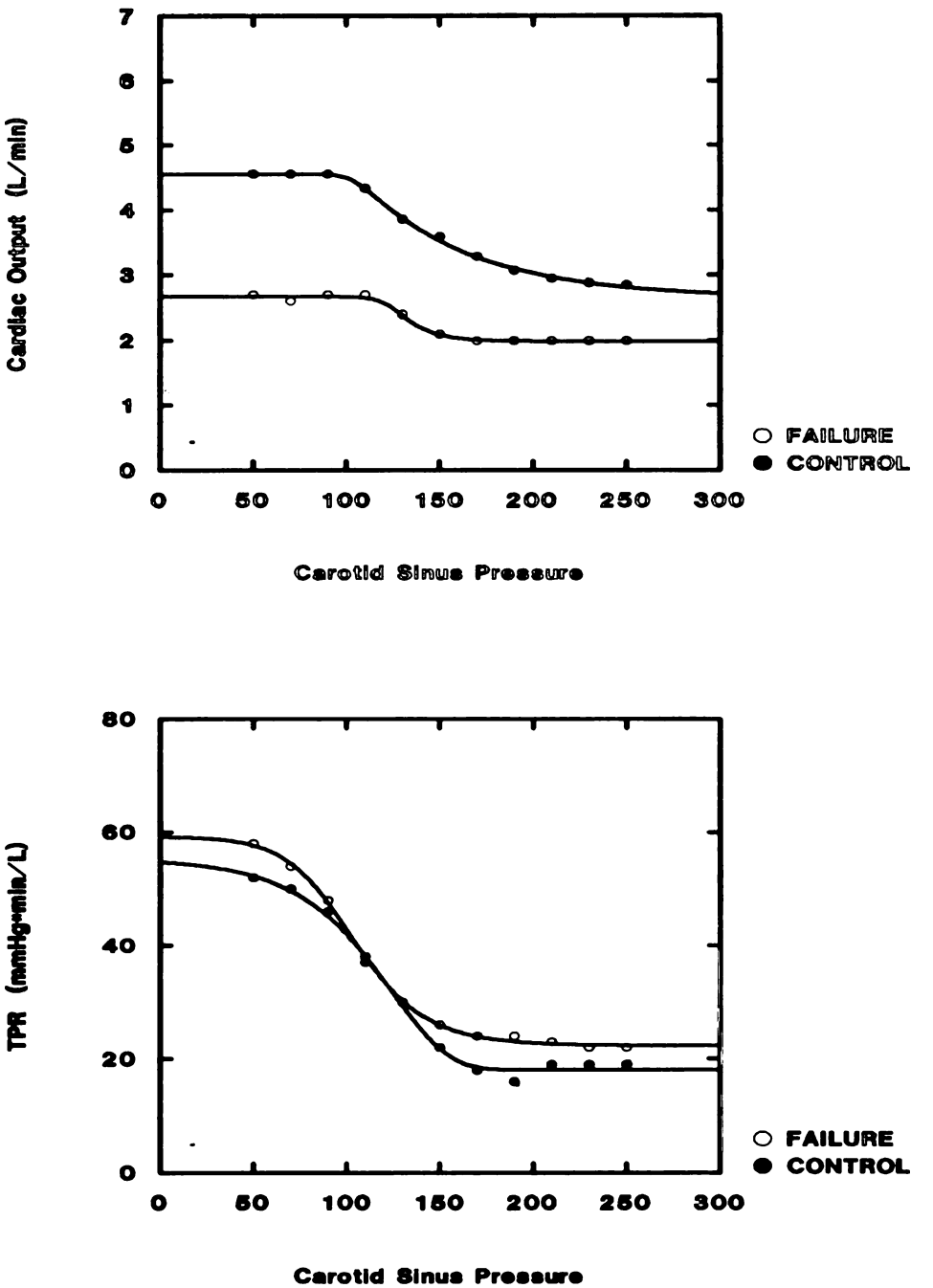


Figure 8. Heart failure related impairments in the arterial baroreflex are due to selective impairment in reflex control of cardiac output. Baroreflex control of total peripheral resistance (TPR) is unaffected by pacing-induced heart failure.

reduction in the range (70%, 1.74±.4 to .52±.5), average gain (66%, -.081±.05 to -.027±.02), and maximum gain (60%, -.116±.05 to -.046±.04) of reflex cardiac output control. For every dog, the degree (expressed as percent of control) of reflex impairment in cardiac output was greater than for heart rate. This difference, however, was not statistically significant by a Wilcoxon non-parametric comparison ($p = .06$).

These data confirm the second hypothesis which predicted that impairment in reflex control of blood pressure would occur primarily because of a selective impairment in cardiac responses. Although not conclusive, this finding is supportive of a peripheral or efferent site of reflex dysfunction since an afferent or central site would be expected to affect both efferent limbs of the reflex.

Effects of Heart Failure on Reflex Function: Pacing Curves

As originally designed, stimulus-response curves generated during RVP in Phase I and II were to be used as a means to eliminate the cardiac reflex responses. If pacing was effective in eliminating reflex changes in cardiac output, reflex control of TPR could be examined in relative isolation. In addition, this might have provided an additional means to address the primacy of cardiac impairment as the cause for overall reflex depression. The changes in reflex parameters during pacing associated with heart failure are shown in Figure 9. Despite the imposition of RVP, a considerable degree of reflex cardiac control was sustained in the normal dogs (Phase I) due to changes in stroke volume. As in the no-pace curves, heart failure partially abolishes this residual cardiac reflex response. The results of this experiment, therefore, were similar to those of the no-pace data, with a significant depression in the range of blood pressure responses, entirely attributable to a reduction in cardiac output range. Both of these changes in range were due to a significant decrease in the maximum value of

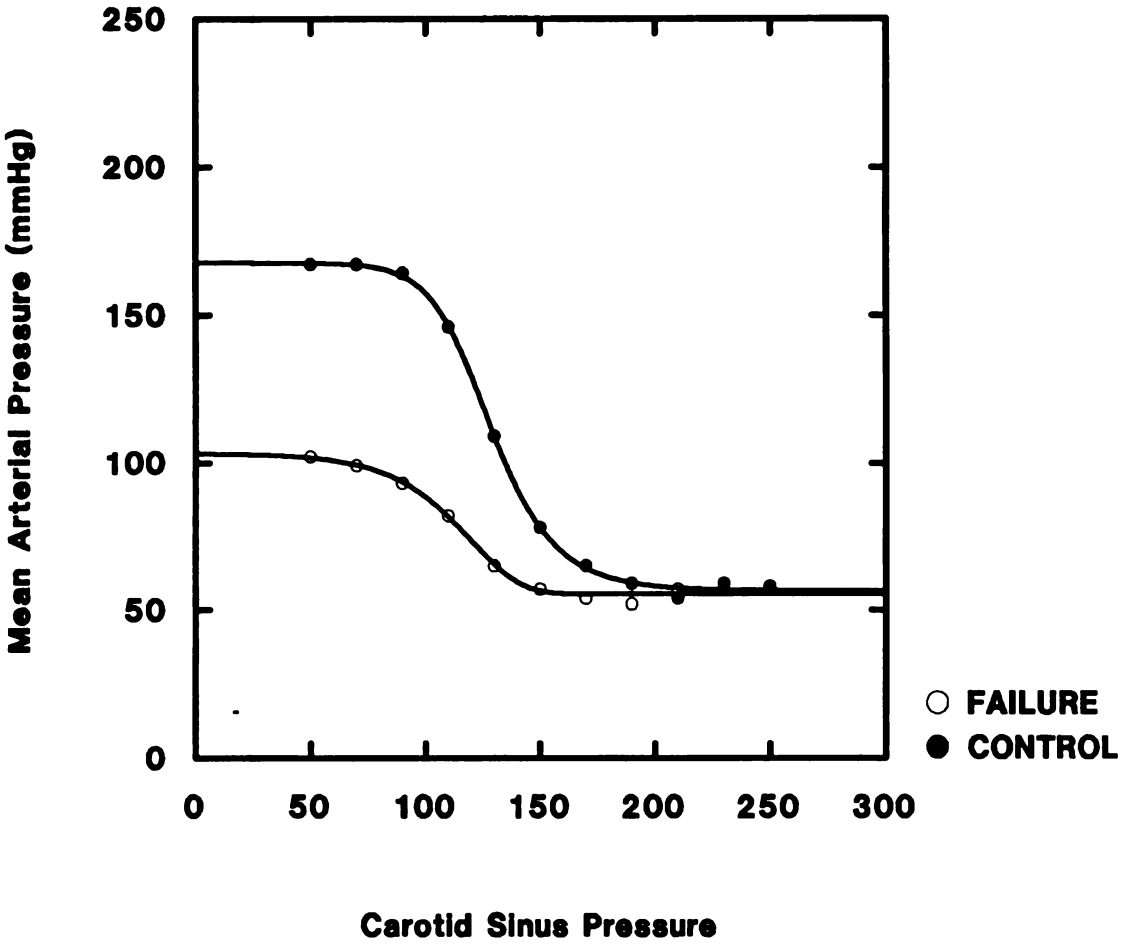
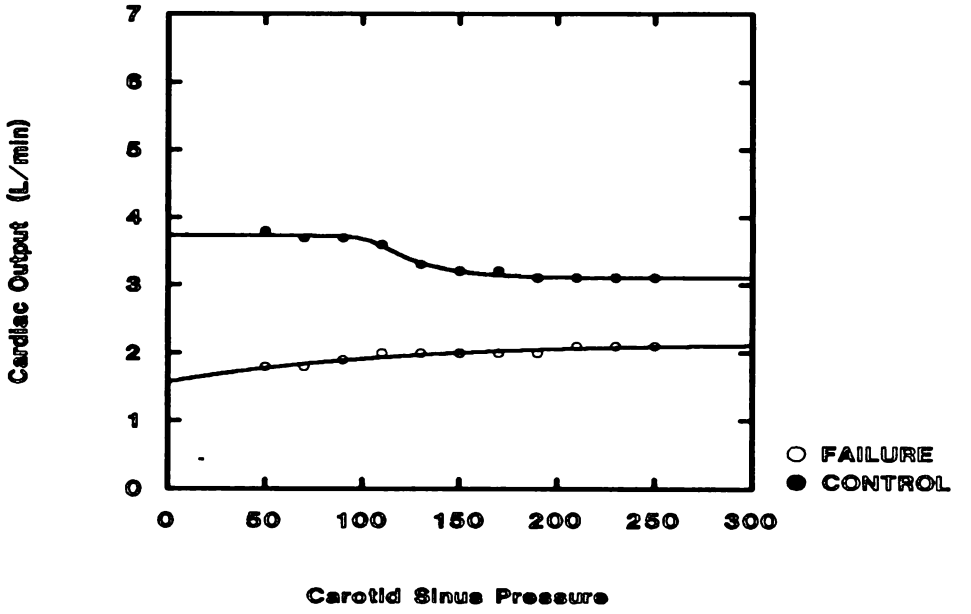


Figure 9. Pacing Curves: Heart failure reduces the range of reflex control of blood pressure and cardiac output during pacing. Reflex control of TPR was not affected by heart failure. Stimulus response curves were generated during rapid ventricular pacing.



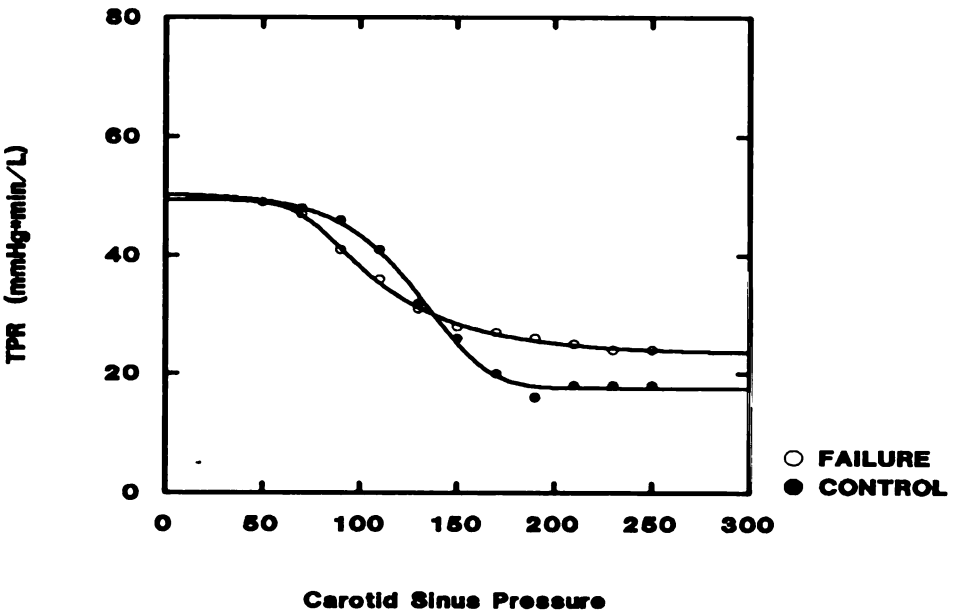


Figure 9. (cont'd.)

MAP (39%, 168±32 to 102±22) and CO (51%, 3.78±1.1 to 1.84±.6) attained during carotid sinus unloading. Reflex control of TPR during RVP was not affected by heart failure.

Heart Failure and Reflex Impairment are Partially Reversible After Pacing is Discontinued

Figures 10 and 11 and Table 5 show the changes in resting hemodynamics and reflex parameters that occurred when rapid ventricular pacing was discontinued and the dogs were allowed to recover from heart failure. As previously stated, only three dogs successfully completed phase III and only two of these had functional flow probes up to day III-7. As a result, statistical comparisons were not made for cardiac output and TPR recovery data. Comparisons for mean arterial pressure and heart rate were performed with adjustments for the small sample size. Justifications for these comparisons was based on the appearance of clear trends in resting and reflex parameters during the early phase of recovery. The adjustment was a relaxation of the *alpha* level for statistical significance to .30 to maintain a *beta* (power) level of at least .60. To prevent over-interpretations that might result from this relatively liberal statistical approach, comparisons were limited to data at the peak of heart failure (day II-21) with data from day III-7.

Resting mean arterial pressure and heart rate exhibited significant recovery following cessation of RVP. Both variables actually "overshot" the control data in the early stages of recovery. Similar recoveries were also strongly suggested at day III-7 for cardiac output and TPR. This is consistent with previous reports on the magnitude and time course of recovery for this model of heart failure. The reflex impairments in heart rate range and average gain show a similar recovery pattern, with values that actually slightly exceed the control values.

Table 5. Recovery Data: Effects of discontinuing rapid ventricular pacing on resting hemodynamics and baroreflex characteristics for the 3 dogs studied in Phase III. Only two of these 3 dogs had a functional flow probe and left atrial catheter during Phase III. (* $p<.3$ for comparisons of day III-7 with II-21)

	Control	CHF	Recovery		
	I-1	II-21	III-7		III-14
Resting Hemodynamics					
MAP	93±10	76±17	101±18	*	91 14
HR	108±19	144±18	94±37	*	92 16
CO (n=2)	3.39±.2	1.72±.2	4.02±.2		
TPR (n=2)	26±5	33±12	20±2		
LAP (n=2)	3±2	22±3	7±.7		3 .7
Reflex Parameters					
MAP					
Range	155±33	60±21	125±28	*	119 27
Max Gain	-4.00±1.0	-1.39±1.0	-3.39±3.3	*	-2.19 1.9
Avg Gain	-2.49±.5	-.89±.6	-2.09±1.9	*	-1.35 1.1
HR					
Range	105±24	67±22	115±27	*	106 32
Max Gain	-2.56±1.0	-1.53±1.1	-3.18±2.9	*	-4.89 4
Avg Gain	-1.58±.5	-1.07±.7	-1.92±1.6	*	-1.57 1.3

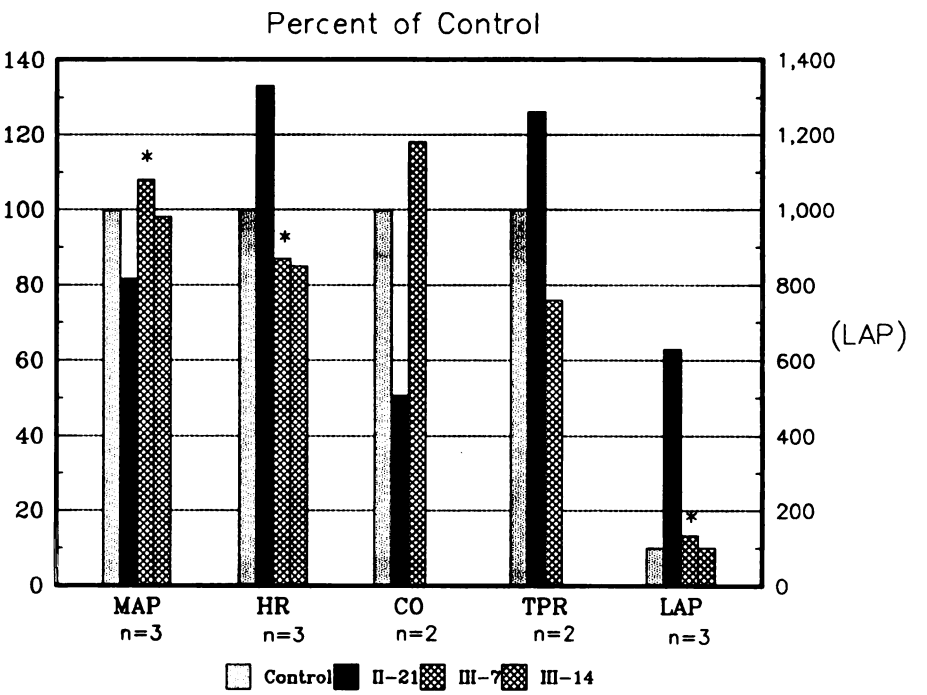


Figure 10. Phase III reversal of resting hemodynamic abnormalities.

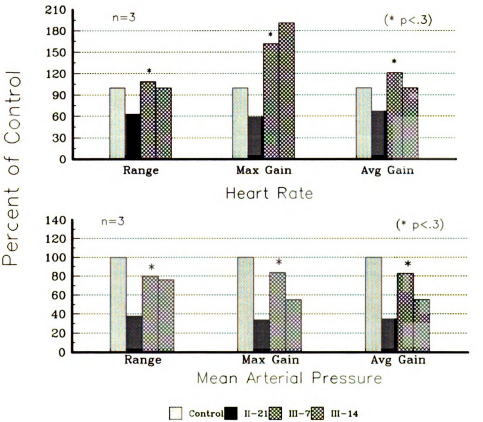


Figure 11. Phase III reversal of arterial baroreflex abnormalities.

Reflex control of blood pressure also shows a rapid recovery pattern, but without evidence of an "overshoot". These findings suggest that at least part of the baroreflex dysfunction associated with heart failure is mediated by some rapidly adapting mechanism; perhaps a neuro-endocrine mechanism. This is also suggested by the rapidity with which the impairments develop in Phase II (Figure 12). Most of the changes were evident within 3 days of failure.

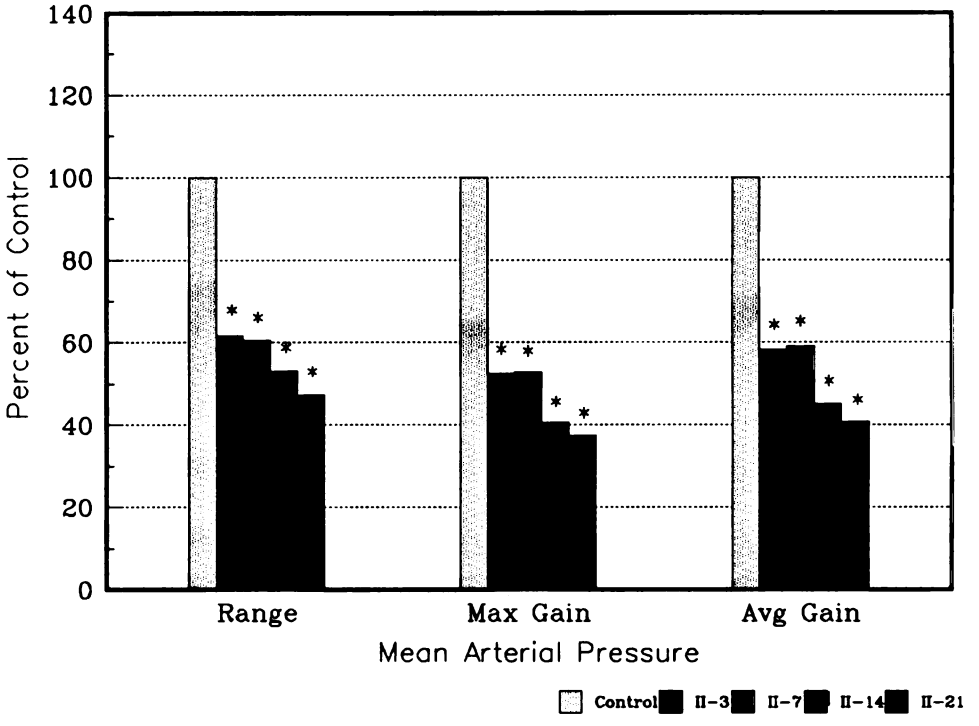


Figure 12. Time course for the development of abnormalities in the arterial baroreflex as a result of Phase II pacing. (* $p<.05$ compared to control values, day I-1)

DISCUSSION

Goals of the Study

The primary aim of this study was to determine if baroreflex control of blood pressure in conscious subjects was impaired by the presence of congestive heart failure. Two subordinate aims were 1) the characterization of reflex abnormalities as either generalized or selective for cardiac or vascular responses, and 2) to determine if reflex impairments were reversible.

With respect to the first aim, the results confirmed the findings of others, that baroreflex control of heart rate is depressed, but provided the important additional information that the regulated output of the reflex is also poorly controlled. In addition, the cause for the impairment was localized entirely to abnormalities in baroreflex control of cardiac output. Although cardiac unresponsiveness might have been expected, the distinction lies in the *absence* of any effect of heart failure on reflex control of total peripheral resistance. Although not conclusive, this provides strong support for an efferent site of reflex dysfunction, since an afferent or central site would have been expected to cause a generalized depression in both effector arms of the reflex. In addition, the results of this study provide additional evidence supporting the recent findings that the impairments in baroreflex function can be quickly reversed if the heart failure state is resolved.

Each of the goals set forth for this study was therefore met, although the level of confidence for the reversibility data was diminished by the limited number of dogs who were available for Phase III evaluations.

Comparison With Results of Previous Studies

The majority of pre-existing evidence for arterial baroreflex dysfunction in heart failure has been based on demonstrations that the slope of the heart interval-systolic pressure relationship (HI-SAP) is markedly reduced. The results of this study confirm the general hypothesis that baroreflex chronotropic control is abnormal in heart failure, yet with noticeable differences from the previous reports. The magnitude of the depression in heart rate control observed in this study was moderate with a 28% reduction in range and a 25% reduction in average gain. In contrast, the slopes of the HI-SAP relationship were reduced by as much as 95% in previous studies (avg. reduction, 82%). (White, 1981a; White, 1981b; Higgins, 1972; Ellenbogen, 1989) In addition, the major effect of heart failure in this study was to blunt the tachycardic response to baroreceptor unloading while the bradycardic response to baroreceptor hypertension was not significantly affected. Many of the previous studies were limited to HI-SAP analyses of hypertensive stimuli but those that also included hypotensive stimuli found the more profound effect to be an attenuation of the bradycardic reflex response. (White, 1981a; White 1981b) The results of this study would therefore appear to be at odds with those of previous reports. At least three possibilities exist that could potentially explain these discrepancies. First, different forms and durations of heart failure were present in these studies including a pulmonic stenosis-tricuspid avulsion model (White, 1981b; Higgins, 1972), high-output failure from an aorta-caval fistula (White, 1981a), and unspecified causes of naturally occurring heart failure in human patients (Ellenbogen, 1989). Secondly, the subjects with heart failure in these

studies tended to have higher heart rates (shorter heart intervals) than the normal controls. Since the relationship between heart rate and heart interval is nonlinear, higher resting heart rates can cause a small reduction in the sensitivity of heart rate control to appear as a large decrease in the sensitivity of heart interval control. Finally, the transient beat-to-beat analysis used in generating the HI-SAP slopes is inherently biased to fast acting parasympathetic influences with a relative insensitivity to the slower sympathetic responses. While the reflex bradycardic response in normal dogs is almost entirely parasympathetically mediated, Vatner (1974) has shown that sympathetic influences assume a greater role in dogs with heart failure. This shift in the relative roles of the two autonomic influences during heart failure could artifactually reduce the slope of the HI-SAP analysis and accentuate the apparent severity of reflex impairment.

Only White's study (1981b) also included an assessment of baroreflex control of blood pressure. In that report, he examined the range of the reflex change in blood pressure resulting from changes in isolated right carotid sinus pressures in anesthetized dogs with low-output heart failure. Although the normal ranges he observed were less than those of this study (probably due to the effects of anesthesia and the opposing influences of intact aortic baroreceptors), the magnitude of the change in reflex range for blood pressure associated with heart failure was comparable to that observed in this study (48% reduction vs 52% reduction respectively).

Significance of the Results

The large magnitude of the changes in blood pressure control suggest that the effects of heart failure on reflex function are likely to have physiologic consequences. This interpretation is also consistent with the clinical observations that patients with heart failure are unable to effectively attenuate changes in blood pressure resulting

from physical stresses such as postural changes. Using a simple control systems analysis (Appendix A), the effect of a change in open-loop reflex gain on the blood pressure buffering capacity can be estimated by the equation:

$$\frac{\Delta MAP_{hf}}{\Delta MAP_{norm}} = \frac{(1+Go)_{norm}}{(1+Go)_{hf}}$$

where delta-MAP is the change in blood pressure caused by a standardized cardiovascular disturbance and G_O is the open-loop gain of the reflex. Accordingly, the effect of the 59% reduction in average gain for blood pressure would cause a given disturbance in blood pressure to be magnified by a factor of 1.8. A physical stress that would normally cause only a 10 mmHg fall or rise in blood pressure would be magnified to an 18 mmHg disturbance in the presence of heart failure.

Another predicted consequence of abnormal reflex control of blood pressure is a greater lability of blood pressure. This of course, assumes that the frequency of occurrence and severity of spontaneous disturbances in blood pressure are similar in patients with heart failure, and that alternative stabilizing mechanisms do not compensate; assumptions yet to be refuted or confirmed. Blood pressure instability, if it exists in heart failure, could potentially aggravate the primary disturbances in blood flow to peripheral tissues and possibly accentuate the morbidity associated with CHF. Olivari (1983) suggested this after observing that those heart failure patients with blunted reflex responses to orthostatic stress experienced a higher mortality than others with intact reflex responses. Parati *et al* (1986) proposed a similar hypothesis for patients with hypertension. He separated them according to the magnitude of their average 24 hour mean blood pressure. He then sub-stratified these groups into high and low blood pressure variability groups. For almost all degrees of hypertension, the high variability patients experienced a greater incidence of target organ damage. It remains unclear whether this association involves a causal relationship. Nevertheless,

results such as these continue to raise questions regarding the importance of moment-to-moment blood pressure regulation in maintaining health, or at least limiting the progression of disease.

Another interesting question is whether the changes in baroreflex control of blood pressure are truly deleterious, or might they be some means of compensation? For example, clinical experience has clearly shown the benefits of reducing afterload in restoring the circulatory function of patients with heart failure. If so, why doesn't compensatory afterload reduction, through a mild reduction in blood pressure, occur naturally in heart failure? If a mechanism did exist for such compensation, it might also be important to prevent its attenuation by reflexes that regulate blood pressure, hence the "value" of a blunted baroreflex. The asymmetrical effects of heart failure on baroreflex function are consistent with such a theory since the reduction in reflex range and gain were evident primarily in response to baroreceptor unloading. As a result, the ability of the baroreflex to oppose a fall in blood pressure was decreased while the ability to attenuate an increase in pressure was largely unaffected by heart failure.

While perhaps a plausible strategy, the data in this study would argue against reflex changes being adaptive. This is because the impairments in reflex function were entirely manifested in cardiac responses. It would be counter-productive to limit cardiac responsiveness as a means to preserve adaptations designed to support cardiac performance. For similar reasons it seems unlikely that arterial baroreflex impairment represents an adaptive mechanism to increase sympathetic drive to a failing heart and cardiovascular system. (Hirsch, 1987)

The finding that the impairments in reflex function after 3 weeks of heart failure are partially reversible is potentially important from a clinical perspective. The reduced tolerance to physical stress and increased blood pressure lability predicted from a depression in arterial baroreflex function could contribute to the morbidity of congestive heart failure. Though true reversal of heart failure is usually limited to heart

transplant recipients or those recovering from acute, non-progressive forms of heart failure (post myocarditis or myocardial ischemia for example), the hemodynamic abnormalities associated with heart failure can often be improved substantially by medical therapy. If so, the results of this study would suggest that substantial improvement in baroreflex function would be expected to accompany the hemodynamic improvements. Whether restoration of reflex function under these circumstances would be entirely related to improved hemodynamics or possibly some direct effect of medications is a topic of current debate. For example, acute administrations of digitalis glycosides in normal dogs increases the afferent activity of arterial baroreceptors. (Quest 1971, 1974) A similar enhancement of receptor activity is assumed for chronic therapy as well since the bradycardic and hypotensive response to baroreceptor loading remains enhanced. (Reing, 1973) These direct sensitizing effects of digitalis are thought to play an important role in mediating its therapeutic effect in the treatment of patients with heart failure. (Thames, 1982)

Potential Sites of Reflex Impairment

An analysis of the type of baroreflex changes induced by heart failure provides some insight regarding likely sites of impairment. The major observations included a diminished reflex gain and a reduction in the MAX values for HR, CO, and MAP during carotid sinus hypotension. Consideration of a simple control system model of the arterial baroreflex facilitates the analysis (Figure 13).

Baroreceptors -- The "feedback" function of the reflex is provided by the carotid baroreceptors, characterized by their own sensitivity or gain and their own range of responsiveness. Could, as commonly proposed, an isolated defect in receptor function explain the observed impairment in reflex control of blood pressure? The reduction in HR_{max} CO_{max} and MAP_{max} during heart failure would not support such

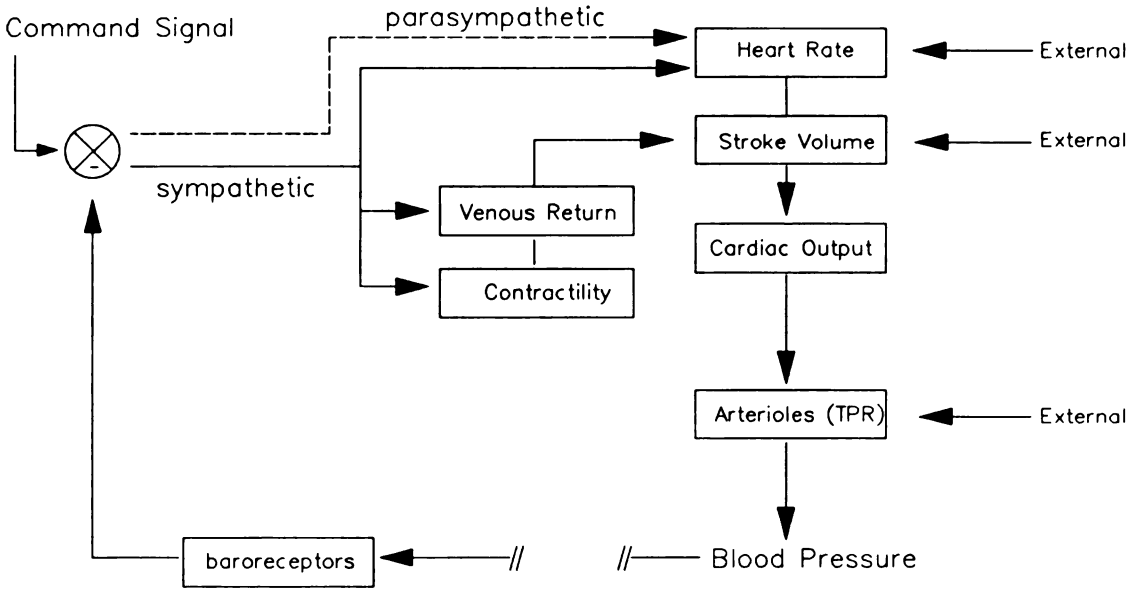


Figure 13. **Functional schematic of the arterial baroreflex control system. Effects designated as "External" represent influences that are independent of the reflex loop. Their effects are simply added to the reflex influences.**

an explanation. The maximal increase in HR, CO, and BP should be insensitive to a change in baroreceptor function since they are inactive at subthreshold pressures and therefore exert no negative feedback restraint on the reference or command signal. The MAX values for the cardiovascular variables is determined by non-receptor influences which includes the sum of the command signal effects and any external (reflex-independent) modifiers. Using this model, the reduction in HR_{max} CO_{max} and BP_{max} must be due to a mechanism *other than* baroreceptor dysfunction.

Could the baroreceptors also be adversely affected by heart failure and contribute to the decrease in reflex gain? Although reduced aortic baroreceptor sensitivity has actually been reported for this model of heart failure (Dibner-Dunlap, 1988), the results of this study do not support this as a significant contributing factor. Since the baroreceptors are common to both cardiac and vascular efferent limbs, any change in their gain or range, should become evident in both efferent components. A statistically different reduction in the reflex range and $gain_{avg}$ for TPR control was not evident in this study. Moreover, asserting the alternative hypothesis, that TPR control is not altered by heart failure, can be made with reasonable confidence (power = .88 and .91 respectfully). Thus, a significant contribution from a change in receptor range and/or gain is generally incompatible with the findings of these experiments. The exception would require a concomitant increase in reflex vascular control at some other site to counterbalance a receptor abnormality (see below).

Central Sites -- The reduction in HR_{max} CO_{max} and BP_{max} could conceivably be due to a reduction in the command signal analog of the control system model. Although the existence of an anatomic or even functional equivalent of this "baroreflex command center" has never been conclusively demonstrated, it would presumably exist proximal to the medullary autonomic efferent centers through which it acts. Because this hypothetical site is "common" to both efferent limbs, the lack of a significant change in TPR_{max} would tend to exclude this as a source of reflex

dysfunction. The differential or selective reflex impairment observed in heart failure is much more suggestive of an efferent source of reflex dysfunction. But at what level does this efferent dysfunction exist, brainstem or spinal autonomic centers, efferent nerve transmission, or an end-organ insensitivity to autonomic stimulation? The data provided in this study do not allow a definitive answer to this question. The fact that reflex control of cardiac output (presumably via reflex control of the heart, see below) is selectively impaired might suggest a parasympathetic lesion because of its preferential cardiac distribution. Presumably, depressed parasympathetic withdrawal could account for the reduced capacity to increase HR, CO, and ultimately BP in response to baroreceptor unloading. Alternatively, the observed baroreflex abnormalities could be due to a decrease in the range and gain of cardiac sympathetic nerve stimulation. Dibner-Dunlap, in a preliminary report, asserted that the "central" gain of baroreflex control of renal sympathetic nerve activity remains normal in this model of heart failure. In addition, current evidence strongly suggests that baroreflex control of sympathetic efferent activity is not end-organ specific. Arterial baroreflex control of sympathetic stimulation to both the heart and vasculature appears to arise from a common medullary site, the C_1 area of the rostral ventro-lateral medulla. (Loewy, 1986; Reis, 1986) This is also supported by neurophysiologic studies of central baroreflex modification. Interventions that increase or decrease reflex sympathetic activity, characteristically do so to both the heart and vasculature simultaneously, suggesting a common origin. (Reis, 1986) As a result, a central sympathetic efferent "lesion" would require a second "lesion", an increase in vascular sympathetic sensitivity, to maintain the normal TPR responses observed in this study.

Forster's (1989) results would seem to support such a "two-lesion" hypothesis since she reported an enhanced vascular responsiveness to alpha agonists *in vitro*. However, when *in vivo* vascular responsiveness has been examined in this model of

heart failure, the results indicate either no change (Kaiser, 1989), or even a slight depression (Wilson, 1988) in vascular sensitivity to sympathetic nerve stimulation, norepinephrine infusions, and nitroglycerin applications.

The unlikelihood of a central site of reflex dysfunction would tend to exclude those potential inhibitory influences thought to act via central interactions. Thus, increased circulating levels of atrial natriuretic peptides, vasopressin, and angiotensin II as well as enhanced cardiopulmonary receptor activity would be unlikely mechanisms for the reflex impairment observed. Evidence against a major role for ventricular receptor activation in heart failure is also suggested by the lack of the generalized pattern of reflex impairment (both cardiac output and TPR) characteristically seen when ventricular receptors are stimulated chemically. (Denison, 1987)

Efferent Sites -- For the reasons presented, the preferential impairment in reflex cardiac output control during heart failure is most supportive of a cardiac site as the major cause for reflex dysfunction. It should be pointed out though, that a depression in reflex control of the heart is not essential, nor necessarily totally responsible, for defective cardiac output control. Other reflex effects on preload, for example, could be contributory. That the heart is at least a component of this effect is clearly shown by the decreased range and gain of heart rate control. Defective control of stroke volume is also suggested. Although not statistically significant ($p = .06$), the magnitude of the impairment in reflex control of heart rate was always less than the magnitude of impairment for cardiac output, implicating defective stroke volume responses. This is also shown by the stimulus-response curves generated during pacing in which heart failure depresses the residual range of cardiac output and ultimately blood pressure. Any change in reflex cardiac output responses under these circumstances must be due to changes in stroke volume. The ability to increase stroke volume in response to baroreceptor hypotension is mediated, at least partially by an increase in contractility. Shimizu (1980), for example demonstrated an increase in left ventricular dp/dt in

response to bilateral carotid occlusion in anesthetized cats that was partially abolished by cardiac sympathetectomy and completely abolished by *B*-adrenergic blockade. Hainsworth, and others have reported similar findings in both anesthetized and conscious animals and have also excluded a cerebral ischemic response as a cause for the observed inotropic response. (Hainsworth, 1972; Aylward, 1985)

The importance of reflex-mediated changes in venous compliance and venous return to the changes in cardiac output are more controversial. Shoukas (1973) continues to assert, primarily on theoretical grounds, that the increase in venous return accompanying carotid sinus hypotension is important in maintaining the cardiac output response. Browse and Donald (1966) however, convincingly showed that the actual magnitude of this increase in venous return is relatively small in dogs and that the reflex cardiac output and pressor responses are not changed when this increase in central blood volume is experimentally diverted. Nevertheless, blunted passive or active (adrenergic) changes in venous compliance might assume greater relative importance in subjects with heart failure and therefore cannot be totally excluded as a possibility.

Time Course and Potential Mechanisms for Reduced Cardiac Responsiveness

The reflex impairment associated with this model of congestive heart failure develops rapidly and resolves quickly if heart failure is reversed. The capacity for partial reversal of reflex dysfunction within days is in contrast to that reported by White (1981) in dogs with high-output heart failure. He found sustained depressions in the HI-SAP slopes for up to 8 months after surgical closure of an aorta-caval fistula. He proposed that structural damage to the baroreceptors and/or vessel walls (aorta, carotid sinus) was the most likely explanation for this finding. Others have speculated

that the increased stroke volume and pulse pressure in this model of high-output failure may have damaged aortic receptors, a situation unlikely to occur in low-output failure.

It could be argued that the relatively short duration of failure in this study was not sufficient to induce long-lasting reflex impairments. However, Ellenbogen (1989) recently reported a similar time course for recovery of baroreflex heart rate responses (atrial remnant) after cardiac transplantation in patients with chronic end-stage heart failure. Structural changes, particularly in the heart, may still be contributory but the rapidity with which the major reflex deficits apparently develop and resolve suggests an important rapidly adapting mechanism, such as a neural endocrine or biochemical change.

This study does not address these issues although existing evidence suggests several possibilities. As mentioned, the observed abnormalities in heart rate control are potentially due to either defective parasympathetic control, ineffective sympathetic nerve activity, or some combination of both. A reduction in the cardiac responsiveness to these neural inputs must also be considered. The possibility that autonomic neurotransmitter release is reduced in failing hearts has been suggested in studies documenting a reduction in the cardiac response to experimental sympathetic nerve stimulation. (Covell, 1966) The reduction in myocardial norepinephrine content and relevant biosynthetic enzyme activity has also fostered the idea that sympathetic neurotransmitter preparation and/or release is impaired in heart failure. (Chidsey 1964, 1965; Pool, 1967; Sole, 1977) There may also exist, a reduction in the myocardial cellular response to released norepinephrine. Down regulation and/or a reduction in the number of beta-adrenergic receptors in failing hearts has been well publicized. (Bristow, 1982; Vatner, 1985) Whether post-receptor responses are also abnormal remains uncertain. Erne (1988) documented attenuated cardiac responses to isoproterenol infusions in men with advanced heart failure of different etiologies. The

heart rate responses to intravenous forskolin infusions however, were normal suggesting an intact post-receptor mechanism for cardiac stimulation. Newman (1978) found a similar reduction in responses to beta-agonists but also found a depression in the length-tension relationship in response to glucagon, a non-adrenergic stimulant of cAMP.

Evidence for other humoral influences on cardiac function is also slowly starting to emerge. Exogenous vasopressin can depress cardiac output in sino-aortic denervated animals. This effect appears to be a direct effect on the myocardium rather than just a change in afterload since the magnitude of cardiac depression is much greater than for equivalent pressor doses of phenylephrine. (Webb, 1986) Conceivably, the high circulating levels of vasopressin present in heart failure might have a similar depressant effect. While this might exert a depressant effect on resting cardiac performance, it would not be a likely explanation for the abnormalities in reflex function seen in heart failure since vasopressin sensitizes reflex function in normal subjects and acts as sites (receptors and central) that are inconsistent with the selective impairment observed in this study.

Exogenous atrial natriuretic peptides are also increased in congestive heart failure. Interestingly, exogenous administrations of ANP has been observed to reduce the tachycardic but not the bradycardic response to baroreflex manipulations, a finding similar to that observed in this study. (Ebert, 1988) Nevertheless, the presumed central site of action of ANP on baroreflex function mentioned earlier would tend to exclude it as a significant contributor to baroreflex dysfunction in this model.

Heart failure can also be associated with increased circulating levels of natural opiates. The evidence for a cardiovascular regulatory role of these opiates is also slowly increasing. Administration of opiate receptor antagonists such as nalmefene to dogs with right heart failure for example, results in a significant increase in cardiac output and heart rate that is sympathetically mediated. (Liang, 1987) Another recent

brief report describes partial restoration of baroreflex control of heart rate in heart failure after the administration of the mu-opiate antagonist, naloxone. (Sakamoto, 1988) The mechanism may involve an opiate-mediated presynaptic inhibition of sympathetic norepinephrine release although central mechanisms have also been postulated. (Dubocovich, 1980)

Angiotensin II enhancement of baroreflex function has already been mentioned although these effects may be species-dependent. Somewhat surprisingly, several studies have suggested that captopril and other converting enzyme inhibitors can actually increase the sensitivity of baroreflex control of heart rate in humans with naturally occurring heart disease. (Mancia, 1982; Ibsen, 1983;) This would suggest a depressant effect of angiotensin II. These observations are not universal though, since other investigators have reported opposing results. (Heavy, 1978)

Changes in the biochemistry of cardiac cellular function could also cause cardiac depression with a time course similar to that observed in this study. In response to an increase in load, myocardial protein can increase by as much as 50% within the first 48 hours. Mitochondrial cytochrome proteins initially increase, but within 3 days, their concentrations per gram of cardiac protein and cardiac weight are reduced. (Rabinowitz, 1973) Although dogs and humans apparently have a limited capacity to shift to different myosin isoenzymes in response to cardiac load, a reduction in total myofibrillar protein has been reported in naturally occurring forms of myocardial failure. (Swynghedauw, 1986; Pagani, 1988) Changes in intracellular calcium kinetics are yet another potential mechanism for rapid development of cardiac dysfunction and perhaps reflex function. Calcium uptake by the sarcoplasmic reticulum for example, can be severely attenuated within minutes to hours of ischemic damage to the myocardium.

Whether these neural, endocrine, or biochemical changes are reversible and whether they play any role in the baroreflex impairments observed in this model of heart failure remains speculative at this point.

Whatever the mechanism involved, the results of this study suggest that it originates in the heart itself rather than some other site in the baroreflex arc. Although not definitive, the results do not support the common assertion that heart failure-related impairments in baroreflex function are related to some fundamental derangement in the neural elements of the reflex. If so, is the reflex really impaired or does this merely represent end-organ dysfunction? Can the two be considered separate? Hypothetically, if there were no end-organ response to the neural reflex components, there could be no homeostatic reflex adjustments of the circulation. This illustrates the necessity of including the end-organs as components in the overall reflex. As a result, even in the absence of significant neural impairments, a depression in end-organ responsiveness can be interpreted as a cause for baroreflex dysfunction.

SUMMARY

Impairment in arterial baroreflex regulation of blood pressure has been assumed for years based on evidence that baroreflex control of heart rate was depressed. However, heart rate responses alone can be unreliable in predicting overall reflex function, and in predicting the characteristics of reflex control of the other efferent components such as cardiac output and total peripheral resistance. The results of this study using an open-loop experimental design confirm previous reports of a depression in arterial baroreflex control of heart rate in conscious dogs with heart failure. The results of this study also provide additional information not previously available:

1) Congestive heart failure rapidly induces a dramatic depression in the open-loop gain and range of carotid baroreflex control of mean arterial pressure in conscious dogs.

2) This depression in reflex control of blood pressure is due to a depression in reflex control of cardiac output. Baroreflex control of total peripheral resistance is not affected in this model of heart failure.

3) The changes in arterial baroreflex function associated with heart failure develop quickly and resolve rapidly as dogs recover from heart failure. This suggests a rapidly adapting mechanism such as a neural, endocrine, or biochemical change (as opposed to a structural change) as the predominant cause for reflex impairment.

APPENDIX

APPENDIX A

Calculation of the Degree to Which Cardiovascular Disturbances are Magnified in Heart Failure as a Result of a Decrease in Open-Loop Baroreflex Gain

The capacity of the arterial baroreflex to attenuate the magnitude of a disturbance in blood pressure is a function of the range and gain of the reflex. If the magnitude of the disturbance is relatively small compared to the range of the reflex, less than 30% for example, then only the gain of the reflex is important in determining the degree of attenuation. Since the gain of the reflex changes as a function of the prevailing blood pressure in the closed-loop state, the average gain will be used in this example for simplicity.

In the closed-loop state, any cardiovascular disturbance that alters blood pressure is sensed by the baroreceptors which initiate rapid reflex compensations to attenuate the magnitude of this disturbance. The degree to which a relatively small disturbance (defined above) is attenuated is related to the open-loop gain (G_o) of the reflex according to the following equation. (Houk, 1980)

$$(1 + G_o) = \frac{MAP_{dist}}{\Delta MAP} \qquad \text{Equation 1}$$

where MAP_{dist} refers to the magnitude of the disturbance (the change in blood pressure that would occur in the absence of any baroreflex compensation) and delta MAP refers to the change in blood pressure actually observed (including the effects of baroreflex compensation). Rearranging Equation 1 gives:

$$(1 + G_o)(\Delta MAP) = MAP_{dist} \qquad \text{Equation 2}$$

If a standard blood pressure disturbance (MAP_{dist}) is applied to a representative dog in both normal (avg. gain = -2.7) and heart failure (avg. gain = -1.1) condition then:

$$(1 + Go_{norm})(\Delta MAP_{norm}) = MAP_{dist} = (1 + Go_{hf})(\Delta MAP_{hf}) \qquad \text{Equation 3}$$

A final rearrangement gives:

$$\frac{(1 + Go_{norm})}{(1 + Go_{hf})} = \frac{(\Delta MAP_{hf})}{(\Delta MAP_{norm})} \qquad \text{Equation 4}$$

Substituting the known values for the group averaged day II-21 gains in this study gives:

$$\frac{-3.7}{-2.1} = \frac{(\Delta MAP_{hf})}{(\Delta MAP_{norm})} \qquad \text{Equation 5}$$

or (rounding to 2 significant digits)

$$1.8 = \frac{(\Delta MAP_{hf})}{(\Delta MAP_{norm})}$$

Thus, the observed change in blood pressure in response to a standard disturbance would be 1.8 times greater in heart failure than under normal conditions.

LIST OF REFERENCES

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Abraham A: The structure of baroreceptors in pathologic conditions in man. in Baroreceptors and Hypertension. P. Kezdi, ed. Pergamon Press Ltd., Oxford England, 1967.

Angell-James JE, George MJ: Carotid sinus baroreceptor reflex control of the circulation in medial sclerotic and renal hypertensive rabbits and its modification by aortic baroreceptors. Circ Res, 47:890, 1980.

Armstrong PW, Stopps TP, Ford SE, DeBold AJ: Rapid ventricular pacing in the dog: Pathophysiologic studies of heart failure. Circ, 74:1075, 1986.

Aylward P, McRitchie R, West M, Chalmers J: Relative roles of vagal and sympathetic effector mechanisms in the baroreflex control of myocardial contractility in conscious rabbits. Pflugers Arch, 403:21, 1985.

Bagshaw RJ, Peterson LH: Sympathetic control of the mechanical properties of the canine carotid sinus. Am J Physiol, 222:1462, 1972.

Bernhardson CS: Type I error rates when multiple comparison procedures follow a significant F test of ANOVA. Biometrics, 31:229, 1975.

Bolter C, Ledsome J: Influence of cervical sympathetic nerve stimulation on carotid sinus baroreceptor afferents. Experentia 36:1301, 1980.

Bristow MR, Ginsburg MR, et al: Decreased catecholamine sensitivity and *B*-adrenergic receptor density in failing human hearts. N Eng J Med, 307:205, 1982.

Browse N, Donald D, Shepherd J: Role of the veins in the carotid sinus reflex. Am J Physiol, 210:1424, 1966.

Campese VM, Romoff M, DeQuattro V, Massry SG: Relationship between plasma catecholamines, plasma renin activity, aldosterone, and arterial pressure during postural stress in normal subjects. J Lab Clin Med, 95:927, 1980.

Chidsey C, Braunwald E, Morrow A: Catecholamine excretion and cardiac stores in congestive heart failure. Am J Med, 39:442, 1965.

Chidsey C, Kaiser G, Sonnenblick E, Spann J, Braunwald E: Cardiac norepinephrine stores in experimental heart failure in dogs. J Clin Invest, 43:2386, 1964.

Chidsey CA, Braunwald E, Morrow AG, Mason DT: Myocardial norepinephrine concentrations in man: Effects of reserpine and congestive heart failure. N Eng J Med, 269:653, 1963.

Cody RJ, Franklin KW, Kluger J, Laragh JH: Mechanisms governing the postural response and baroreceptor abnormalities in chronic congestive heart failure: Effects of acute and long term converting enzyme inhibition. Circ, 66:135, 1982.

Coleman HN, Taylor RR, Pool PE, Whipple GH, et al: Congestive heart failure following chronic tachycardia. Am H J, 81:790, 1971.

Cottle MK: Degeneration studies of primary afferents of IX and Xth cranial nerves in the cat. J Comp Neurol, 122:329, 1964.

Covell JW, Chidsey CA, Braunwald E: Reduction in cardiac response to postganglionic sympathetic stimulation in experimental heart failure. Circ Res, 19:51, 1966.

Cowley AW, Merrill D, Osborn J, Barber BJ: Influence of vasopressin and angiotensin on baroreflexes in dogs. Circ Res, 54:163, 1984.

Cox RH, Bagshaw RJ: Influence of anesthesia on the response to carotid hypotension in dogs. Am J Physiol, 237:H424, 1979.

Dallal GE: Survival: A Supplementary Module for SYSTAT. Evanston IL, Systat Inc., 1988.

Denison AL, Hull SS, Stephenson RB, Cornish KG, Zucker IH: Left ventricular receptor stimulation attenuates baroreflex control of peripheral resistance in conscious dogs. Circ, 72:III-224, 1985.

Denison AL: Interaction of the left ventricular receptor reflex with the carotid baroreceptor reflex in conscious dogs. Doctoral Dissertation, Michigan State University, Department of Physiology, 1987.

Dibner-Dunlap M, Thames M: Arterial baroreflex control of renal sympathetic nerve activity is preserved in heart failure. Circ, Supp 78:II-365, 1988.

Dubocovich M, Langer S: Pharmacological differentiation of presynaptic inhibitory alpha-adrenoceptors and opiate receptors in the cat nictitating membrane. Br J Pharmac, 70:383, 1980.

Ebert TJ, Cowley AW: Atrial natriuretic factor attenuates carotid baroreflex mediated cardioacceleration in humans. Am J Physiol, 254:R590, 1988.

Ebert TJ, Kotrly KJ, et al: Halothane anesthesia attenuates cardiopulmonary baroreflex control of peripheral resistance in humans. Anesthesiology, 63:668, 1985.

Ellenbogen KA, Mohanty PK, Szentpetery S, Thames M: Arterial baroreflex abnormalities in heart failure. Circ, 79:51, 1989.

Erne P, Lipkin D, Maseri A: Impaired beta-adrenergic receptor and normal postreceptor responsiveness in congestive heart failure. Am J Cardiol, 61:1132, 1988.

Forster C, Carter S, Armstrong P: Vascular smooth muscle responsiveness to noradrenaline and phenylephrine following experimental heart failure in dogs. Cardiovas Res, 23:489, 1989.

Francis G: Neuroendocrine manifestations of congestive heart failure. Am J Cardiol, 62:9A, 1988.

Goldsmith SR, Francis GS, Levine TB, Cowley AW, Cohn JN: Impaired response of plasma vasopressin to orthostatic stress in patients with congestive heart failure. J Am Coll Card, 2:1080, 1983.

Greenberg TT, Richmond WH, Stocking RA, et al: Impaired atrial receptor responses in dogs with heart failure due to tricuspid insufficiency and pulmonary artery stenosis. Circ Res, 32:424, 1973.

Guo GB, Sharabi FM, Abboud FM, Schmid PG: Vasopressin augments baroreflex inhibition of lumbar sympathetic nerve activity in rabbits. Circ, 66:Supp II-35, 1982.

Guo GM, Thames MD, Abboud FM: Arterial baroreflexes in renal hypertensive rabbits: selectivity and redundancy of baroreceptor influence on heart rate, vascular resistance, and lumbar sympathetic nerve activity. Circ Res, 53:224, 1983.

Hainsworth R, Karim F: Left ventricular inotropic and peripheral vasomotor responses from independent changes in pressure in the carotid sinuses and cerebral arteries in anesthetized dogs. J Physiol, 228:139, 1973.

Higgins CB, Vatner SF, Eckberg DL, Braunwald E: Alterations in the baroreceptor reflex in conscious dogs with heart failure. J Clin Invest, 51:715, 1972.

Hirsh AT, Dzau V, Creager MA: Baroreceptor function in congestive heart failure: Effect on neurohumoral activation of regional vascular resistance. Circ Supp IV:IV-36, 1987.

Houk JC: Homeostasis and control principles. In: Medical Physiology. Fourteenth edition. ed. Mountcastle, V.B., CV Mosby Co., St. Louis, pg. 246, 1980.

Hull SS, Stephenson RB: Central angiotensin II augments baroreflex gain in conscious dogs. Circ, 72:III-18, 1985.

Ibsen H, Egan B, Osterziel K, Vander A, Julius S: Reflex hemodynamic adjustments and baroreflex sensitivity during converting enzyme inhibition with MK-421 in normal humans. Hypertension, 5:I184, 1983.

Ishikawa N, Kallman CH, Sagawa K: Rabbit carotid sinus reflex under pentobarbital, urethane, and chloralose anesthesia. Am J Physiol, 246:H696, 1984.

Kassis E: Cardiovascular response to orthostatic tilt in patients with severe congestive heart failure. Cardiovas Res, 21:363, 1987.

Keith IC, Kidd C, Malpus CM, Penna PE: Reduction of baroreceptor impulse activity by sympathetic nerve stimulation. J Physiol, 238:61P, 1974.

Kendall MG, Stuart A: The Advanced Theory of Statistics, Vol 2, 3rd ed, New York: Hafner Publishing Co, 1973.

Lam RL, Tyler HR: Electrical responses evoked in the visceral afferent nucleus of the rabbit by vagal stimulation. J Comp Neurol, 97:21, 1952.

Levine TB, Francis GS, Goldsmith SR, Cohn JN: The neurohumoral and hemodynamic response to orthostatic tilt in patients with CHF. Circ, 57:1070, 1983.

Liang C, Imai N, Stone C, Woolf P, Kawashima S, Tuttle R: The role of endogenous opioids in congestive heart failure: effects of nalmefene on systemic and regional hemodynamics in dogs. Circ, 75:443, 1987.

Mancia G, Parati G, Pomidossi G, Grassi G, et al: Modification of arterial baroreflexes by captopril in essential hypertension. Am J Cardiol, 49:1415, 1982.

Moe G, Stopps T, Howard R, Armstrong PW: Early recovery from heart failure: Insights into the pathogenesis of experimental chronic pacing-induced heart failure. J Lab Clin Med, 172:426, 1988.

Mohanty PK, Arrowood JA, Ellenbogen KA, Thames MD: Neurohumoral and hemodynamic effects of lower body negative pressure in patients with congestive heart failure. Am H J, 118:78, 1989.

Motulsky H, Ranshas LA: Fitting curves to data using nonlinear regression: a practical and nonmathematical review. FASEB J, 1:365, 1987.

Munch P, Thoren P, Brown A: Dual effects of norepinephrine and mechanism of baroreceptor stimulation. Circ Res, 61:409, 1987.

Newman WH: A depressed response of left ventricular contractile force to isoproterenol and norepinephrine in dogs with congestive heart failure, Am H J, 93:216, 1977.

Newman WH: Volume overload heart failure: length-tension curves, and response to B-agonists, calcium, and glucagon. Am J Physiol, 735:H690, 1978.

Olavari MT, Levine T, Cohn J: Abnormal neurohumoral responses to nitroprusside infusions in congestive heart failure. J Am Coll Card, 2:411, 1983.

Pagani E, Alousi A, Grant A, Older T, Dziuban S, Allen P: Changes in myofibrillar content and Mg-ATPase activity in ventricular tissue from patients with heart failure caused by coronary artery disease, cardiomyopathy, or mitral valve insufficiency. Circ Res, 63:380, 1988.

Parati G, Pomidossi G, Bertinieri G, DiRienzo M, Mancia G: Blood Pressure variability: Its mechanisms and its clinical implications. in Neural Mechanisms and Cardiovascular Disease. B. Lown, ed. Vol 5, Springer-Verlag, New York, 1986.

Pool PE, Covell J, Levitt M, Gibb J, Braunwald E: Reduction of cardiac tyrosine hydroxylase activity in experimental congestive heart failure. Its role in depletion of cardiac norepinephrine stores. Circ Res, 20:349, 1967.

Quest JA, Gillis R: Carotid sinus reflex changes produced by digitalis. J Pharm Exp Ther, 177:650, 1971.

Quest JA, Gillis R: Effect of digitalis on carotid sinus baroreceptor activity. Circ Res, 35:247, 1974.

Rabinowitz M: Protein synthesis and turnover in normal and hypertrophied heart. Am J Cardiol, 31:202, 1973.

Rapundalo S, Briggs FN, Feher J: Effects of ischemia on the isolation and function of canine cardiac sarcoplasmic reticulum. J Mol Cell Cardiol, 18:837, 1986.

Reing C, Thibodeaux H, Gillis R, Kot P: Influence of baroreceptor reflexes in cardiovascular responses of the dog to acetylstrophanthidin. J Pharm Exp Ther, 184:641, 1973.

Riegger GAJ, Elsner D, Kromer EP, et al: Atrial natriuretic peptide in congestive heart failure in the dog: Plasma levels, cyclic guanosine monophosphate, ultrastructure of atrial myoendocrine cells, and hemodynamic, hormonal, and renal effects. Circ, 77:398, 1988.

Riegger GAJ, Liebau G, Holzchuh M, et al: Role of renin-angiotensin system in the development of congestive heart failure in the dog as assessed by chronic converting enzyme blockade. Am J Cardiol, 53:614, 1984.

Riegger GAJ, Liebau G: The renin-angiotensin-aldosterone system, antidiuretic hormone, and sympathetic nerve activity in an experimental model of congestive heart failure in the dog. Clin Sci, 62:465, 1982.

Rowell LB: Adjustments to upright posture and blood loss. in Human Circulation, Regulation During Physical Stress, Oxford Univ Press, New York, 1986.

Sakamoto S, Liang C: Partial restoration of baroreflex sensitivity by naloxone in heart failure. Circ, Supp 78:II-366, 1988.

Sampson S, Mills E: Effects of sympathetic stimulation on discharges of carotid sinus baroreceptors. Am J Physiol, 218:1650, 1970.

Scher AM, Your AC: Reflex control of heart rate in the unanesthetized dog. Am J Physiol, 218:780, 1970.

Schmid PG, Guo GB, Abboud FM: Different effects of vasopressin and angiotensin II on baroreflexes. Fed Proc, 44:2388, 1985.

Shimizu T, Bishop V: Role of carotid sinus and cardiopulmonary reflexes on left ventricular dP/*dt* in cats. Am J Physiol, 238:H93, 1980.

Shoukas A, Sagawa K: Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. Circ Res, 33:22, 1973.

Sinoway LI, Minott JR, Davis D, et al: Delayed reversal of impaired vasodilation in CHF after heart transplantation. Am J Cardiol, 61:1076, 1988.

Sleight P, Widdicombe JG: Action potentials in fibers from receptors in the epicardium and myocardium of the dog's left ventricle. J Physiol, 181:235, 1965.

Smyth HS, Sleight P, Pickering GW: Reflex regulation of arterial pressure during sleep in man: A quantitative method of assessing baroreflex sensitivity. Circ Res, 24:109, 1969.

Sole M, Kamble A, Hussain M: A possible change in the rate limiting steps for cardiac norepinephrine synthesis in the cardiomyopathic syrian hamster. Circ Res, 44:814, 1977.

Stephenson RB, Donald DE: Reflexes from isolated carotid sinuses of intact and vagotomized conscious dogs. Am J Physiol, 238:H815, 1980.

Stephenson RB, Donald DE: Reversible vascular isolation of carotid sinuses in conscious dogs. Am J Physiol, 238:H809, 1980.

Swynghedaun B: Adaptation of muscle contractile proteins. Physio Rev, 66:710, 1986.

Teo KK, Man GC, Kappagoda CT: Interaction of left atrial receptors and carotid sinus baroreceptors on heart rate in the dog. Am J Physiol, 248:H631, 1985.

Thames MD, Miller B, Abboud FM: Sensitization of vagal cardiopulmonary baroreflexes by chronic digoxin. Am J Physiol, 243:H815, 1982.

Thoren P: Characterization of left ventricular receptors with non-medullated vagal afferents in the cat. Circ Res, 40:231, 1977.

Tomomatsu E, Nishi K: Increased activity of carotid sinus baroreceptors by sympathetic stimulation and norepinephrine. Am J Physiol, 240:H650, 1981.

Undesser KP, Hasser E, Johnson AK, Haywood JR, Bishop VS: Lesions of the area postrema prevent enhancement of arterial baroreflex inhibition of sympathetic activity by vasopressin in conscious rabbits. Fed Proc, 43:1067, 1984.

Vatner DE, Vatner SF, Fuji AM, Homcy CJ: Loss of high affinity cardiac *B*-adrenergic receptors in dogs with heart failure. J Clin Invest, 76:2259, 1959.

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, 8:153, 1974.

Whipple GH, Sheffield LT, Woodman LT, Theophilis EG, Friedman S: Reversible congestive heart failure due to rapid ventricular stimulation of the normal heart. Proc New Eng Cardiov Soc, 20:39, 1962

White CW: Abnormalities in baroreflex control of heart rate in canine heart failure. Am J Physiol, 204:H793, 1987.

Wilkinson L: Nonlinear Module, in SYSTAT: The System For Statistics. Evanston IL, Systat Inc. 1988.

Wilson JR, Douglas P, Hickey WF, Lanoce V, Ferraro N: Experimental congestive heart failure produced by rapid ventricular pacing in the dog: Cardiac effects. Circ, 75:857, 1987.

Wilson JR, Matthai W, Lanoce V, Frey M, Ferraro N: Effect of experimental heart failure on peripheral sympathetic vasoconstriction. Am J Physiol, 254:H727, 1988.

Wood JE, Litter J, Wilkins RW: Peripheral venoconstriction in human congestive heart failure. Circ, 13:524, 1956.

Zelis R, Delea CS, Coleman HN, Mason DT: Arterial sodium content in experimental congestive heart failure. Circ, 41:213, 1970.

Zelis R: The contribution of local factors to the elevated venous tone of congestive heart failure. J Clin Invest, 54:219, 1974.

Zucker IH, Niebauer MJ, Holmberg MJ: Aortic baroreceptor characteristics in dogs with chronic volume overload. The Physiologist, 26:A-103, 1983.