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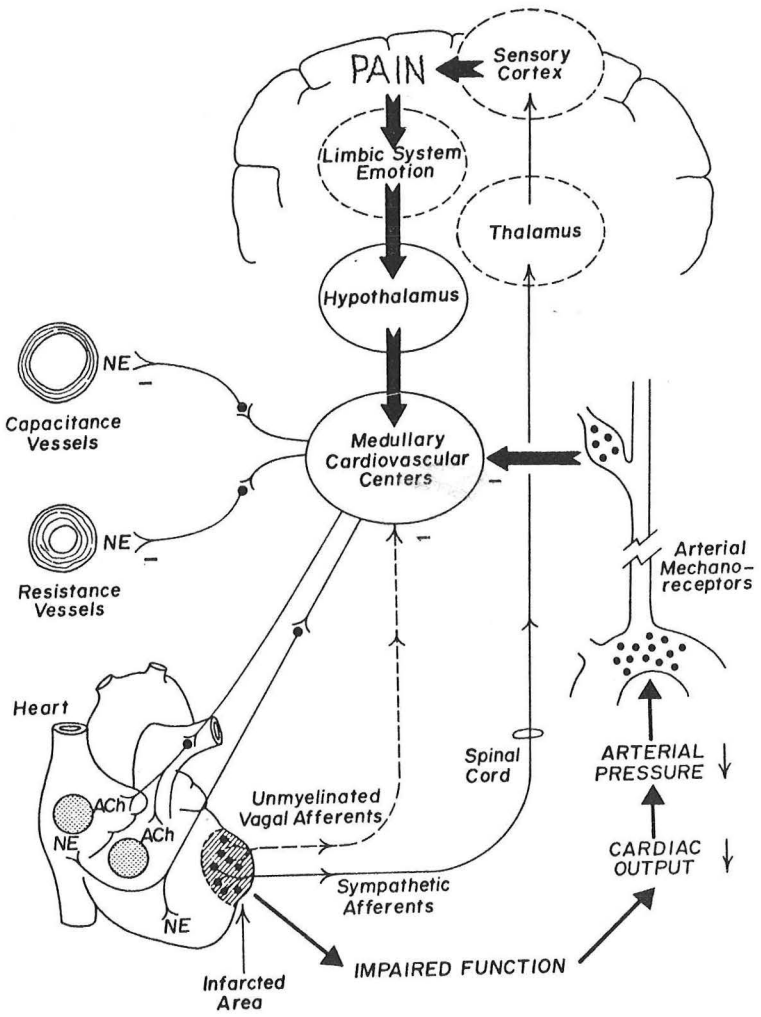
CARDIAC RECEPTORS, THEIR FUNCTION IN HEALTH AND DISEASE



MEDICAL GRAND ROUNDS

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I. INTRODUCTION

Humans have evolved to attain an upright posture. This position affords the species certain advantages and certain disadvantages. For early humans the advantages were an increased ability to see predators because of a higher plane of their eye sight above the ground as well as an increased agility so that they were at home in the trees, on land, or in the water. For the purposes of the present discussion, I will be concerned more with the disadvantages that the upright posture poses. A major disadvantage is the pooling of blood in our lower extremities. This situation occurs mainly because the capacitance vessels of the body are placed below the level of the heart. To cope with this pooling of blood, we have achieved homeostatic control mechanisms which tend to decrease the amount of blood pooling. The first of these is the muscle pump which, when activated, tends to compress the veins which have valves and therefore direct the venous blood back toward the heart. A second set of homeostatic mechanisms, which I discussed last time that I gave grand rounds, came from the arterial baroreceptors. These receptors sense a decrease in blood pressure secondary to pooling of blood in the lower extremities and will tend to activate certain cardiovascular adjustments to increase the blood pressure back toward normal. A third major set of compensatory mechanisms come from the cardiopulmonary, or what are sometimes called the low pressure baroreceptors. The receptors are located in the pulmonary artery and in the heart. When these receptors are unloaded they will reflexly activate the cardiovascular system to restore blood pressure and plasma volume back to normal. It is the latter control mechanism, the cardiac receptors, which will be discussed in detail in this monograph.

II. HISTORY, THE VON BEZOLD-JARISH REFLEX

It has been stated by White (1957) that William Harvey demonstrated to Charles I that the heart was insensitive to pain. He did this by showing that the son of Count Montgomery, a young man who had survived the chest wall injury that left his heart exposed, did not experience discomfort when his heart was pinched or pricked. However, in 1866 Cyon and Ludwig concluded that there were in fact depressor nerves originating from pressure sensitive nerve endings of the heart and that these endings permitted the heart "to reflexly regulate the resistance which it itself has to overcome."

In 1867 von Bezold and Hirt observed that blood pressure and heart rate fell following the intravenous injection of veratrine. These effects were abolished by vagotomy, demonstrating the reflex nature of this response. Later, Jarish and Richter (1939) demonstrated that this reflex came from the ventricular myocardium. In 1947 Dawes confirmed that the greatest affect of this reflex occurred with selective injection into the left anterior descending or the left circumflex coronary arteries. It was not until 1955 that Paintal demonstrated that the most likely receptors to be stimulated by the veratrum alkaloids were the ventricular mechanoreceptors, although he did note that approximately a third of the atrial receptors were also stimulated by these drugs. Somewhat later Dabholkar (1961) demonstrated that direct injection of veratradine into the artery supplying the left atrium of the dog would cause a reflex bradycardia and hypotension. Part of this Bezold-Jarish response involved a reflex

parasympathetic coronary vasodilation (Feigl, 1975). It's likely that part of this response also orginated from the region of the coronary sinus (Juhász-Nagy and Szentivanyi, 1961). Very recently in the conscious dog, Zucker and Cornish (1981) have demonstrated that veratradine injection into the coronary artery causes bradycardia, hypotension and systemic vasodilation. These investigators did not observe a significant change in myocardial contractility. The mechanisms of the decrease in systemic vascular resistance was sympathetic withdrawal as well active cholinergic vasodilation.

Daly and Verney (1926-27) were among the first to demonstrate that an increase in intraventricular blood pressure or, alternatively, a negative pressure applied to the ventricles, caused a reflex slowing of the heart when the aortic pressure was maintained constant. They demonstrated the reflex nature of this response by severing the vagus nerves and abolishing it. Adrian in 1933 was the first to record the discharge of afferent fibers which innervated stretch receptors with a cardiac rhythm. He was able to distinguish these receptors from the aortic depressor fibers. Amann and Schaefer (1943) were also among the very first to record from nerve fibers in the right atrium. Whitteridge (1948) recorded the impulse activity of afferent fibers from the atria and pulmonary veins in the vagus nerves of dogs. He was the first to demonstrate that these fibers were C fibers since they survived cooling down to 4°C, a process which blocks the myelinated but not the unmyelinated sensory nerve fibers.

III. METHODS USED TO STUDY CARDIAC RECEPTORS

There have been several methods devised to study cardiac receptors. These include: (1) Anatomical and histological studies. (2) Studies of nerve recordings of afferent fibers from cardiac receptors. and (3) Studies of reflex cardiovascular responses to either stimulation of the afferent nerve directly or, alternatively, stimulation of the receptive area by physiological or pharmacological means. An additional method used to study the reflex responses to the cardiac receptor stimulation has been to ablate or reversibly interrupt the afferent neural discharge.

Studies of the anatomy of cardiac receptors have demonstrated that there are two major types of endings within the heart. These endings are in the form of either complex unencapsulated endings of the either the diffuse or compact type, or the nerve net (Nettleship, 1936; Nonidez, 1941; Sleight and Widdicombe, 1965a; Whitteridge, 1948; Coleridge et al, 1957; Paintal, 1963a; Linden, 1973; Floyd et al, 1974; Tranum-Jensen, 1975). Both types of endings have been described in humans (Johnston, 1968) (Fig. 1). It is not clear from the histological studies whether these endings subserve different functions according to their morphology. However, interconnections have been found between the unencapsulated endings and the nerve net suggesting that they may be functionally similar (Coleridge et al, 1957, Lloyd, 1979). In each of the vagus and sympathetic nerves there are approximately 300 myelinated and 2000 unmyelinated fibers in the cat (Agostoni et al, 1957; Emery et al, 1972). This very high ratio of unmyelinated to myelinated fibers suggests that receptors with unmyelinated afferent fibers are quantitatively more important in the reflex control of the cardiovascular system.

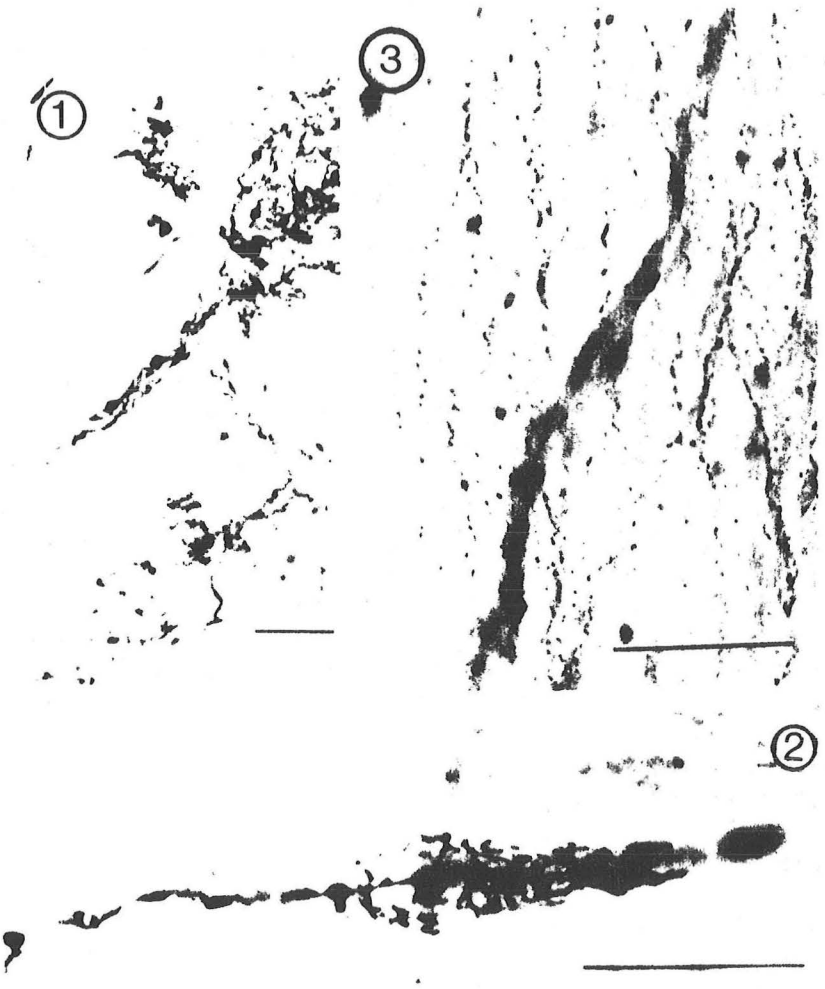

Figure 1. Example of diffuse (panel 1) and compact (panel 2) unencapsulated and nerve net (panel 3) endings in human heart's. The solid lines in each panel represent 100 μm.

A second method of studying cardiac receptors has been to examine their discharge characteristics. Thus, a number of investigators have recorded from afferent nerves which innervate the atria, ventricles or pericardium. The advantage of such studies is the ability to accurately determine the receptive field for the fiber that is being studied. It is also possible to determine the fiber size, i.e. whether it is unmyelinated i.e. a C-fiber, or myelinated, i.e. an Aδ-fiber. Also, it is possible to determine specifically the pharmacological and physiological stimuli that activate the receptor under a variety of circumstances. Below, I will discuss individual fiber response characteristics that have been determined with regard to both atrial and ventricular receptors. A significant limitation of these types of studies, however, is that they do not establish if a particular fiber type has a physiologically important role in a reflex response.

The last method of studying cardiovascular receptors is to perturb them with a physiological or pharmacological stimulus and then to observe the reflex cardiac or hemodynamic affects that are elicited. The advantage

of this approach is that it allows one to examine under perhaps more physiologically relevant (although this latter point can be disputed) conditions whether or not a cardiac receptor can have a meaningful effect upon the cardiovascular system. Perhaps the primary disadvantage of this technique is that often it does not precisely locate a population of receptors to the heart. For instance, aortic occlusion not only causes an increase in pressure of the left ventricle but also increases the pressure in the left atrium and the pulmonary arteries and possibly even the right side of the heart. Thus, this type of stimulation, which has been frequently used to excite cardiovascular responses, stimulates a diverse population of receptors located thoughout the cardiopulmonary system. Related to these types of studies are the reversible (cold blockade) or irreversible (nerve transection) afferent nerve interruption types of studies. These studies are useful in that they can help to demonstrate if cardiac receptors exert a tonic control of the cardiovascular system. However, the procedures for interruption of the nerves, whether they be reversible or irreversible, are very often not specific for any one fiber type. Thus, although cold blockade has been suggested to interrupt conduction through the myelinated fibers as the temperature is decreased to approximately 5°C, it is recognized that a certain number of unmyelinated fibers are also blocked at these temperatures. Thus, it is only possible to demonstrate that the unmyelinated fibers are responsible for a given effect if that effect disappears as the temperature is lowered below 5°C. Lastly, a disadvantage of this type of study is that it is usually not possible to eliminate only cardiac sensory fibers. Thus, nerve interruption studies often eliminate nerves from the heart, lung, mediastinum, chest wall and the gastrointestinal tract.

IV. ATRIAL REFLEXES

1. Nerve Recording Studies

Based on discharge patterns that are related to various parts of the atrial pressure waves, two main types of atrial receptors, the type A and B receptors, have been described (Paintal, 1963a, Arndt, 1979). Both receptor types are innervated by myelinated afferent fibers which are located in the vagus nerve. The ratio of these two receptors varies from one species to another. In the cat there is a ratio of approximately 1:1 (Langrehr, 1960a; Paintal, 1963a; Arndt et al, 1971a). In the dog there are many more type B than type A receptors (Coleridge et al, 1957; Langrehr, 1960a). In monkeys the ratio is many more type A than type B receptors (Chapman and Pearce, 1959). There is no data for humans since nerve recording studies cannot ethically be performed.

a. Type B receptors

The firing of these receptors usually begins in late systole just after the beginning of the aortic upstroke. Unlike the aortic baroceptors, which always start at the same time after the Q wave of the electrocardiogram, the type B receptors begin at varying intervals. This varying onset of discharge is due to changes in respiration. Thus during inspiration the first impulse tends to occur earlier and earlier (Whitteridge, 1948). It is possible to distinguish left atrial receptors from right atrial receptors. In this regard, left atrial receptors increase their firing

with premature atrial and ventricular contractions (Paintal, 1963b). On the other hand, right atrial receptors decrease their firing following premature contractions (Paintal, 1963b). The difference in the responses to premature contractions between the right and left atrial receptors may exist because premature contractions decrease venous return to the right but not to the left atrium.

The type B receptors discharge in a cresendo pattern whereas aortic baroreptors reach an immediate peak frequency which is usually constant throughout the discharge. An important identifying characteristic of the atrial type B receptors is their discharge pattern which is closely related to the v wave of the atrial pressure tracing. An exception to the relation of the type B discharge to the atrial pressure wave sometimes occurs at rapid heart rates when the discharge may persist until the P wave of the electrocardiogram and appear to be an intermediate or possibly even a type A atrial receptor. This situation likely occurs as a result of high atrial pressures so that the v wave never decreases below the threshold pressure which stimulates the receptor (Paintal, 1953a; Hakumäki, 1970).

The atrial type B endings are slowly-adapting stretch receptors that respond to pulsatile changes in atrial filling (Arndt et al, 1971a). Their activity appears to be closely related to the volume of fluid inside the atrium (Paintal, 1953a; Henry and Pearce, 1956; Coleridge et al, 1957; Mühl et al, 1956; Kramer, 1959). The atrial v wave to which these endings respond very likely is an accurate reflection of atrial volume (Opdyke et al, 1948; Little, 1949, 1960; Irisawa et al, 1959). The type B endings also respond to the amplitude of the v wave and to the rate of rise of the v wave (Paintal, 1976) (Fig. 2).

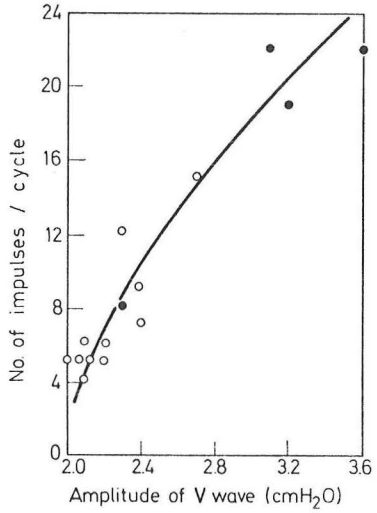

Figure 2. Graph shows the relation of activity in a type B atrial receptor to the amplitude of the v wave (Paintal, 1963b).

The type B receptors will adapt to slowly rising atrial pressure (Paintal, 1963b). Because of this adaption, their activity also depends upon the duration to which the pressure is raised. Type B receptors are usually silent during atrial contraction (a wave of the atrial pressure tracing) even though the atrial pressure may be highest at this time. This

may be because the volume of the left atrium is actually quite low at this time. Arrhythmias that raise left atrial pressure and volume can cause a discharge of the type B receptors (Paintal, 1963a). This is partly because the atrium contracts against a closed AV valve.

The discharge of the type B receptors is not visibly affected by anoxia and for this reason will continue to respond normally for some time after circulatory arrest (Paintal, 1953a; Coleridge et al, 1957). Also, the type B receptors are not stimulated by phenyldiguanide or serotonin (Paintal, 1953b; Mott and Paintal, 1953), but they do respond to veratrum alkaloids (Paintal, 1955, 1957; Kramer, 1959; Neil and Joels, 1961).

The type B receptors are innervated by myelinated afferent fibers. The endings of the type B receptors are located primarily in the pulmonary venous- and caval-atrial junctions, to a lesser extent in the body of the atria and more rarely in the appendages of the atria (Paintal, 1953a; Coleridge et al, 1957, 1964b; Langrehr, 1960a; Kappagoda et al, 1972; Linden, 1973). A variety of maneuvers are known to stimulate the type B receptors. These include distention of the left atrium by saline infusion, distention of a balloon in the left atrium or in the venous-atrial junctions, or negative pressure breathing (Henry and Pearce, 1956; Ledsome and Linden, 1964) (Fig. 3). On the other hand, hemorrhage decreases the activity of these receptors.

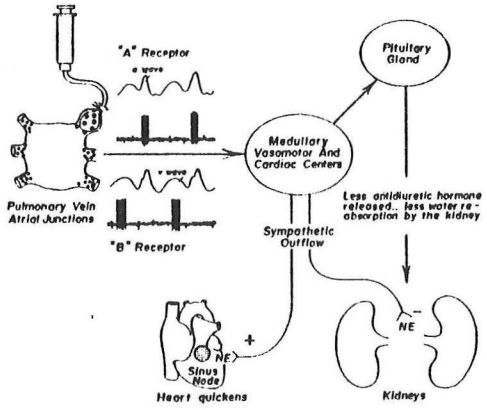

Figure 3. Effect of mechanical distention of the receptors subserved by myelinated vagal afferents at the pulmonary venous-atrial junction. The increased rate of firing in these fibers causes an increase in sympathetic outflow specifically directed to the sinus node so the heart rate increases without a change in contractility. The output of antidiuretic hormone from the posterior lobe of the pituitary gland may be reduced so less of the water filtered by the glomeruli of the kidney is reabsorbed. (See below for controversey about the effects of atrial distension on ADH secretion.) Normally these receptors discharge rhythmically with each cardiac cycle. The type A receptors discharge in unison with atrial contraction (a wave) and the B receptors with atrial filling (v wave) as shown by the recording of atrial pressure. Thus they signal to the brain the heart rate, the vigor of atrial systole, and the degree of atrial filling. NE = norepinephrine. (Shepherd, JT and Vanhoutte, PM. The Human Cardiovascular System, Raven Press, New York, pp 351, 1971).

Propranolol increases the firing of the atrial type B receptors because there is an increase in left atrial pressure (Gilmore and Zucker, 1974). Conversely, left stellate ganglion stimulation decreases left atrial pressure and therefore decreases atrial type B receptor stimulation

(Zucker and Gilmore, 1974). In addition, these receptors have a lower threshold of response with dynamic stimuli than with static stimuli suggesting that a phasic pressure augments their resting discharge (Recordati et al, 1975). Thus, the absolute tension and the rate of change of tension of the atrial muscle during atrial filling will determine the discharge rate of these receptors (Recordati et al, 1975).

b. Type A receptors

The type A receptors fire with the atrial a wave, i.e. just after the P wave of the electrocardiogram. Ectopic atrial contractions produce a burst of firing of the type A receptors but do not cause a sustained increase in firing such as occurs with the type B receptors.

The natural stimulus to the atrial type A receptors is thought by some investigators to be atrial contraction with an increase in wall tension because these receptors actually begin to discharge before the start of the atrial a wave (Paintal, 1963b; Recordati et al, 1976) (Fig. 4). The rise in atrial pressure also may be an important stimulus since the later burst of impulses of the type A receptor is attributable to the a wave of the atrial pressure pulse (Paintal, 1963a). The type A receptors behave like slowly-adapting stretch receptors in response to a sinusoidal stimulus (Arndt et al, 1971). These receptors probably do not sense volume (Paintal, 1963a; Arndt, 1971; Recordati et al, 1976). In addition, the type A receptors generally do not fire during the atrial v wave because of a lack of tension in the atrial wall at that time (Fig. 4).

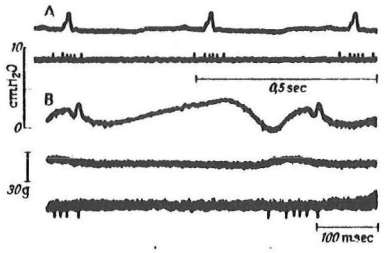

Figure 4. Impulses in a fiber from atrial type A receptors. Panel A is a section of a continuous record with EKG and impulses in a fiber from a left atrial receptor. B is a sweep consisting of (from above downwards) left atrial pressure, left atrial myogram indicating contraction of the left atrium and impulses in the fiber. The first burst of impulses in the sweep (i.e. B) corresponds to the first burst in A. Note the first impulse of each burst is attributable to atrial contraction and not the a wave because it appears before the a wave (Paintal, 1963a).

The differences between the type A and B receptors as described above is controversial since at least one study has demonstrated that one receptor type can be converted to the other under certain circumstances (Kappagoda et al, 1976) although it has yet to be proven that such circumstances occur in normal physiological situations (Paintal, 1979).

The type A receptors may signal heart rate rather than atrial pressure since they respond to changes in rate but not to changes in amplitude of the a wave or the rate of pressure rise (Arndt et al. 1971b; Brambring et al, 1969) (Fig. 5).

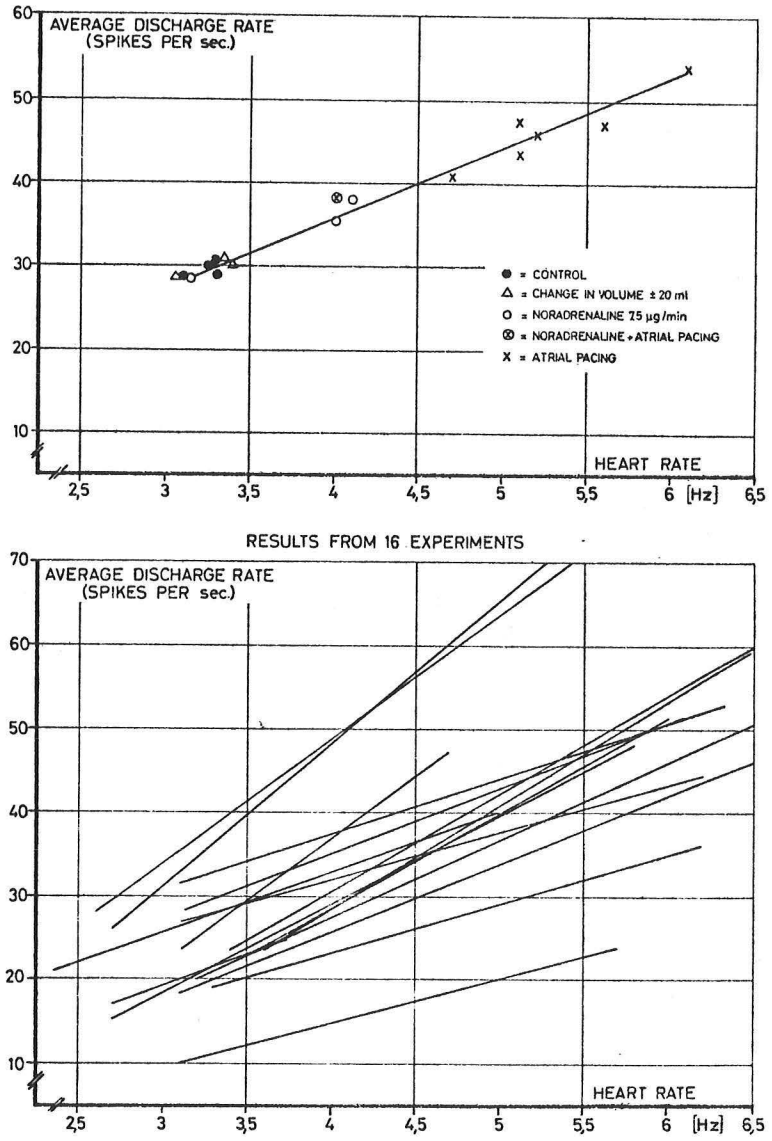

Figure 5. Relationship between average discharge rate and heart rate. Upper panel part: Representative example, lower panel part: calculated regression lines for 16 fibers (Arndt, 1971).

The rate of firing of type A receptors is maximal for each cardiac cycle. These fibers therefore operate at saturation whereas type B receptors operate within their threshold range (Arndt et al, 1971, 1974). The increase in firing of the type A receptors with premature atrial

contractions is probably because of the contraction against a closed AV valve. To explain the differences in receptive properties between the type A and type B atrial receptors, investigators have proposed that these receptors are oriented differently within the atrial wall with respect to coupling with the visco-elastic elements (in-series vs. in-parallel) and, therefore will respond to stretch or contraction differently (Chapman and Pankhurst, 1976). In all other respects however, the receptor types respond to a dynamic sinusoidal stretch stimulus in identical fashions (Arndt et al, 1974). Unlike the type B receptors, the type A receptors do not change their firing rate with either volume infusion or hemorrhage (Recordati et al, 1976). However, they do respond positively to interventions which increase systolic function such as isoproterenol infusion or stellate ganglion stimulation and negatively to interventions that decrease systolic function such as propranolol or removal of the stellate ganglion (Recordati et al , 1976). Like the type B receptors, the atrial type A receptors are innervated by myelinated afferent fibers.

c. Unmyelinated atrial afferent fibers

There are many afferent fibers from the atria which have a conduction velocity within range for the unmyelinated or C-fibers. In fact, there are probably more slowly conducting or unmyelinated fibers than there are rapidly conducting or myelinated fibers (Agostoni, 1957; Coleridge and Coleridge, 1972). The unmyelinated afferent fibers from the atria can be classified into either type A or type B discharge patterns similar to that discribed above for the receptors innervated by myelinated afferent fibers (Thorén, 1976). The unmyelinated afferent fibers have a sparse resting discharge, but their receptors will respond to stretch (Coleridge et al, 1973) or to transfusion of blood with a threshold response occurring at 2-3 mmHg (Thorén, 1976). It appears, however, that the unmyelinated atrial afferent fibers have a higher threshold and a lower sensitivity to supra-threshold pressures than the myelinated atrial afferent fibers.

During volume transfusion the activity of the unmyelinated atrial receptors increases in parallel to the increase in left atrial pressure. These receptors tend to fire with the v wave so that the endings appear to respond to atrial distention and not to atrial contraction. The activity of these receptors is also modulated by the respiratory cycle. In fact, they are mostly active during end-inspiration and during early expiration (Thames et al, 1977). With volume loading the receptors become active throughout the respiratory cycle. Augmenting respiration with CO_2 inhalation increases the average frequency of discharge because the atria are quite distensible and this maneuver increases their transmural pressure.

The atrial C-fibers, in contrast to the myelinated type A and B receptors which are located at the veno-atrial juctions, are located throughout the atria, in the interatrial septum and in the atrial appendages (Thorén, 1976).

d. Sympathetic atrial afferent fibers

Atrial afferent fibers that are located in the sympathetic nerves have been studied electrophysiologically using balloon distension or otherwise

mechanically stimulating the atria (Malliani et al, 1973a and Holton, 1977). These fibers respond to balloon distension by increasing their discharge. Electrical stimulation of the afferent fibers in the inferior cardiac nerve has demonstrated that the cardiovascular system can be either reflexly excited or inhibited depending upon the frequency of stimulation. Low frequency stimulation causes inhibition and high frequency stimulation causes excitation. Volume expansion causes a reflex discharge mediated by these afferents which inhibits renal sympathetic efferent nerve activity. On the other hand, the lumbar sympathetic nerve activity is not altered by stimulation of these afferent fibers. They can discharge with either the atrial a or v pressure wave and respond either to the volume infusion with an increase in discharge or to hemorrhage with a decrease in the discharge (Malliani et al, 1973a). The physiological importance, of these afferents is presently not known (Linden, 1981).

2. Reflexes mediated by vagal afferent fibers

a. The Bainbridge reflex

In 1915 Bainbridge noted that venous filling increased the heart rate. He postulated that this might be due to a reflex. In fact, there are two possible mechanisms which could account for an increase in heart rate during volume loading. One possibility is that there is local stretch of the pacemaker region which enhances automaticity and increases heart rate. A second possibility is that there may be a reflex response eminating from the heart that causes a cardio-cardiac reflex to augment the heart rate. In the past, arguments have been presented that volume infusion in monkeys does not elicit the tachycardia (Zucker and Gilmore, 1975). This observation has cast some doubt on the validity of this reflex in species which phylogenetically are closer to humans. However, the tachycardia response appears to be dependant upon the underlying heart rate. At rapid heart rates the effect is not seen (Zucker and Gilmore, 1975). However, with slower heart rates there appears to be a progressive tachycardia with volume loading (Vatner and Zimpfer, 1981). In this latter study, the tachycardia was demonstrated to be a reflex since it could be prevented by ganglionic blockade with hexamethonium or by vagotomy. In this study the efferent pathway was determined to be in the vagus nerve. However, the afferent pathway could not be determined. There is also evidence that the Bainbridge reflex exists in humans who are volume loaded (Giuntini et al, 1966 and Koubenec et al, 1978).

To determine the etiology of the Bainbridge reflex, investigators have utilized distention of the atrio-caval or pulmonary vein junctions with small balloons (Fig. 3). Stimulation of the right or left atrial receptors in this manner also increases heart rate in 1-2 minutes (Ledsome and Linden, 1964, Kappagoda et al, 1972, Linden, 1973; and Pelletier and Shepherd, 1973). Distention of these very localized regions of the atria may increase, decrease or not change mean arterial pressure and usually does not alter myocardial contractility, even with very large increases in heart rate (Daly et al, 1937; Doutheil and Kramer, 1959; Edis et al, 1970; Ledsome and Hainsworth, 1970; Furvinal et al, 1971; Carswell et al, 1970). Systemic vascular resistance and respiration are not effected by localized left veno-atrial distention (Ledsome and Hainsworth, 1970; Furvinal et al,

1971; and Carswell et al, 1970). In an early investigation, Ledsome and Linden (1964) demonstrated that the average pressure necessary to elicit the Bainbridge reflex was 24 mmHg (range 6 to 48 mmHg). In only a few of the distentions (4 of 29) could they demonstrate a response to a pressure less than 10 mmHg. These investigators argued that the volume but not the pressure was the important parameter to measure since it was necessary to elicit a certain degree of stretch of these receptive areas. However, it is unlikely that left atrial pressure reaches the very high levels to which these receptive areas were distended . Therefore, it is very possible that reflexes generated by Ledsome and Linden (1964) and others using a similar technique may be applicable only to the situation of severe heart failure, myocardial ischemia or acute mitral regurgitation when there are transient increases in atrial and pulmonary venous pressure to over 15-20 mmHg. One possibility, however, that may alter the significance of this reflex is that the simultaneous distention with pressures <15 mmHg of all the receptor areas, which would occur in the intact organism, might generate reflexes comparable to those which occur in the anesthetized animal when only part of receptive area is stretched.

Some of the reflex tachycardia due to localized veno-atrial distention may come from activation of sympathetic afferent fibers (Bishop et al, 1976), but the majority of the reflex is conducted by afferent fibers which travel with the vagus nerves (Ledsome and Linden, 1964). In addition, the specific vagal afferent fibers which mediate this affect are most likely myelinated since it possible to block the reflex tachycardia by cooling the vagus nerve down to 8°C (Kappagoda et al, 1978, 1979b; Linden et al, 1980). The increase in heart rate results from an increase in sympathetic efferent activity (Ledsome and Linden, 1964; Karim et al, 1972; and Linden, 1975). Edis et al (1970) determined that the effect of veno-atrial distention generally caused an increase in heart rate only if the initial heart was less than 140 beats per minute (Fig. 6). However, if the initial heart rate was greater than 140 beats/min, a bradycardia often ensued (Edis et al, 1970). The physiological importance of veno-atrial distension in the conscious animal may be to augment venous return thereby increasing cardiac output (Coleridge et al, 1957; Linden, 1975).

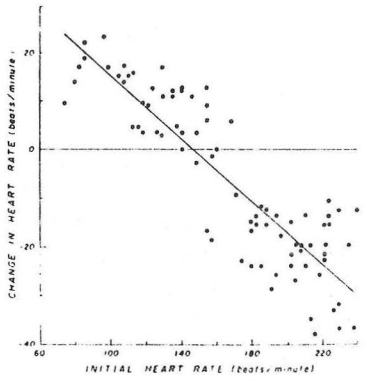

Figure 6. Relationship between initial (predistension) heart rate and change in heart rate with 2 ml distension of pulmonary vein-atrial junctions in six dogs at controlled carotid sinus pressures with aortic nerves cut (Edis et al, 1970).

Atrial distension also increases urine flow and decreases renal sympathetic discharge (Ledsome and Linden, 1964; Karim et al, 1972; Mason and Ledsome, 1974; and Linden, 1975, 1976, 1979). If only the veno-atrial junctions are distended, sympathetic tone to other organs generally remains unaltered. However, hindlimb vasoconstriction has been reported with mitral valve obstruction, although with this form of stimulation receptive areas other than the veno-atrial junctions may have been affected (Mason and Lesome, 1974). The increase in sympathetic activity to the heart and the decrease in sympathetic activity to the kidney is not accompanied by any change in sympathetic discharge to either the spleen or the lumbar sympathetic nerves (Karim et al, 1972).

The atrial receptors may cause the diuresis which is associated with an expanded fluid volume (Gauer and Henry, 1963). A decrease in anti-diuretic hormone (ADH) may not be important for this reflex response to occur (Linden, 1975; Gotez et al, 1975). In this respect, Kappagoda et al (1975b) have demonstrated that a diuresis could still be obtained after ablation of the posterior pituitary in dogs. However, there may have been incomplete ablation in some dogs studied and other investigators (De Torrente et al, 1975) have questioned the sensitivity of the bioassay used by Linden and Kappagoda. Lindens' group (1981), have attempted to further demonstrate the presence of a non-ADH diuretic substance released in response to veno-atrial balloon distension in dogs. They have been able to obtain plasma extracts that exert an effect on the Malphigian tubules of the blood-sucking bug Rhodnius Prolixus (Kappagoda et al, 1979a). Other investigators believe that the atrial receptors can control ADH secretion (De Torrente et al, 1975). However, a problem with most of the studies which have demonstrated a reflex decrease in ADH secretion in response to atrial distention is that the atrial distention has not been a pure stimulus. Thus it is possible that increased pressures upstream from the left atrium such as in the pulmonary artery, the right ventricle or the right atrium may have been increased or the left ventricular diastolic pressure may have been decreased. Further, large increases in left atrial pressure from 13-17 mmHg were necessary in De Torrente's study to cause the significant decrease in ADH. However, De Torrente et al, (1975) used a very sensitive radioimmuno assay to measure ADH; such a sensitive assay has not been employed by Lindens' group. In conclusion, it appears that there is still a significant controversy over the effect of left atrial distention and specifically veno-atrial distention on the control of anti-diuretic hormone. One cannot conclude with certainty that there is supression of ADH with an increase in veno-atrial distention that is important, physiologically, in mediating the diuresis which results from this procedure. However, distension of the entire left atrium very likely decreases the release of vasopressin, increases urine flow and decreases urine osmolarity (Figs. 7, 8).

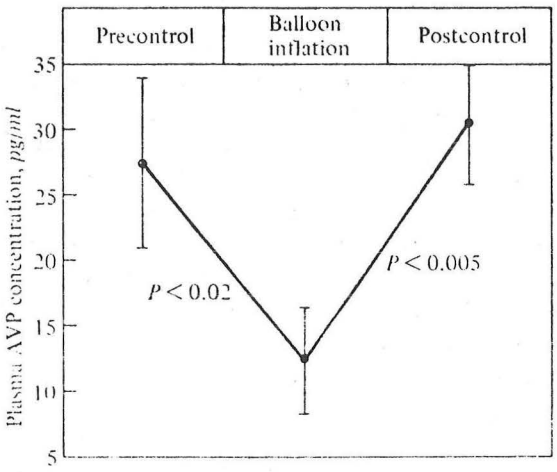

Figure 7. Effect of an increase in left atrial pressure on plasma arginine vasopressin concentration in intact dogs (De Torrente et al, 1975).

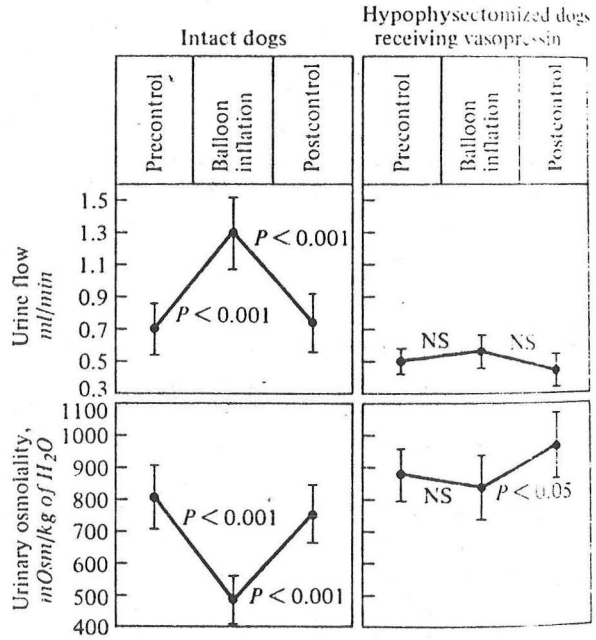

Figure 8. Effect of an increase in left atrial pressure on urine flow (above) and urinary osmolality (below) in intact dogs (left-hand panels) and in hypophysectomized dogs receiving a constant infusion of vasopressin (right-hand panels) (De Torrente et al, 1975).

The use of larger balloons to distend the left atrium affects the left atrium and areas of the pulmonary vasculature which are upstream from the left atrium. The reflex responses from this type of stimulation are bradycardia and hypotension (Edis et al, 1970; Pelletier and Shepherd, 1973; and Lloyd, 1974). The bradycardia and hypotension may be transient and may be followed by a tachycardia and a pressor response. However, this manuever generally causes a decrease in systemic vascular resistance which is related to the increase in absolute left atrial pressure, the rate of increase of left atrial pressure and the existing pressure before left atrial distention (Lloyd, 1975). Thus, for a 25 cm H_2O increase in left

atrial and pulmonary artery pressures, systemic vascular resistance transiently will decrease 26-35% and achieve a steady state 12-21% below predistension values (Lloyd, 1972). Since, the responses from pulmonary artery distention are less than the responses from left atrial distention it is likely that the majority of the reflex response to left atrial distention originates from the left atrium.

Thorén (1981) has postulated that distention of the whole of the left atrium likely involves C-fibers. In this respect, stimulation of vagal afferent fibers with high intensities or frequencies that may elicit C-fiber stimulation generally causes a depressor reflex (Daly and Verney, 1926-27; Aviado and Schmidt, 1955; and Salisbury et al, 1960). However, as mentioned above, the problem with using electrical stimulation is that nerves from other organs may be stimulated so that it is not possible to determine what reflex hemodynamic effect would be elicited by stimulating C-fibers from the atria. In addition, a problem with electrical stimulation is that it excites all afferent fibers in the vagus nerve simultaneously and at the same frequency whereas cardiac fibers normally have a range of thresholds and pressure-discharge curves (Brown, 1979).

Lastly, there is evidence of a tonic effect which comes from the atria as well as other regions of the heart and inhibits the efferent sympathetic discharge (Mancia et al, 1975; and Mancia and Donald, 1975a). This type of inhibition is thought to be mediated primarily by the unmyelinated fibers (80%) rather than the myelinated fibers (20%) (Öberg and Thorén, 1972, 1973a, b).

V. VENTRICULAR REFLEXES MEDIATED BY VAGAL AFFERENT FIBERS

1. Nerve Recording Studies

a. Myelinated ventricular afferent fibers

Ventricular receptors which are innervated by myelinated fibers demonstrate a discharge in early systole just before the aortic valve opens (Paintal, 1955). Premature atrial contractions decrease the firing of these receptors most likely because of a decrease of ventricular pressure rise. In certain species, such as the cat, these receptors are stimulated by veratrum alkaloids (Paintal, 1955; Neil and Joels, 1961; and Coleridge et al, 1964b). The discharge of these receptors is enhanced during aortic or pulmonary artery occlusion (Paintal, 1955; Coleridge et al, 1964b). The discharge frequency of some endings is related to the rate of rise of pressure (Kolatat et al, 1957).

These receptors are likely tension or pressure receptors since they begin to discharge at the onset of left ventricular contraction which is at or just before the increase in pressure within the ventricle. Coleridge et al (1964b) noted two types of afferent fibers from the ventricles including one type that discharged with a cardiac rhythm that was probably myelinated since its activity was blocked by cooling the vagus down to a temperature of 7°C. These fibers responded at various times during the cardiac cycle. Their receptive field was well circumscribed and they increased their discharge in response to ventricular distention. However, these fibers are thought to be relatively unimportant since they are not often found in

nerve recording studies (Coleridge and Coleridge, 1972).

Other receptors in the ventricular myocardium show no evidence of being sensitive to distention. Although many endings are located on or near the coronary artery vessel wall (Brown, 1965), it has been argued that these receptors are not coronary baroreceptors since they do not respond to changes in the coronary pulse pressure but only to mean coronary pressure or ventricular contraction (Paintal, 1972). Other receptive units innervated by myelinated afferent fibers have been located in or near the coronary sinus. These receptive units appear to be influenced by ventricular contraction and possibly coronary pressure (Muers and Sleight, 1972a, b)

b. Unmyelinated ventricular afferent fibers

These fibers were first described by the Coleridges in 1964. They generally can be generally broken down into two types of fibers. The first type innervate mechanoreceptors which respond to aortic occlusion or epinephrine injection approximately 60% of the time. Epinephrine is the most powerful stimulus and when injected causes these receptors to display a cardiac rhythmicity with discharge during systole (Muers and Sleight, 1972a; Sleight and Widdicombe, 1965). These fibers can likewise be stimulated by application of nicotine to the epicardial surface of the heart (Sleight and Widdicombe, 1965; and Coleridge et al, 1964b) or by injection of veratradine (Coleridge et al, 1964b). Thus, it is very likely that these are the same receptors which were recorded by Jarisch and Zotterman (1948) and Amann and Schaefer (1943). In general, fewer of these fibers are located on the right than on the left ventricle (Sleight and Widdicombe, 1965; Coleridge et al, 1964b; Muers and Sleight, 1972b; Oberg and Thorén, 1972). At very high ventricular pressures or during vigorous cardiac activity caused by injection of norepenephrine or epinephrine, the discharge rate of the unmyelinated mechanoreceptors increases and they fire in phase with the cardiac rhythm, particularly during systole (Muers and Sleight, 1972b; Sleight and Widdicombe, 1965). The unmyelinated mechanoreceptors with vagal afferent fibers may be activated by myocardial ischemia, hypoxia, severe hemorrhage or hyperkinetic ventricular contractions (Oberg and Thorén, 1973a, b; Baker et al, 1979a). The response of these receptors to hypoxia probably is related to altered wall motion rather than the altered PO_2 per se (Baker et al, 1979a). The spontaneous resting discharge rate of the mechanoreceptors is very often quite low with either a cardiac or a non-cardiac rhythm. The location of these receptors is throughout the left ventricle and the intervertricular septum and, as mentioned above, to a smaller extent in the right ventricle. They tend to respond to gradual occlusion of the aorta with their discharge activity increasing in parallel to changes in the left ventricular end-diastolic pressure (Thorén, 1979) (Fig. 9).

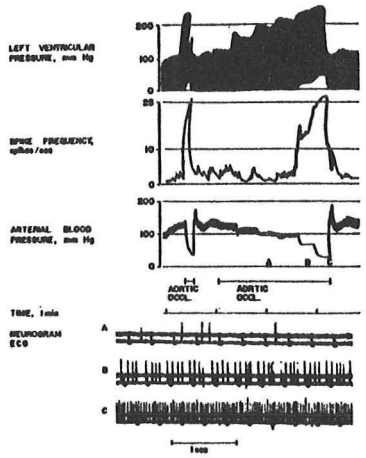

Figure 9. Effects of progressive obstruction of the ascending aorta on left intraventricular pressure, arterial blood pressure and spike frequency in two unmyelinated cardiac afferent fibers. The neurograms are recorded at times denoted by letters. An increased receptor activity is obtained first when the intraventricular diastolic pressure is significantly elevated. The receptors then fire with a cardiac rhythm (neurogram B). With a complete aortic occlusion the receptors fire continuously (neurogram C) (Oberg and Thorén, 1972).

The ventricular receptors with unmyelinated afferent fibers, which respond to increases in left ventricular end-diastolic pressure are quite sensitive to volume expansion or epinephrine administration. These receptors respond to veratradine and interpericardial nicotine and, as shown by Oberg and Thorén (1972), they respond to digitalis glycosides. Oberg and Thorén (1972) postulated that these receptors, which likely form part of the Bezhold-Jarish reflex, were the receptors which mediate the reflex bradycardia with the left ventricular distention (see below). However, this conclusion must be considered a hypothesis which really cannot be proven.

The response characteristics of unmyelinated ventricular receptors are altered markedly by changes in ventricular inotropism (Thorén, 1977). Even though these unmyelinated afferent fibers generally do not respond to changes and systolic pressure, more than half of those studied by Thorén (1977) were active in systole and when they increased their firing in response to intervention such as volume infusion they tended to increase their discharge during systole. Another, somewhat paradoxical observation is that during ventricular fibrillation there is a decrease in firing of these receptors despite an increase in the left ventricular end-diastolic pressure (Thorén, 1977) (Fig. 10). A study by Thames et al (1977) confirmed Thorén's observations and demonstrated that the unmyelinated left ventricular receptors were sensitive to both diastolic and systolic pressure. They were sensitive to systolic pressure because phenylephrine infusion caused a greater discharge than did volume infusion.

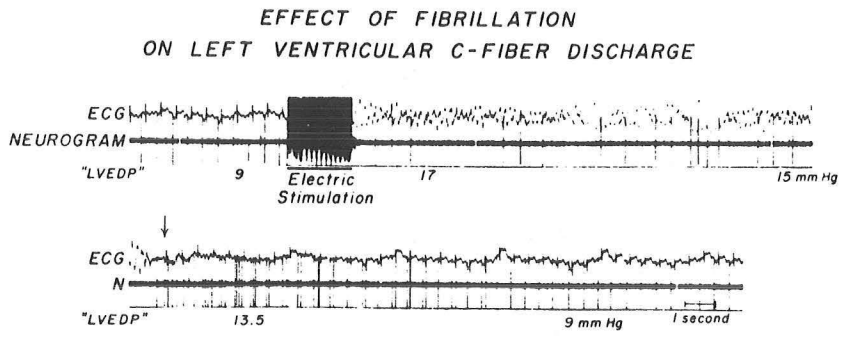

Figure 10. Activity in a left ventricular C-fiber during ventricular fibrillation of induced by electrical stimulation of epicardial surface. The receptor has cardiac-modulated spontaneous activity. During fibrillation, activity decreases immediately, but after spontaneous defibrillation (arrow) traffic markedly increases before it returns to control. Values for end-diastolic pressure (before and after fibrillation) are shown on line marked LVEDP (Thorén, 1977).

The Coleridges in 1964 were among the first to describe the unmyelinated vagal afferent fibers which had an irregular discharge with no obvious activity relationship to the cardiac cycle. These investigators felt that these fibers innervated chemoreceptors since they could be stimulated by veratradine, capsaicin and phenyldiguanide. When these fibers were stimulated, their activity increased in a bursting pattern without apparent relation to the cardiac cycle. These fibers will respond to coronary occlusion probably because of the generation of bradykinin and or prostaglandins (Baker et al, 1979b; Coleridge and Coleridge, 1980; and Kaufman et al, 1980). See below under section on coronary occlusion for more complete description of effects of bradykinin and prostaglandins. Unlike the mechanoreceptors, the chemoreceptors with unmyelinated vagal afferents from the ventricles may increase their discharge in response to hypoxia (Baker et al, 1979a). The increase in receptor discharge occurs without a relation to the cardiac cycle and is probably not related to altered ventricular mechanics.

2. Reflexes

Distention of the left ventricle was shown to cause a reflex vasodepression as early as 1926 by Daly and Verney. The afferent pathway for this reflex lies in the vagus nerve. The peripheral vasodilation is due to withdrawl of sympathetic vasoconstrictor activity and the bradycardia is due to increased vagal outflow (Doutheil and Kramer, 1959; Avaido and Schmidt, 1959; Salisbury et al, 1960; Ross et al, 1961; Öberg and Thorén, 1973b and Thorén, 1979). Other investigators (Bergel and Makin, 1967) have demonstrated that the reflex vasodepressor response to the epicardial application of nicotine is mediated by activation of the sympathetic cholinergic nervous system. This vasodepressor effect is much more difficult to elicit from the right ventricle than from the left ventricle (Aviado and Schmidt, 1955; Abrahamsson and Thorén, 1972; Thorén, 1979). Öberg and Thorén (1973) argued that the left atrial receptors are

probably not responsible for the reflex hypotension following aortic constriction. However, the role of the atrial afferent stimulation in this reflex response is uncertain at present. It is interesting that the bradycardia and the reflex renal vasodilation elicited by ventricular receptors stimulation during aortic occlusion is greater than the bradycardia and the reflex vasodilation elicited by carotid baroreceptor stimulation (Oberg and Thorén, 1973b) (Figs. 11, 12). However, quantitation of the stimuli to both the left ventricle and to the aortic region were not very accurate in this study.

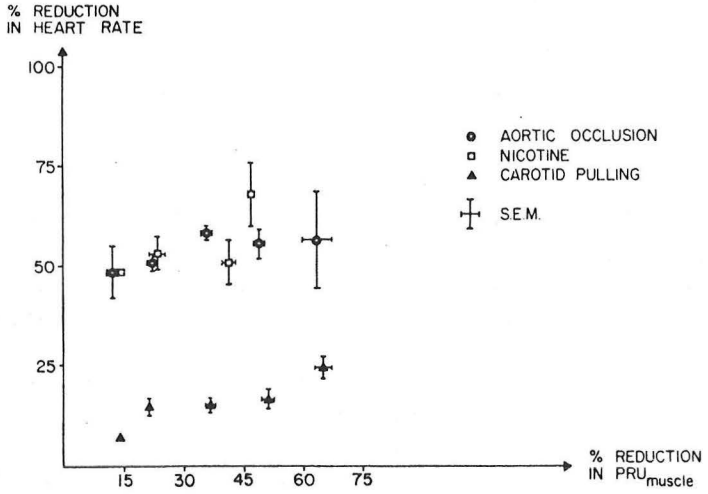

Figure 11. Diagram showing the relation between percent decrease in vascular resistance in skeletal muscle vessels and in heart rate when arterial baroreceptors and left ventricular receptors are stimulated. The data are classed with regard to magnitude of vascular resistance change in muscle vessels. Activation of the ventricular receptors by means of aortic occlusion are represented by 87 tests in eleven cats, by means of nicotine administration by 13 tests in 8 cats, while 63 carotid baroreceptor stimulation tests were performed in 10 cats. Note the considerably greater reflex effects on heart rate for a given reflex change in vascular resistance of skeletal muscle vessels when the left ventricular receptors are stimulated (Oberg and Thorén, 1973b).

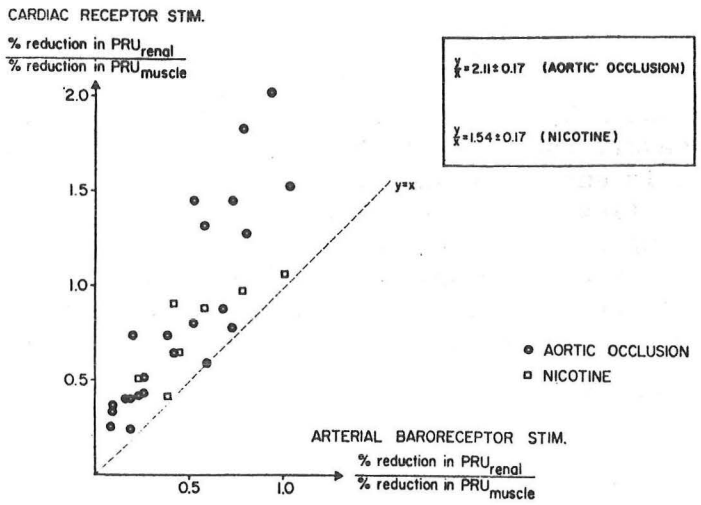

Figure 12. Comparisons of the renal and skeletal muscle vascular resistance responses to ventricular (cardiac) receptor and baroreceptor stimulation tests. To "normalize" the data from all such comparisons, the effects of activation of the low receptor groups are expressed as the quotient between renal and muscle vessel responses. Each "paired" comparison is represented by one point in the diagram; different symbols are used when ventricular activation was produced by aortic occlusion or by nicotine. Note that the data are displaced to the left and above the identity line, indicating that, for a given muscle vessel response in the two reflex mechanisms, the renal vessel responses are more pronounced when the ventricular receptors are stimulated. The mean ratio x/y or slope of the lines described by the two groups of data presented in the diagram are statistically different from the ratio of identity or slope of 1 (Öberg and Thorén, 1973b).

One cannot definitely state whether the myelinated or the unmyelinated ventricular afferent fibers mediate the bradycardia and hypotension induced by distension of the left ventricle. However, since the direct effect of stimulating the myelinated fibers appears to be quite weak and excitatory rather than inhibitory, it is most likely that the vagal afferent fibers mediate this response (Öberg and Thorén, 1973a). In contrast to the reflex vasodepression caused by distension of the left ventricle, a decreased stimulation of cardiac receptors innervated by these unmyelinated vagal afferent fibers, for instance with hemorrhage, causes an excitation of the cardiovascular system (Fig. 13).

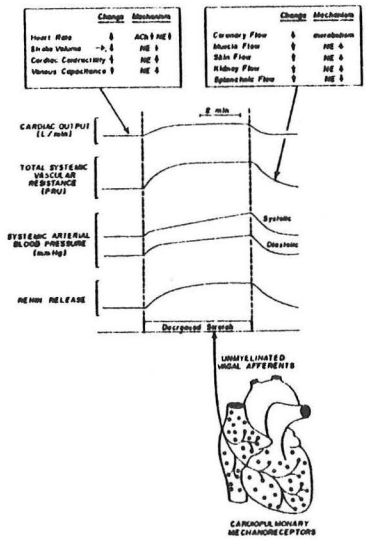

Figure 13. Hemodynamic effects of a decrease in activity of the mechanoreceptors in the cardiopulmonary region. The continuous inhibition of the solitary tract nucleus in the medulla of the brain is lessened, and there is increased sympathetic outflow to the heart and blood vessels and decreased vagal activity to the heart. The constriction of the systemic vascular beds results in an increase in total systemic vascular resistance. The cardiac output is maintained by the increased rate and contractility, and maintenance of its filling pressure by the reflex constriction of the systemic veins. The coronary flow is increased by the increased products of metabolism of the myocardial cells and by activation of betareceptors. The systolic and diastolic pressures are increased so an adequate perfusion pressure to the brain and coronary vessels is sustained. If the decreased pressure is due to hemorrhage, the cardiac output decreases in spite of the increase in rate and contractility because the venoconstriction is unable to provide an adequate filling pressure owing to the continuing blood loss. ACh = acetylcholine. NE = norepinephrine. PRU = peripheral resistance units (Shepherd, JT and Vanhoutte, PM. The Human Cardiovascular System, Raven Press, New York, pp 351, 1979).

The reflex depressor and bradycardia responses which are elicited by the epicardial application of nicotine are accompanied by a reflex decrease in cardiac function (Bergel and Makin, 1967). There is also vasodilation of the capacitance vessels (Salisbury et al, 1960; Ross et al, 1961). Further, activation of this reflex in cats by either aortic occlusion or by intrapericardial administration of nicotine causes more renal than skeletal muscle vasodilation. This is the opposite of what happens when the arterial baroreceptors are stimulated (Oberg and Thorén, 1973b). The reflex effect on muscle capacitance vessels is of similar magnitude to the venodilation caused by baroreceptor stimulation (Oberg and Thorén, 1973b).

Reflexes conducted by vagal afferent fibers interact with reflexes from carotid baroreceptors and carotid chemoreceptors. When the vagii are

cut, there is a greater gain of the carotid sinus reflex so that, when the carotid pressure is raised from 75 to 125 mmHg there is a greater decrease in the mean and systolic arterial pressure. However, the increased gain of the carotid sinus reflex does not extend over the whole range of intrasinus pressures. Thus, transection of the vagii does not affect the reflex vasodilation elicited by increasing intrasinus pressures above 125 mmHg (Koike et al, 1975).

Carotid chemoreceptor stimulation causes reflex skeletal muscle vasoconstriction, cutaneous vasodilation and systemic vasoconstriction. These responses are potentiated following bilateral vagotomy. This supressive effect from the cardiopulmonary afferent nerve fibers is thought to be distinct from any tonic vagal restraint since it involves vasodilator and vasoconstrictor responses and occurs without a supression of the resting adrenergic tone (Koike et al, 1975).

There is also a tonic inhibitory input from unmyelinated cardiac afferent nerve fibers that is abolished by cutting or cooling (but not by anodal blockade) of the vagus nerves (Oberg and Thorén, 1972, 1973a, b; Mancia and Donald, 1975; Thorén et al, 1975; Thorén et al, 1977). The tonic inhibition is greatest when there is an increased pressure or volume in the ventricles or when coronary occlusion is present (Oberg and Thorén, 1972, 1973a, b). The tonic inhibitory activity comes equally from the atria and the ventricles, suggesting occlusion at the level of the vasomotor center in the brain (Fig. 14). The tonic reflex effect of this inhibitory sympathetic discharge is to decrease flow to skeletal muscle, the kidney, intestine and to inhibit myocardial contractility (Shimizu and Bishop, 1980). The tonic reflex inhibition of myocardial contractility from the cardiopulmonary region is less than the tonic inhibitory activity from the carotid sinus afferents (Shimizu and Bishop, 1980). However, these two systems appear to compensate for each other when either one is eliminated.

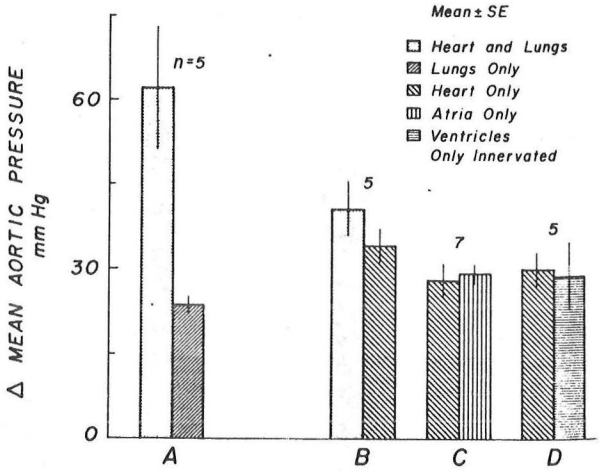

Figure 14. Grouped data from various series of studies of changes in aortic blood pressure during vagal cold block. Response shown as changes from control values. A: Heart and lung were in situ (left) and only the lungs were in situ (right). B: Heart and left lung were in situ (left) and only the heart was in situ (right). C: Lungs were removed and heart was in situ (left) and only the atria were in situ (right). D: Lungs were removed and intact heart was in situ (left) and heart was in situ but only the ventricles were innervated (right) (Mancia and Donald, 1975).

Vagal afferent nerve fibers from the heart are probably not important in the transmission of pain since intrapericardial injection of nicotine in the conscious dog does not elicit manifestations of pain (Sleight, 1964).

VI. PERICARDIAL REFLEXES

Afferent nerve fibers innervating the parietal pericardium are present in the vagus nerve (Adrian, 1933; Widdicombe, 1954; and Sleight and Widdicombe, 1965b). Also there are afferent fibers from the parietal pericardium which are located in the sympathetic efferent nerves (Holmes and Torrance, 1959). The afferent fibers from the pericardial receptors are generally in the Aδ group, i.e. finely myelinated. They can be stimulated by traction on the pericardium or distention of the pericardium and may therefore fire during pericardial tamponade. The receptors do not respond to intrapericardial injections of nicotine or veratradine injected into the right atrium. Likewise they do not respond to asphyxia. The reflex effects of these receptors are not known at the present time.

VII. VENTRICULAR REFLEXES MEDIATED BY SYMPATHETIC AFFERENT FIBERS

1. Nerve Recording Studies

An anatomical description of cardiac afferent fibers which travel with the sympathetic efferent nerves was provided first by Nettleship (1936) and Nonidez (1941). The receptor endings from these fibers exist in the heart as free, unmyelinated terminals which are diffusely scattered in the extracellular spaces. There are both myelinated and unmyelinated sympathetic afferents which come from the heart. The myelinated fibers are Aδ fibers, i.e. thinly myelinated fibers (Emery et al, 1976, 1977). The cell bodies of these sensory nerves are located in the upper five thoracic dorsal root ganglia (White et al, 1957). Each of the sympathetic afferent fibers generally have a wider distribution of receptor endings than do the vagal afferent fibers. This may be due to branching of the sympathetic afferents (Sleight and Widdicombe, 1965; Malliani et al, 1973a; Nishi et al, 1974; Coleridge et al, 1978). In particular, the epicardial receptors from the surface of the left ventricle seem to follow this pathway (Ueda et al, 1969; Malliani et al, 1973b; Hess et al, 1974).

The myelinated sympathetic afferents from the heart discharge spontaneously in phase with the cardiac cycle at normal blood pressures. However, they do not necessarily discharge with every beat of the heart. They respond to changes in blood pressure and coronary flow, but only when the latter is sufficiently reduced to cause cardiac failure (Malliani et al, 1973a).

Also, there are unmyelinated sympathetic afferent fibers from the heart (Hirsch and Borghard-Erdle, 1961; Peterson and Brown, 1971; Malliani et al, 1973b; Tranum-Jensen, 1975). The unmyelinated sympathetic afferents from the heart can be subdivided into mechanosensitive and chemosensitive fibers (Ueda et al, 1969; Nishi et al, 1974; and Coleridge et al, 1978). The sympathetic afferent mechanoreceptors from the heart are widely scattered over the atria, ventricles, vena cavea, pulmonary arteries and veins and the pericardium (Ueda et al, 1969; Nishi et al, 1974;

and Coleridge et al, 1978). This wide distribution of receptive endings for single fibers may result from the branching of these fibers (Nishi et al, 1974 and Coleridge et al, 1978). The unmyelinated mechanoreceptor endings usually have a sparce and more irregular discharge than do the vagal afferent endings. If these fibers do discharge, it is often related to the cardiac cycle but does not necessarily occur with every beat (Coleridge and Coleridge, 1980). The receptive fields of these fibers are mechanically very sensitive to touch perhaps because they are located close to the surface of the heart and are therefore easily stimulated. This is in contrast to the much smaller discharge evoked by even large increases in transmural pressure (Coleridge et al, 1978). These endings are stimulated by changes in cardiac volume and by the extent of wall motion. These mechanoreceptors are considered high-threshold, rapidly adapting receptors. With a premature ventricular contraction there is usually a burst of three to four impulses with the augumented beat (Ueda et al, 1969). Bradykinin has been shown to sensitize these unmyelinated afferent fibers and cause them to discharge rhythmically with the cardiac cycle (Uchida and Murao, 1974a; Nishi et al, 1977; and Baker et al, 1980) (Figs. 15, 16).

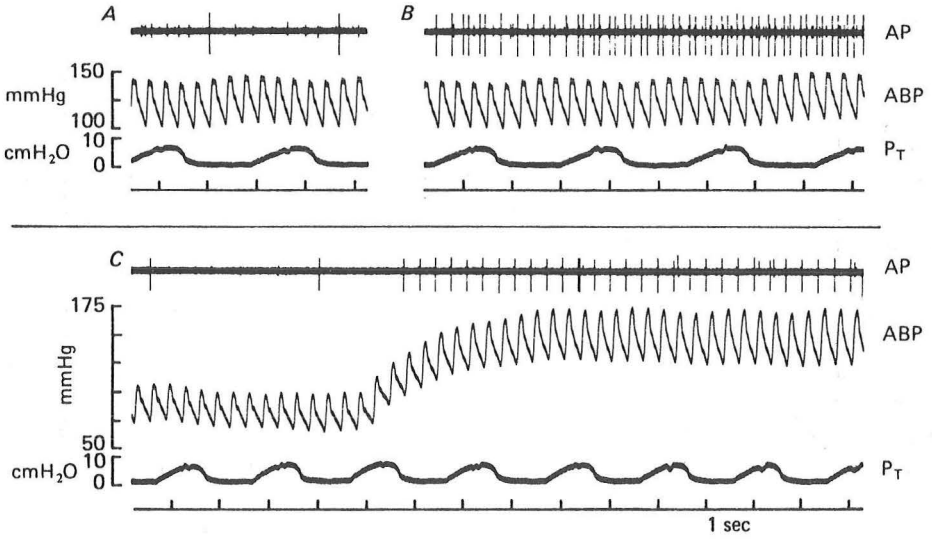

Figure 15. Stimulation of a sympathetic Aδ fiber (conduction velocity, 12.0 m/sec) whose mechanosensitive ending was in the wall of the left ventricle. A, before and B, 20 sec after 1 ml bradykinin (1 μg/ml) was applied to the ventricular wall; left ventricular end-diastolic pressure (not shown) was unchanged at 6 mmHg. C, effect of occluding the descending thoracic aorta; left ventricular end-diastolic pressure increased from 6 to 13 mmHg. (In C, the respirator frequency was increased). AP, action potentials; ABP, arterial blood pressure measured in the aortic arch; P_T, tracheal pressure (Baker et al, 1980).

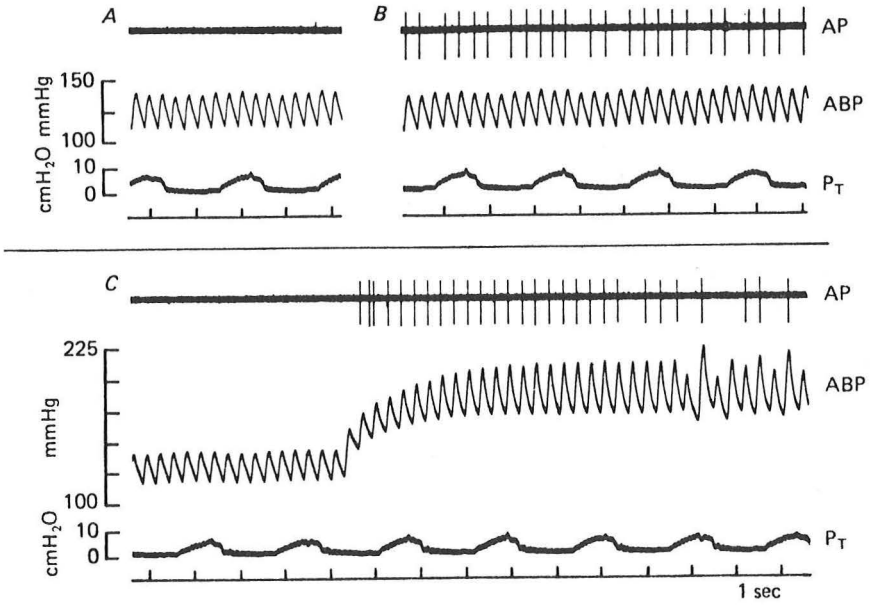

Figure 16. Stimulation of a sympathetic C-fiber (conduction velocity, 2.1 m/sec) whose mechanosensitive ending was in the pleura overlying the aorta. A, before and B, 25 sec after 0.5 ml bradykinin (1 µg/ml) was dripped onto the pleural ending. C, effect of increasing blood pressure in the aortic arch by occluding the descending thoracic aorta. AP, action potentials; ABP, arterial blood pressure (aortic arch); P_T, tracheal pressure (Baker et al, 1980).

In addition to the mechanoreceptors in the ventricle, there is a smaller group of chemoreceptors which are innervated by unmyelinated sympathetic afferent fibers (Fig. 17). These receptors have a sparse irregular resting discharge (Baker et al, 1980). In general they do not have a cardiac rhythm (Baker et al, 1980). Bradykinin as well as prostaglandins have been demonstrated to stimulate these chemosensitive receptors (Baker et al, 1979b; and Coleridge and Coleridge, 1980).

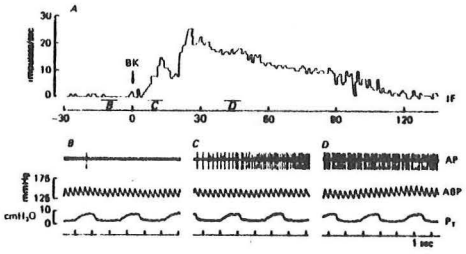

Figure 17. Stimulation by bradykinin of a sympathetic Aδ fibre (conduction velocity, 5.3 m/sec) whose chemosensitive ending was in the wall of the right ventricle near the origin of the pulmonary artery. A, 0.5 ml bradykinin (BK, 1 µg/ml) was dripped onto the right ventricular epicardium; note the initial and delayed peaks in the afferent response. B,C and D, action potentials and pressure recorded during the periods indicated by the correspondingly lettered bars in A. IF, impulse frequency recorded by a ratemeter; AP, action potentials; ABP, arterial blood pressure; P_T, tracheal pressure (Baker et al, 1980).

Casati et al (1979) have likewise located a group of unmyelinated sympathetic afferent fibers which innervate receptors that responded to a variety of stimuli including aortic occlusion, isoproterenol, coronary occlusion and especially to ventricular fibrillation. These endings had a sparse irregular resting discharge activity without any fixed relationship to the cardiac cycle. None of these fibers had multiple sensory fields. Occasionally during stimulation, for instance with aortic occlusion, these fibers discharged with every cardiac cycle. Casati et al (1979) concluded that these fibers were mechano- not chemoreceptors and that they should not be considered purely nociceptive since they responded to stimuli that were not painful such as volume infusion (Fig. 18). Some of these fibers may have innervated chemoreceptors rather than mechanoreceptors although testing with chemicals (Coleridge and Coleridge, 1979) was not used to discriminate the receptor types. In this regard, the coronary chemosensitive receptors, as described by the Coleridges, may be the same receptors that have been shown by others to respond to acetylcholine, sodium cyanide and asphyxia. Such fibers are mechanically insensitive (Nishi and Takenaka, 1973).

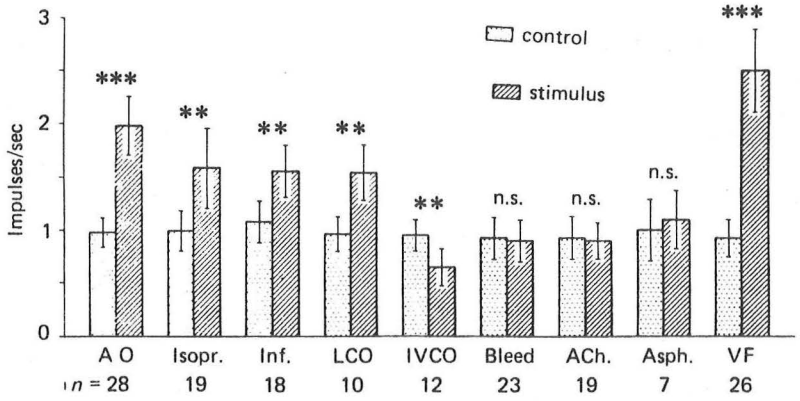

Figure 18. Effects on the impulse activity of the various experimental interventions. AO, aortic occlusion; Isopr., iv injection of isoprenaline; Inf, iv infusion of isotonic solution; LCO, left coronary occlusion; IVCO, inferior vena cava occlusion; Bleed, bleeding; ACh, iv injection of acetylcholine; Asph., asphyxia; VF, ventricular fibrillation, n = number of fibres studied; ***P<0.001; **P<0.02; n.s., not statistically significant (Casati et al, 1979).

2. Reflexes

The stimulation of sympathetic afferent fibers causes mainly an excitatory or pressor reflex (Brown and Malliani, 1971; Peterson and Brown, 1971; Malliani et al, 1972, 1973b). Specifically, stimulation of the Aδ fibers causes a weak pressor response whereas stimulation of the C-fibers causes a strong pressor response (Peterson and Brown, 1971). Thus, direct electrical stimulation of these afferents in vagotomized animals causes a reflex tachycardia and an increase in myocardial contractility that is mediated by an increase in sympathetic efferent discharge (Peterson and Brown, 1971; Malliani et al, 1972, 1973b; Pagani et al, 1974). Volume infusion into cats with a high spinal transection causes a reflex tachycardia and pressor response that is mediated by sympathetic afferents (Bishop et al, 1976). Thus, part of the Bainbridge reflex (described above) may be mediated by sympathetic afferent fibers. Studies also have demonstrated that coronary occlusion can excite sympathetic afferent fibers

(Brown, 1968). These afferent fibers will also respond to increases in coronary pressure and coronary sinus occlusion (Brown and Malliani, 1971). Thus, tugging or occluding the left main coronary artery in lightly anesthetized cats causes a pseudaffective or pain-like response (Brown, 1968). Lactic acid and potassium also have been demonstrated to stimulate unmyelinated but not myelinated sympathetic afferents from the heart (Uchida and Murao, 1974c, 1975) (Figs. 19, 20). In this regard, intracoronary injection of lactic acid produces a pseudaffective response in lightly anesthetized dogs (Guzman et al, 1962,1964). Investigators have speculated that the sympathetic afferent fibers may signal pain particularily during myocardial ischemia and that they may initiate pathophysiological reflexes which mediate various cardiac arrhythmias particularily those induced by ischemia (see below) (Brown, 1968; Ueda et al, 1969; Brown and Malliani, 1971; Schwartz et al, 1976b).

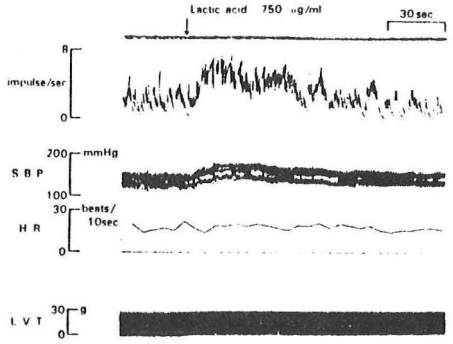

Figure 19. Effect on activity of an Aδ fiber of application of 750 µg/ml lactic acid to left ventricular surface. From top down: integrated action potentials, systemic blood pressure, heart rate, and left ventricular tension. Downward arrow indicates application of agent (Uchida and Murao, 1975).

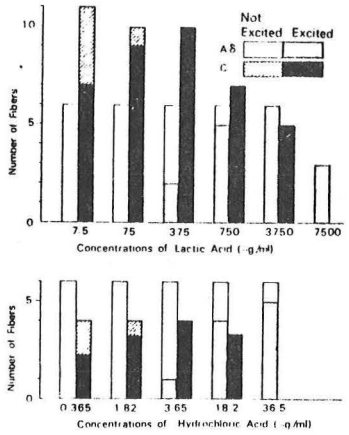

Figure 20. Relationship between concentration of acid solutions and excitation of afferent sympathetic nerve fibers (Uchida and Murao, 1975).

VIII. FUNCTION OF CARDIAC RECEPTORS IN PATHOLOGICAL AND OTHER CONDITIONS

1. Myocardial Ischemia

a. Reflexes from coronary occlusion

Coronary occlusion activates the receptive endings of both myelinated and unmyelinated vagal afferent fibers from the heart (Recordati et al, 1971; Öberg the Thorén, 1972, 1973a, b; Thorén, 1972, 1976b). Specifically, coronary occlusion stimulates the coronary mechanoreceptors with unmyelinated vagal afferents (Brown 1965, 1966). The increase in afferent activity from these receptors usually occurs within 20 to 90 seconds of coronary occlusion (Thorén, 1973b, 1976b). The increase in C-fiber activity occurs with a rhythmicity to the cardiac cycle and in parallel with the ischemic bulging of the myocardium suggesting that mechanical rather than chemical factors activate the receptors (Thorén, 1972, 1976b). Also, there is evidence that mechanoreceptors with finely myelinated afferent fibers which course with the sympathetic efferent nerves increase their activity during coronary occlusion (Bosnjak, 1979).

The reflex cardiovascular response from coronary occlusion could either be an increase or a decrease in blood pressure because activation of the sympathetic afferents reflexly increases sympathetic efferent discharge whereas activation of the vagal afferent fibers reflexly decreases sympathetic efferent discharge (Malliani et al, 1969). In general, the response to coronary occlusion is a pressor response and it is usually, but not always, necessary to cut the vagal afferent fibers to observe an increase in sympathetic efferent discharge (Brown and Malliani, 1971; Weaver et al ,1981) (Figs. 21, 22). Thus, vasoconstriction in the hindlimb, mesentery and skeletal muscle is prevented in response to coronary occlusion if vagal afferents are intact (Pelletier, 1979). The arterial baroreceptors will, in general, oppose the hypotensive response that is mediated by vagal afferents. Thus, the baroreceptors limit the decrease in blood pressure resulting from activation of cardiac receptors with vagal afferents.

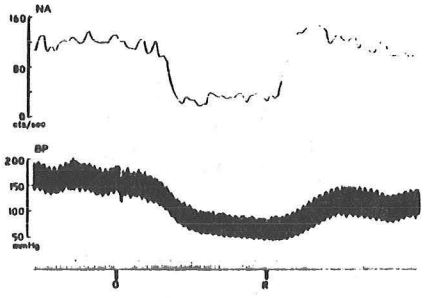

Figure 21. Renal nerve and systemic blood pressure responses to left circumflex artery occlusion in a cat with its vagus nerves intact. Coronary occlusion causes renal nerve activity and blood pressure to decrease (Weaver et al, 1981).

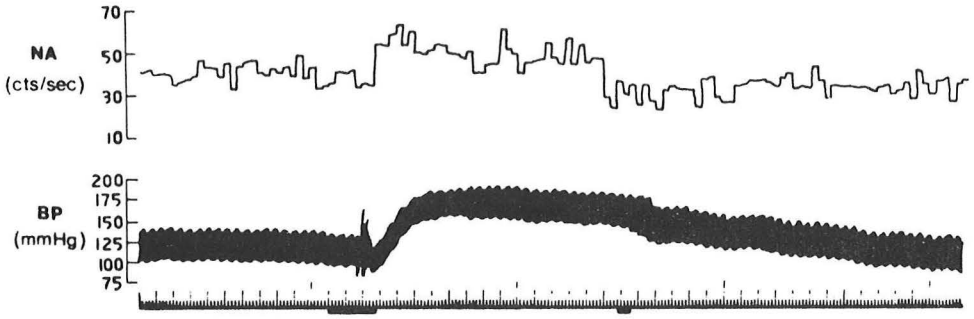

Figure 22. Renal nerve and systemic blood pressure responses to occlusion of the left anterior descending artery in a cat with its cardiac nerves intact. NA is renal nerve activity. First marker on time base indicates occlusion, and 2nd marker indicates release of occlusion. Coronary occlusion produced excitation of renal nerve activity and a pressor response (Weaver et al, 1981).

Coronary occlusion activates the mechanoreceptors with myelinated and unmyelinated sympathetic afferent fibers probably because of wall motion abnormalities (Uchida and Murao, 1974c). In addition, hypotension induced by occluding the vena cavae or administration of nitroglycerin, decreases the discharge Aδ and sympathetic afferent C-fibers (Uchida and Murao, 1974b). It is possible that the depressor responses mediated by vagal afferent fibers may be associated with the excess vasodilation which occurs with cardiogenic shock, for instance, after a myocardial infarction (Constantin, 1963).

Stimulation of receptors subserved by the circumflex coronary artery with veratradine or nicotine causes a greater bradycardia and hypotension than stimulation of receptors subserved by the left anterior descending coronary artery (Walker et al, 1978). This reflex effect is most likely dependant upon the numbers of receptors present rather than a difference in drug concentration or muscle mass perfused. In the same light, a greater reflex bradycardia, systemic vasodepression and decrease in renal nerve activity can be elicited by circumflex than by left anterior descending coronary occlusion (Thames et al, 1978; Thames and Abboud, 1979). It has been speculated that the reflex renal vasodilation may be beneficial in protecting patients with cardiogenic shock. Thus, in one series of patients with acute renal failure, the cause could be related to coronary ischemia (i.e. post-myocardial infarction shock) in only 2% of the cases (Hanley et al, 1972). Comparison of hemorrhagic to coronary artery embolization-induced hypotension demonstrates that with the latter, renal blood flow and urine-concentrating capability are better maintained (Gorfinkel et al, 1972). The difference between these two causes of shock may be due to a reflexly reduced renal sympathetic efferent discharge caused by the coronary artery embolization and the resulting myocardial ischemia (Kezdi et al, 1974). The decreased renal discharge can be demonstrated to be reversed by vagus nerve transection suggesting that stimulation of cardiac receptors by coronary occlusion buffers the increased sympathetic discharge resulting from the arterial hypotension-induced baroreceptor stimulation (Donald and Shepherd, 1979).

Consistent with the hypothesis of more receptors which cause inhibitory effects on the inferior-posterior myocardium and more receptors which cause excitatory effects on the anterior myocardium has been the finding that patients with Prinzmetal's angina can have a reflex bradycardia with spasm of the vessels supplying the inferior wall and a tachycardia with spasm of vessels supplying the anterior wall (Perez-Gomez et al, 1979) (Fig. 23).

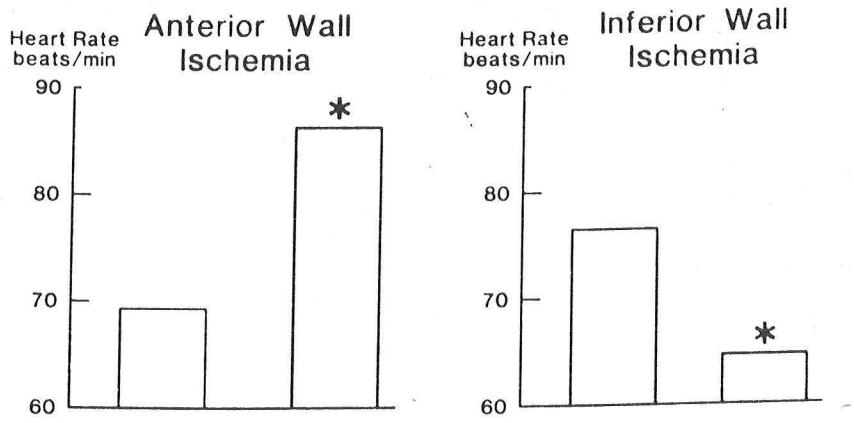

Figure 23. Opposite effects of anterior wall ischemia and posterior wall ischemia on heart rate in patients with coronary artery spasm: Left bar in each panel is average control value, and right bar is average value during spasm. *P<0.05 (Perez-Gomez et al, 1979).

There has been a debate on the significance of the coronary ischemia-induced spinal excitatory reflex mediated by cardiac sympathetic afferent nerves. Malliani (1980) believes that such a reflex exists and provides evidence from his own studies (Malliani et al, 1969; Brown and Malliani, 1971) demonstrating the existence of this reflex. Malliani also has quoted both human and monkey studies which tend to support the existance of an excitatory reflex mediated by sympathetic afferents from the heart (Webb et al, 1972; Littler et al, 1973; Randall et al, 1978; Guazzi et al, 1975; Maseri et al, 1978). Conversely, Felder and Thames (1980) discount many of the studies quoted by Malliani pointing out that there is no consistant pattern of ST elevation (Littler et al, 1973) and that the response to pain was a centrally mediated phenomenon resulting from a "stressful event" and therefore due to activation of higher cerebral centers (Littler et al, 1973; Maseri et al, 1978). In this regard, Felder and Thames (1979) have demonstrated that occlusion of the left anterior descending and the circumflex coronary arteries, with the vagii cut and the carotid sinus pressure controlled, does not elicit an increase in cardiac efferent sympathetic nerve activity. However, after a high spinal cord transection these investigators noted an increase in sympathetic efferent activity. This data demonstrates that there is descending inhibition from higher brain stem or cortical centers upon the spinal pathways. This observation suggests that patients with high spinal cord transections may demonstrate an exaggerated sympathetic response to myocardial ischemia. In conclusion, however, it appears that the importance of the excitatory cardiovascular

response to coronary occlusion which is mediated by a sympathetic afferent pathway from the heart is still a controversial matter. It is my opinion that this excitatory response is usually quite weak or negligible except in special circumstances such as the situation of post-cardiopulmonary bypass (see below).

There is evidence that sympathetic afferent fibers may mediate the pain associated with coronary artery occlusion (Brown, 1968; Ueda et al 1969; Brown and Malliani, 1971). Thus, coronary occlusion in lightly anesthetized cats causes a pseudaffected response which is associated with an increase in sympathetic efferent nerve activity (Brown, 1967) (Fig. 24). In dogs, cardiac pain can be elicited by occlusion of the left circumflex coronary artery (White et al, 1933). The afferent pathways for this response are not in the vagii but rather are in the stellate ganglia and in the upper four thoracic ganglia. In patients with coronary artery disease, cardiac pain travels over the upper three or four thoracic and in the lower two cervical dorsal spinal cord roots (White, 1957). Removal of the stellate ganglia and the entire length of the cervical chains does not relieve angina as long as the upper three thoracic ganglia are left intact (White, 1957). However, removal of both stellate ganglia and excision of the first to the fifth thoracic sympathetic ganglia relieves cardiac pain in man (Lindgren and Olivecrona, 1947). Other operations that have been attempted in humans have been a paravetebral anesthetic block or a posterior rhizotomy of the appropriate dorsal roots of the spinal cord. These operations were performed in the late 1940's and 50's. It was stated that the patients who received such operations were not at risk even though they could not be warned of the myocardial ischemia by experiencing angina (White, 1957). In fact, it was stated that, following surgery, the patients who had received one of these operations still felt a sense of constriction at the suprasternal notch which was often accompanied by dyspnea and palpitations. I disagree with this point of view and would agree with MacKenzie (1924) who believed that angina is an important warning signal which, tells a patient, that he or she must slow down.

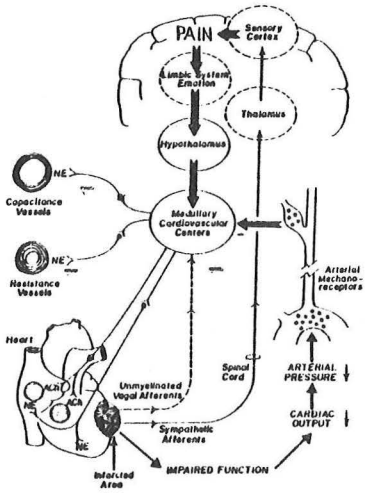

Figure 24. Factors involved in the cardiovascular response to myocardial infarction. Ach = acetylcholine, NE = norepinephrine, - inactivation (Shepherd, JT and Vanhoutte, PM. The Human Cardiovascular System. Raven Press, New York, pp 351, 1979).

Another symptom that frequently bothers patients, particularly those with posterior-inferior myocardial infarctions is nausea and vomiting (Chadda et al, 1975). Abrahamsson and Thorén (1972) demonstrated that stimulation of unmyelinated vagal afferent fibers either with chemicals or with coronary occlusion caused gastric relaxation. These investigators speculated that this gastric relaxation could lead to the nausea and vomiting associated with an acute myocardial infarction. Their observations were extended recently by Johannsen et al (1981) who demonstrated in dogs that the gastric relaxation was much greater with inferior myocardial than with anterior myocardial injection of veratradine. Thus, from these studies and from studies on the differental hemodynamic reflex effects elicited by posterior-inferior vs. anterior coronary artery occlusion, the largest population of ventricular receptors appear to be located on the posterior-inferior surface of the heart.

There is recent information that successful reperfusion of the right coronary artery following intracoronary thrombolytic therapy in 13 of 15 patients caused a bradycardia and hypotension (Wei et al, 1982). In contrast only 1 of 7 patients with successful left coronary artery reperfusion demonstrated this hemodynamic vasodepressor pattern. On the other hand, 3 of 7 patients with successful left coronary artery reperfusion demonstrated hypertension, tachycardia or an increase in ventricular ectopy while only 1 of 15 patients with successful right coronary artery reperfusion demonstrated this pattern. Three patients with transient reperfusion of the circumflex artery and subsequent re-occlusion demonstrated changes in blood pressure and heart rate while 0 of 9 patients with persistent occlusion demonstrated any reflex cardiovascular changes. The authors concluded that reperfusion of the acutely ischemic posterior-inferior myocardium causes a Bezold-Jarish-like reflex. Patients with anterior reperfusion more commonly demonstrate an excitatory reflex.

b. Bradycardias and hypotension associated with cardiac receptor stimulation

It has been reported that up to 77% of patients with acute posterior myocardial infarctions have bradyarrhythmias and/or hypotension (George and Greenwood, 1967; Adgey et al, 1971; Webb et al, 1972) (Table I). Conversely, only 30% of patients with acute anterior infarctions experience these problems. The bradyarrhythmias occur even when the hypotension would be expected to cause a reflex tachycardia through stimulation of the arterial baroreceptor reflex.

TABLE I - INCIDENCE OF BRADYARRHYTHMIA AMONG 284 PATIENTS RELATED TO TIME AFTER ONSET OF SYMPTOMS AND SITE OF INFARCTION, 1966-69

	No. of patients:				Total no. of patients
	Within 1st hr.	Within 2nd hr.	Within 3rd and 4th hr.	> 4 hr.	
Sinus or nodal bradycardia:	75 (26%)	9 (3%)	5 (2%)	19 (7%)	108 (38%)
Anterior infarct	24 (18%)	5 (4%)	1 (0·7%)	2 (1·5%)	32 (24%)
Posterior infarct	48 (36%)	4 (3%)	3 (2%)	16 (12%)	71 (53%)
A.V. block, second-degree or complete	17 (6%)	2 (0·7%)	1 (0·4%)	8 (3%)	28 (10%)
Anterior infarct	1 (0·7%)	0	1 (0·7%)	1 (0·7%)	3 (2%)
Posterior infarct	15 (11%)	2 (1·5%)	0	7 (5%)	24 (18%)

(Adgey et at., 1971)

Zipes (1969) listed several causes of bradyarrhythmias in association with acute myocardial infarction. These included: (1) acute elevation in blood pressure with resulting baroreflex stimulation; (2) sympatholytic (i.e. propranolol) or parasympathomimetic drugs (morphine or digitalis); (3) coronary chemoreflex in association with acute myocardial infarction (see description of coronary chemoreflex below); (4) central command associated with a fear or startle reaction or pain eliciting a response like the diving reflex; (5) valsalva, carotid sinus or glossopharyngeal reflexes (i.e. like vasovagal reflex); (6) humoral substances (adenosine, nucleotides or enzymes containing glutamic and aspartic acid, or potassium) released into sinus node artery; and (7) ischemic damage to the SA node or the conduction system leading to second or third degree heart block.

Ectopic beats occur more frequently when the rhythm is slow (Han et al, 1966a, b; Han, 1969). A slow heart rate in the normal ventricle creates a greater dispersion of refractory periods. This situation leads to an increase in the reentrant activity and hence ectopic beats. The possibility of ventricular fibrillation thus is increased at slow heart rates. Further, in a dog model, it has been demonstrated that there is a more rapid onset and a greater incidence of ventricular arrhythmias after coronary occlusion at slower heart rates (Han, 1969) (Figs. 25, 26).

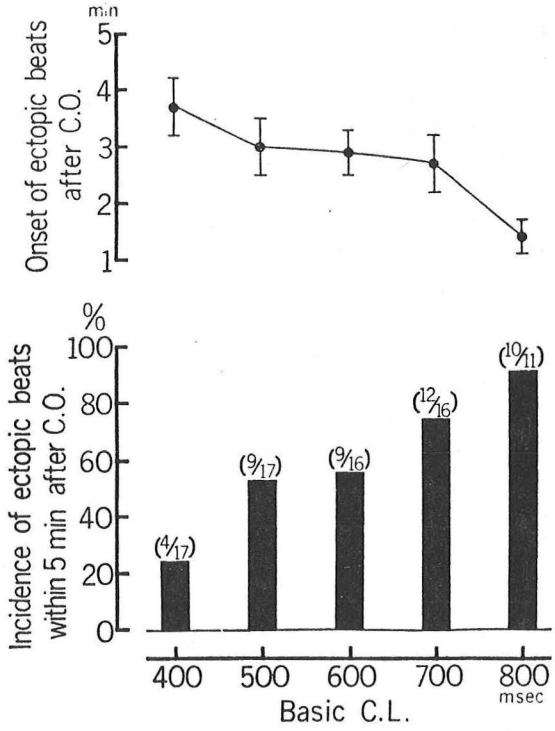

Figure 25. The cumulative data obtained from 77 trials of coronary occlusion in 8 dogs. The incidence of closely coupled ectopic beats is shown in the lower part, and the average time (±S.E.) of onset of ectopic beats after the start of coronary occlusion is shown in the upper part for different cycle lengths (Han, 1969).

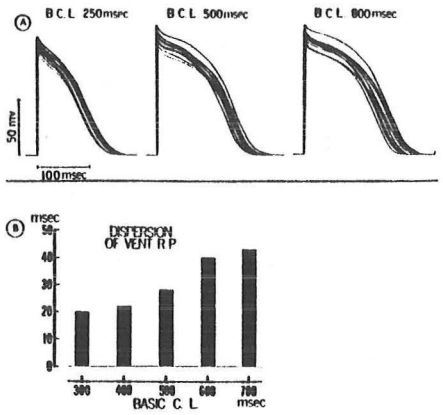

Figure 26. Increase of asynchrony of depolarization at slow ventricular rates. A, temporal dispersion of transmembrane action potential durations in 8 ventricular fibers at three basic cycle lengths (B.C.L.) B, temporal dispersion of refractory periods (R.P.) determined at 6 epicardial points of the ventricle at cycle lengths (C.L.) between 300 and 700 msec (Han, 1969).

Overactivity of the sympathetic nervous system, for instance during left stellate stimulation in a dog, also leads to a greater dispersion of refractory periods but decreases the ventricular fibrillation threshold (Han et al, 1964). Epinephrine transiently decreases then increases the ventricular fibrillation threshold and causes an increased dispersion of refractory periods. The difference between sympathetic overactivity and the response to injection of epinephrine is thought to be due to the non-uniform distribution of catecholamines during stellate stimulation and to a more uniform distribution following injection of epinephrine.

There is, however, controversy about the beneficial effects of increasing heart rate in the face of a sinus bradycardia associated with an acute myocardial infarction. In this regard, Kent et al (1972) demonstrated a deleterious effect of increasing heart rate during ischemia. This effect appeared to be caused by an increase in the temporal dispersion of refractory periods and a decrease in the ventricular fibrillation threshold (Figs. 27, 28). Their argument was that Han (see above) had not performed his studies of ventricular refractory periods and fibrillation thresholds in the setting of ischemia. As noted above, this claim was untrue (Han, 1969). Kent and his co-workers suggested that the deleterious effects of increasing heart rates in the setting of ischemia was due to a greater imbalance between oxygen supply and demand which was created when the heart rate and blood pressure were increased by giving atropine. They felt that their evidence demonstrated the protective effect of the bradycardia and hypotension. In addition, their reasoning lead them to conclude that atropine was not a benign drug and could be associated with an even larger imbalance between myocardial oxygen supply and demand and possibly cause malignant arrhythmias (Epstein et al, 1973).

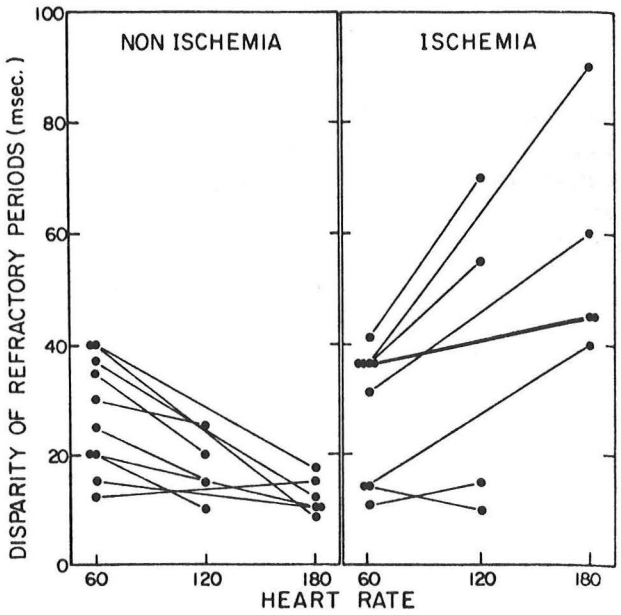

Figure 27. The influence of heart rate on the disparity of refractory periods in the absence of ischemia (left panel) and during ischemia (right panel). Six animals studied at heart rates of 60 and 180 under both ischemic and nonischemic conditions (Kent et al, 1973).

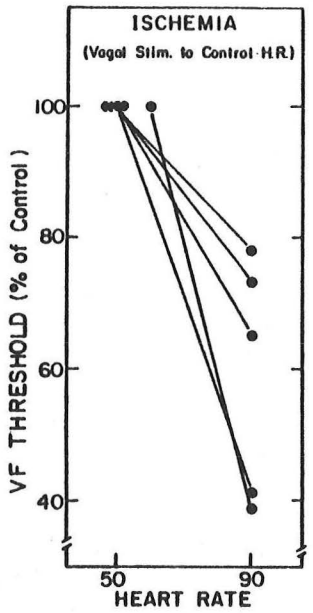

Figure 28. Ventricular fibrillation (VF) threshold as a function of heart rate in five animals during ischemia. Heart rate controlled by vagal stimulation (Kent et al, 1973).

As mentioned above, hypotension may also be associated with an acute myocardial infarction. Thus, pacing the heart in the setting of complete heart block increased cardiac output by 28% in one study (Lassers et al, 1968). Patients who sustain a bradycardia in the early phase of an acute myocardial infarction may have less mortality even if they have co-existent hypotension. This suggests that the bradycardia and possibly the hypotension may be protective for the myocardium (Rotman et al, 1972; Gauer et al, 1973) (Fig. 29). Other evidence indicates that bradycardias are associated with less ST elevation in the setting of an acute myocardial

infarction (Redwood et al, 1972). However, it is well recognized that a variety of factors other than ischemia can influence the ST segment changes. Unfortunately some of these earlier studies have not taken into account the extent of the infarction or other possible factors which may influence prognosis.

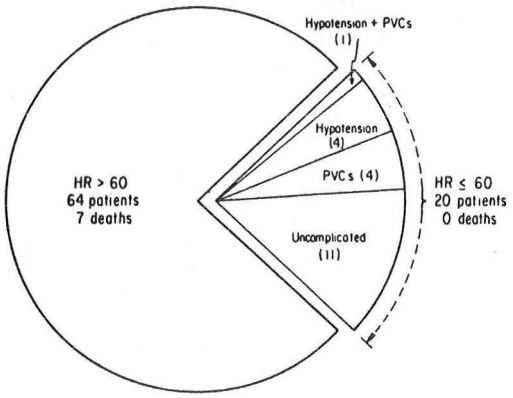

Figure 29. Bradycardia and its complications in the prehospital phase of acute myocardial infarction. HR = heart rate; PVCs = premature ventricular contractions (Gauer et al, 1975).

Chadda et al (1975) studied 68 patients with the bradycardia-hypotension syndrome. Fifty-eight percent of these patients developed symptoms from decreased systemic perfusion. Only a few (14%) had evidence of heart failure or chest pain (20%). However, a large number had nausea and vomiting. The majority of patients (76%) had an inferior myocardial infarction and considering this group, sinus bradycardia was the most common arrhythmia (Table II). The patients with inferior infarctions also had more frequent arrhythmias. However, the death rate in the patients with inferior infarctions was comparable to that in patients with anterior infarctions. Administration of atropine increased the heart rate and the blood pressure and tended to decrease the number of ventricular premature contractions (Figs. 30, 31, 32). Thus, this data tends to corroborate the findings of Han et al (1966a, b) and suggests that the problem with arrhythmias may be exacerbated in the setting of acute myocardial infarction with slow heart rates. However, this potentially dangerous situation may be offset by the protective effect of the bradycardia and hypotension which lessens the myocardial oxygen demands and may therefore limit the size of the myocardial infarction. These offsetting effects therefore may result in a comparable mortality between anterior and inferior infarctions. Of course it is necessary to compare infarctions of equal size, which was not done in Chadda's study, to accurately make comparisons of the morbidity and mortality in two groups of patients.

TABLE II Distribution of bradyarrhythmia, Ventricular Premature Contractions, Mortality and Effects of Atropine Therapy in 68 Patients with Bradycardia-Hypotension Syndrome*

Symptoms	Atropine Therapy: Response	Atropine Therapy: No Response	Ventricular Premature Complex	No. of Deaths
52 Patients with Inferior Myocardial Infarction				
Sinus bradycardia	28	0	11	2
Atrioventricular dissociation	4	0	1	0
Nodal rhythm	4	0	1	0
Complete heart block	7 (5 NSR, 2 2°b1)	1	3	2
Second degree block	5	1	3	0
First degree block	2	0	1	0
Total	50	2	20	4
14 Patients with Anterior Myocardial Infarction				
Sinus bradycardia	2	0	0	1
Atrioventricular dissociation	0	0	0	0
Nodal rhythm	2	0	1	0
Complete heart block	2	5	4	2
Second degree block	2	0	0	0
First degree block	1	0	1	0
Total	9	5	6	3

NSR = normal sinus rhythm; 2°b1 - second degree block.
* Both patients with subendocardial infarction had sinus bradycardia (Chadda et al, 1975).

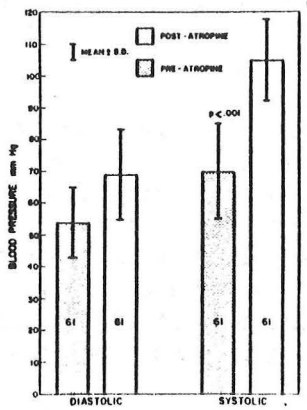

Figure 30. Effect of atropine administration on blood pressure (Chadda et al, 1975).

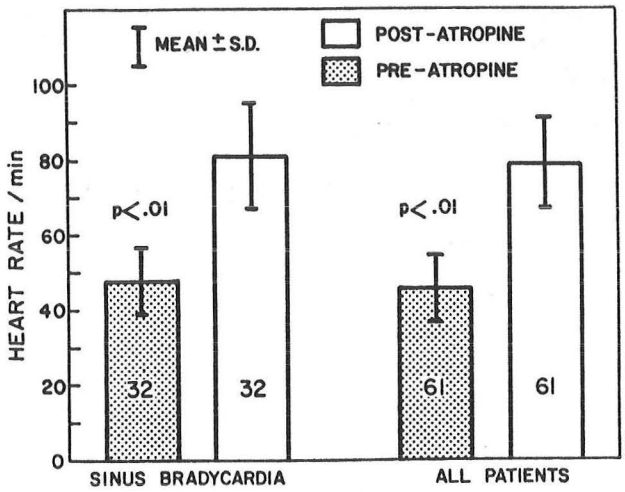

Figure 31. Effect of atropine administration on heart rate (Chadda et al. 1975).

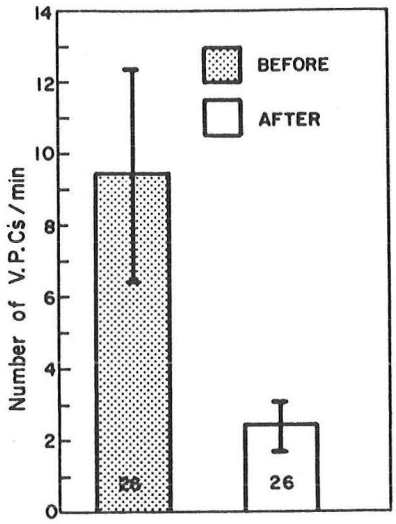

Figure 32. Effect of atropine administration on the number of ventricular premature complexes (V.P.C's) (Chadda et al, 1975).

c. Mediators of reflexes caused by coronary occlusion

i. Bradykinin

There are several possible mediators of the cardiovacular reflexes elicited by coronary artery occlusion. The potential candidates include bradykinin, prostaglandins, potassium, hydrogen ions, lactate and hypercapnia. As mentioned earlier, there are several possible ways to evaluate the importance of these potential mediators. The first way is to use afferent nerve recording studies to determine if receptors can be excited during injection during one of these mediators. A second way would be to determine the reflex cardiovascular response to injection or application of one of these factors.

Bradykinin has been demonstrated to efflux in increased amounts from the coronary sinus following coronary occlusion (Furukawa et al, 1969; Kimura et al, 1973) (Fig. 33).

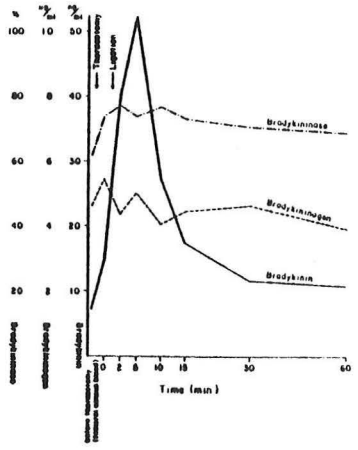

Figure 33. Changes of mean values of bradykininogen, bradykinin, and bradykininase in coronary sinus blood before and after ligation of the coronary artery (Kimura et al, 1973).

Bradykinin stimulates sensory endings in the heart and causes a vagally-mediated reflex bradycardia (and occasionally a tachycardia) and hypotension (Neto et al, 1974; Needleman, 1976; Staszewska-Barczak et al, 1976) (Fig. 34). Specifically, bradykinin stimulates vagal C-fibers with chemosensitive but not those with mechanosensitive endings in the heart and great vessels of a dog. Bradykinin also stimulates sympathetic afferent fibers (Baker et al, 1980). Both mechanosensitive and chemosensitive receptors with sympathetic afferents respond to bradykinin (Baker et al, 1980). Bradykinin stimulates the chemosensitive receptors with a bursting discharge type of pattern that does not have any relation to the cardiac rhythm. On the other hand, bradykinin stimulates the mechanosensitive unmyelinated afferent sympathetic fibers that discharge rhythmically in phase with the cardiac cycle (Uchida and Murao, 1974a; Nishi et al, 1977; Baker et al, 1980).

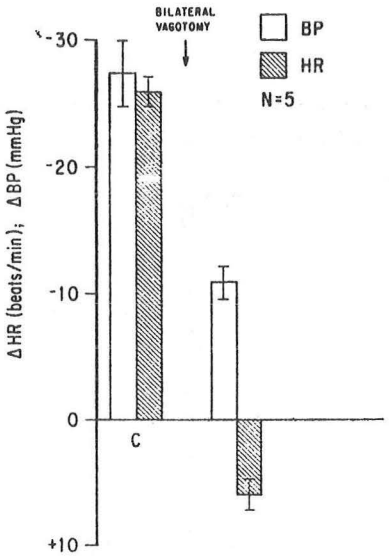

Figure 34. Changes in blood pressure and heart rate produced by intracoronary injection of 1.0 μg of bradykinin before, as indicated by C, and after bilateral cervical vagotomy. Each point represents the mean ± SEM of 5 experiments (Neto et al, 1974).

Both bradykinin and lactic acid stimulate sympathetic afferent fibers when they are applied topically to the myocardium and cause reflex vasoconstrictor and pseudaffective responses in animals (Uchida and Murao, 1974a, 1975; Staszewska-Barczak et al, 1976; Baker et al, 1980; Lombardi et al, 1981). The effect of bradykinin is to stimulate both myelinated and unmyelinated mechanoreceptors with afferent fibers which run with the sympathetic efferent nerves (Uchida and Murao, 1974a; Nishi et al, 1977; Baker et al, 1980). These receptors may be polymodal since they respond to both chemical and mechanical events such as aortic occlusion, coronary occlusion, and bradykinin injection (Lombardi et al, 1981). However, systolic pressure must be raised to very high levels to activate these endings. For instance, systolic pressure must be raised to >200 mmHg to activate these "polymodal" receptors (Lombardi et al, 1981). This data suggests that these receptors normally do not function as mechanoreceptors.

Other studies of sympathetic afferent fibers from the heart have demonstrated that stimulation with bradykinin, cyanide or serotonin causes an excitation of the cardiovascular system similar to that described above (Nishi and Takenaka, 1973; Uchida and Murao, 1974a; Takenaka et al, 1975). The same afferents can be stimulated by ischemia (Ueda et al, 1969; Uchida and Murao, 1974c; Brown and Malliani, 1971). On the other hand, the reflex excitatory effects following the injection of bradykinin into the coronary arteries can be demonstrated only if the vagii are cut (Neto et al, 1974). In this regard, the reflex excitatory effect from bradykinin following epicardial application with the vagii intact, increases after vagotomy (Staszewska-Barczak et al, 1976).

The chemosensitive endings in the heart with sympathetic afferents which can be activated by bradykinin also can be stimulated by large increases in arterial pressure and cardiac volume; these stimuli are considered to be noxious (Baker et al, 1980). These observations strengthen the argument that the chemosensitive endings with sympathetic afferents from the heart which are stimulated by bradykinin are not polymodal as Lombardi has suggested but most likely are nociceptive

receptors. In other organs bradykinin has also been demonstrated to be a mediator of the response to pain. This has been shown to be true particularly for the skin (Beck and Handwerker, 1974; Guilbaud et al, 1976) and possibly in the heart (Sutton and Lueth, 1930; Guzman and Lim, 1962). Bradykinin may also be a mediator of inflammation (Lewis, 1970). Other investigators have argued against bradykinin as a mediator of pain during coronary artery occlusion since the action of bradykinin can be suppressed by acetylsalicylic acid and dipyron whereas the afferent neural activity from coronary occlusion, hypoxia, and injection of epinephrine or isoprenaline is not affected by pretreatment with either of the inhibitors mentioned above (Vogt et al, 1979).

ii. Prostaglandins

Prostaglandins are generated by the myocardium, smooth muscle in the coronary arteries and platelets in the blood. These compounds are released in response to hypoxia, myocardial ischemia (Fig. 35), and increases in preload (Berger et al, 1976; 1977; Needleman, 1976; Staszewska-Barczak et al, 1976). PGE_2, PGA, $PGF_{2\alpha}$, PGI_2, and TxB_2 are all released in experimental animals following coronary artery occlusion (Alexander et al, 1973; Kraemer et al, 1976; Berger et al, 1976; Ogawa et al, 1980; Sakai et al, 1980). The collagen-induced aggregation of human platelets causes the formation of PGE_2 and $PGF_{2\alpha}$ (Smith et al, 1973). These prostaglandins also are formed in association with the secretion of endogenous ADP and serotonin. In addition, atrial pacing causes the release of $PGF_{2\alpha}$ in patients with coronary artery disease with stable angina pectoris (Berger et al, 1977).

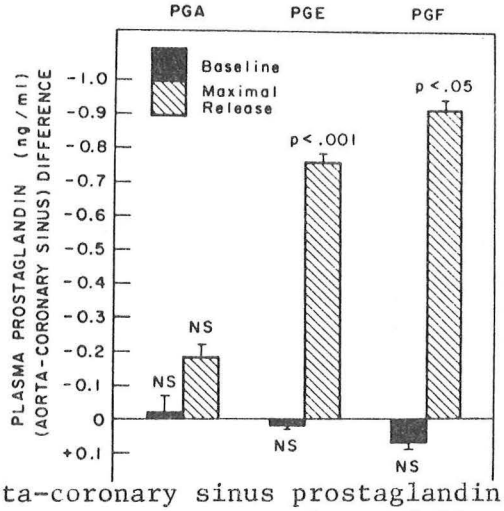

Figure 35. Mean aorta-coronary sinus prostaglandin differences at baseline and at time of maximal prostaglandin release following left anterior descending coronary artery occlusion in seven dogs. Negative values indicate cardiac prostaglandin release. Vertical bars represent standard errors. Statistical significance of coronary sinus prostaglandin levels compared to aortic levels was determined by a paired t-test. NS = not significant (Berger et al, 1976).

Prostaglandins are known to stimulate receptors in the atria, ventricles, pulmonary artery, and aorta with afferent fibers in the vagus (Coleridge et al, 1978; Baker et al, 1979b; Coleridge and Coleridge, 1980). These investigators have determined that the chemosensitive C-fibers, but

not the mechanosensitive C-fibers, are stimulated by prostaglandins. The firing of the fiber remains elevated for several minutes after stimulation even though the prostaglandins very likely are rapidly destroyed. The most consistent stimulation of the cardiac C-fibers comes from PGE_2 and less frequently from $PGF_{2\alpha}$. More recently it has been suggested that prostacyclin (PGI_2), perhaps a more potent coronary vasodilator than the other prostaglandins, stimulates vagal afferent C-fibers (Roberts et al, 1980). In cats, but not in dogs, $PGF_{2\alpha}$ causes a vagally mediated bradycardia and hypotension (Koss and Nakano, 1976). This reflex comes from the coronary arteries or the myocardium since it is not observed when this substance is injected in the aorta distal to the coronary ostia (Fig. 36).

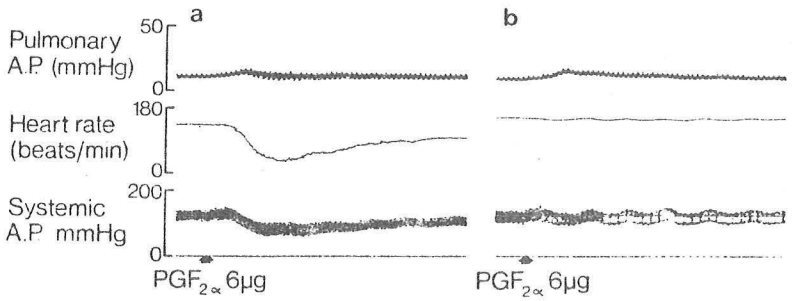

Figure 36. Effects of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 6μg total dose=1.8μg/kg) injected at the level of the origin of the coronary arteries (a) and into the ascending aorta distal to the exit of the coronary arteries (b). Note that the pronounced bradycardia and hypotension is observed only when this agent is able to enter the coronary circulation. Each panel represents 3.5 minutes (Koss and Nakano, 1976).

Prostacyclin or PGI_2 causes a reflex bradycardia and hypotension when it is injected into the left atrium of dogs. This response is dependent upon an intact vagal pathway (Hintze et al, 1979 1981; Chapple et al, 1980). It is unclear whether this response is mediated by cardiac vagal afferent nerves. However, these investigators thought that a reflex was necessary for a portion of the response since there was less bradycardia and hypotension following vagal nerve transection than there was after administration of atropine. Prostacyclin or the generation of another prostaglandin may mediate the reflex bradycardia that has been observed during administration of acetylstrophanthidin (Thames, 1978) or coronary arteriography (Frink et al, 1975).

The excitatory reflex elicited by epicardial application of bradykinin can be reduced by the pretreatment with indomethacin. This suggests that prostaglandins may mediate the reflex sympathetic efferent activation caused by the epicardial application of bradykinin. It has also been demonstrated that PGE_1 and PGE_2 (but not $PGF_{2\alpha}$) can potentiate the excitatory response elicited by epicardial application of bradykinin (Staszewska-Barczak et al, 1976). The effect of potentiation by PGE_1 of the response to bradykinin has been confirmed by sympathetic afferent nerve recording studies (Baker et al, 1978). However, topically applied prostaglandins by themselves generally do not result in any reflex response (Staszewska-Barczak et al, 1976). An exception to the lack of a reflex response elicited by prostaglandins is the muscle vasoconstrictor response

which has been elicited by $PGF_{2\alpha}$ application to the heart. This response is mediated by afferent fibers running with the sympathetic efferent nerves in dogs (Parker and Strandhoy, 1981).

It has been suggested that bradykinin and prostaglandins are released by the ischemic myocardium or factors associated with the ischemic process. These two factors may act in concert to stimulate the sympathetic afferent nerves and to signal the pain of myocardial ischemia (Alexander et al 1973; Block et al, 1974; Wennmalm et al, 1974; Staszewska-Barczak et al, 1976) (Figs. 37, 38, 39). This hypothesis is consistent with the observation by Uchida and Murao (1975) that aspirin inhibits prostaglandin synthesis and reduces the stimulation of sympathetic afferents during coronary artery occlusion. As stated by Coleridge and Coleridge (1978) "the discovery of the action of these naturally occurring substances on afferent nerves of the heart and great vessels and of the reflex effects thereby induced is one of the more important developments in the long history of the chemoreflexes. Of particular interest is the possibility that these or related chemicals may be an integral part of the transduction process at the sensory nerve terminal".

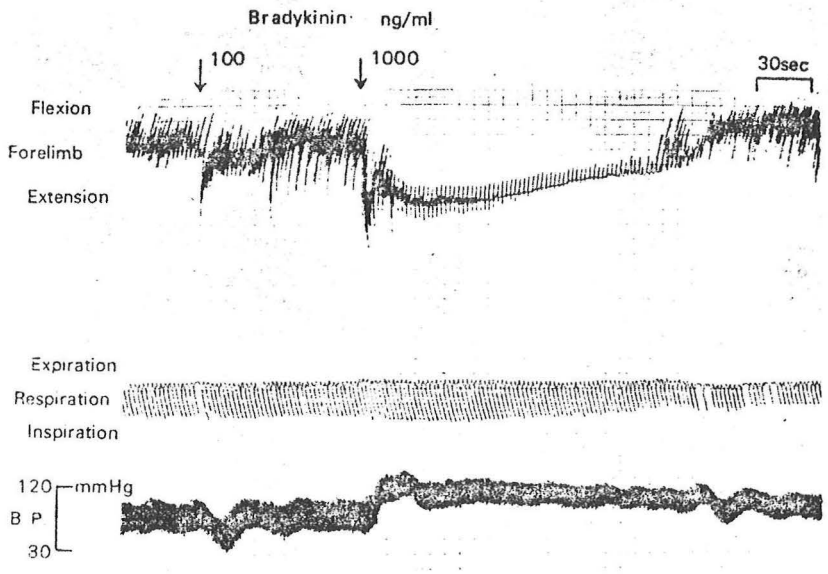

Figure 37. Somato-autonomic reactions elicited by applications of bradykinin acetate solutions on the left ventricular wall. From the top: Motion of the right forelimb, spontaneous respiration and systemic blood pressure. High frequency component of the top record indicates shudder. Note, suppression of shudder, augmented spontaneous respiration, a rise in blood pressure and extension of forelimb, consistent with a pseudaffective response to bradykinin (Ucheda and Murao, 1974).

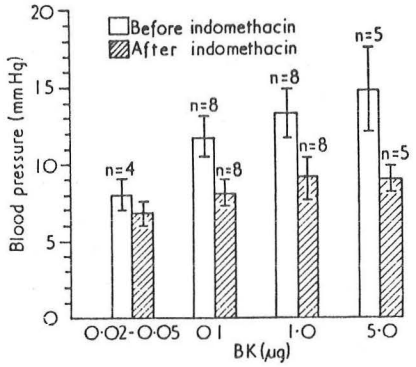

Figure 38. Indomethacin (5 mg/kg, iv) reduces the reflex hypertension elicited by epicardial application of bradykinin (BK). The mean (±SEM; bars) increases in blood pressure induced by four different doses of bradykinin is shown. Indomethacin produced a significant reduction ($P<0.05$) of the pressor response to all but the lowest dose of bradykinin (Staszewska-Barczak et al, 1976).

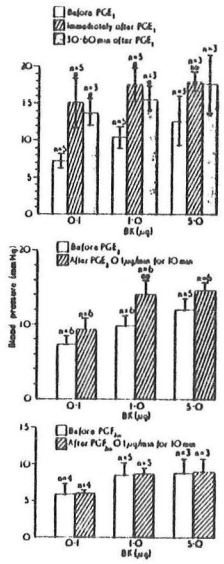

Figure 39. The histograms illustrate the relative activity of the three prostaglandins, E_1, E_2, and $F_{2\alpha}$ (0.1 μg/min for 10 min), as potentiators of the reflex pressor responses induced by epicardial bradykinin. The values are the mean (±SEM; bars) maximum increase in blood pressure induced by three doses of bradykinin (0.1, 1, and 5 μg). *$P<0.02$; **$P<0.05$ (Staszewska-Barczak et al, 1976).

Thus, it is possible that the heavy demands placed upon the myocardium, perhaps in the setting of a coronary stenosis, can locally decrease oxygen tension thereby stimulating the production of bradykinin synthesis (Fig. 40). The bradykinin produced may, in turn, stimulate the local release of prostaglandins. These two factors acting separately or perhaps together may cause local coronary vasodilation. They may also stimulate sympathetic afferent fibers within the myocardium and elicit pain. Lastly, these two factors may initiate a reflex bradycardia and depressor response which would decrease the demand of the myocardium for oxygen (Needleman, 1976).

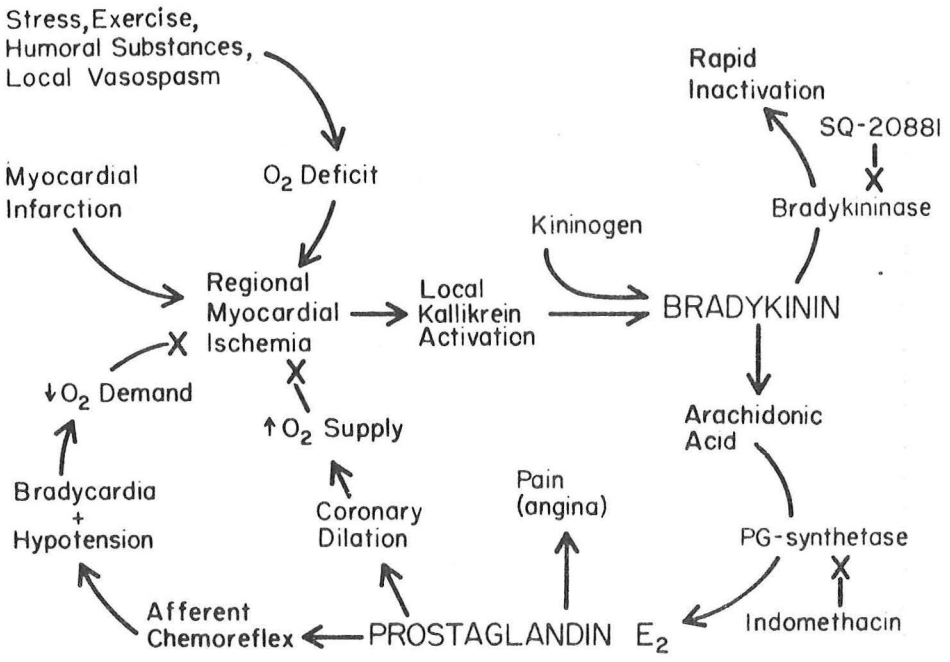

Figure 40. Hypothetical scheme for the interrelationship between bradykinin and prostaglandin in the heart (Needleman, 1976).

Considering studies of patients with coronary artery disease, aspirin and indomethacin, potent inhibitors of the prostaglandins, have been shown to decrease TxB_2 concentrations, but have not been demonstrated to alter the frequency or severity of chest pain in patients with Prinzmetal's angina (Robertson et al, 1980a, b; Chierchia, 1980). Further, Hirsh et al (1981) failed to demonstrate an increase in TxB_2 by any of several provocative tests in patients with stable angina pectoris. However, patients with unstable angina pectoris were demonstrated to have increased production of TxB_2 (Hirsh et al , 1981). Thus, prostaglandin production may be involved with chest pain or cardiovascular reflexes in only certain of the more severe forms of myocardial ischemia.

iii. Hypoxia, Hypercapnia

Both mechanosensitive and rarely chemosensitive vagal afferents may be stimulated by hypoxia (Baker et al, 1979a). The response of the mechanosensitive afferent vagal fibers is probably a result of a wall motion abnormality since these fibers fire with a cardiac rhythm. The rare chemosensitive fiber which fires in response to hypoxia does so in a sporadic or bursting pattern that is unrelated to the cardiac cycle. These fibers may be aberrently located aortic body glomus tissue and perhaps should be called chemoreceptors rather than receptors with chemosensitive endings (Baker et al, 1979a). The effect of hypercapnia on these endings not been tested. However, local coronary hypoxia and hypercapnia in animals with and without vagotomy (PO_2 = 43 mmHg, PCO_2 > 100 mmHg, pH = 6.96) does not cause any reflex hemodynamic effects (Mark et al, 1974). This same gas mixture in the blood profoundly activates the aortic chemoreceptors.

iv. Serotonin

The aggregation of human platelets causes the release of serotonin (Smith et al, 1973). Serotonin causes a hypertensive cardiogenic chemoreflex when it is infused into the proximal left coronary artery of dogs (Eckstein et al, 1971; James et al, 1975; Hagman et al, 1978; Urthaler et al, 1978; Parker and Strandhoy, 1981). The afferent pathway for this reflex lies in the vagus nerve. The actual receptive area for this response very likely is the aortic body which is supplied by a small branch of the proximal left coronary artery (Coleridge et al, 1967). The hypertensive reflex is markedly diminished in the conscious dog which shows an initial depressor and a later smaller pressor response than is observed in the unconscious animal (Zucker and Cornish, 1980). It has been postulated that there is a marked increase in blood pressure resulting from liberation of serotonin by platelets. This hypertensive response may help to preserve coronary flow by dislodging the platelet aggregation. Similar types of responses have been noted with $PGF_{2\alpha}$ which, along with serotonin, is released by platelets in animals (Smith et al, 1973; Hamberg and Samuelsson, 1974). It has been speculated that the coronary hypertensive reflex elicited by local release of $PGF_{2\alpha}$ or serotonin within the coronary vascular bed may be responsible for the early hypertension which occurs in some patients soon after a myocardial infarction.

d. Hypertension associated with acute myocardial infarction

A number of patients develop hypertension spontaneously during angina (Figueras and Cinea, 1981). However, it is often not possible to reproduce the angina by simply elevating the blood pressure to the same level as the patient experienced during the angina pectoris. Some investigators have argued that, some patients, particularly who have variant angina, may develop the increase in blood pressure as a consequence and not as a cause of the angina. One might speculate that ischemia caused the hypertension by stimulting a cardiogenic reflex with a sympathetic afferent pathway. However, this suggestion is speculative and has not been proven at the present time. Many investigators however, have demonstrated that the onset of chest pain and the increase in blood pressure occur virtually simultaneously suggesting that the increase in blood pressure frequently does not precede the chest pain and therefore is unlikely to be a cause of it (Guazzi et al, 1975; Scheidt et al, 1976; Figuero et al, 1979).

A retrospective analysis of 87 consecutive infarction patients has recently been completed to determine the incidence of myocardial infarction-related hypertension (Dye et al, 1978). It could be demonstrated that a subgroup of these patients had not previously had a myocardial infarction, had not been hypertensive previously, and had not received medication on admission to elevate their blood pressure. Of this patient population 43% (19 of 44 patients) were hypertensive on admission with a blood pressure averaging 165/106. This hypertension persisted for an average of 9 hours. In 11 patients the blood pressure increased before the onset of chest pain suggesting that pain was not the etiology of the hypertensive response in these patients. There was no relation to the site of myocardial infarction (9 were anterior and 10 were posterior).

However, most patients (10 of 11) that were studied with coronary angiography had severe proximal coronary artery occlusions involving the left anterior descending or the left circumflex coronary arteries. The authors speculated that this response was a hypertensive coronary chemoreceptor reflex. The hypertension did not adversely affect prognosis unless the patient had been previously hypertensive. On the other hand, there was no evidence that the hypertension improved prognosis. The authors therefore cautioned against vigorous therapy of the hypertension since it appeared to not adversely affect prognosis and was limited to a relatively short period of time.

e. Hypertension following cardiopulmonary bypass surgery

In the immediate post-operative period following cardiopulmonary bypass, especially with coronary artery bypass surgery, a significant number of patients develop hypertension (Estafanous et al, 1973; Fouad et al, 1978; Fouad et al, 1979). This clinical situation is quite serious since it may be associated with hemorrhage, myocardial decompensation, and/or arrhythmias (Estafanous et al, 1973; Chaptal et al, 1975; Viljoen et al, 1976). These patients have an unchanged cardiac output and an increased total peripheral vascular resistance (Fouad et al, 1978). The hypertension cannot be related to overtransfusion (Fouad et al, 1978). Either right or left unilateral stellate ganglion blockade causes a rapid return of the blood pressure to normotensive levels and returns vascular resistance to normal in two thirds (18 of 27) of the patients. The return of the systemic vascular resistance to normal is not due to a reduction of cardiac output although heart rate significantly decreases. These data suggest that this phenomenon is a cardiogenic reflex perhaps mediated by sympathetic afferent fibers traveling through the stellate ganglion. It is unclear, however, how important pain and the relief of pain is for this syndrome, although post-bypass hypertension occurs in patients who have not sustained a myocardial infarction (Tarazi et al, 1978).

2. Coronary Angiography

It is well recognized that injection of contrast dye into the coronary arteries results in a bradycardia. Eckberg et al (1974) demonstrated that the cardiac response contrast injection was due to the hyperosmolarity of the contrast solution and was not merely a result of the increase in coronary artery pressure. These investigators also noted that a greater effect could be elicited by injection into vessels supplying the sinus node artery but could still be caused by injection into the contralateral vessels. Since atropine abolished the response they postulated that it was a reflex originating from the heart with an efferent pathway in the parasympathetic nerves. Other investigators have demonstrated that the bradycardia response to left anterior descending injection was a reflex which could be inhibited by selective intracoronary injection of atropine (Frink et al, 1975). On the other hand, the response to injection of contrast dye into the right coronary artery was a combination of a direct and a reflex effect of the dye upon the pacemaker tissue. The direct effect was a result of the dye entering the sinus and AV nodal arteries which commonly arise from the right coronary artery (Frink et al, 1975). Thus, it appears that the effect of injection of contrast material into the right coronary artery results in a greater sinus bradycardia when the right coronary artery

is the dominant vessel supplying blood to the pacemaker regions of the heart (Perez-Gomez and Garcia Aguado, 1977) (Fig. 41).

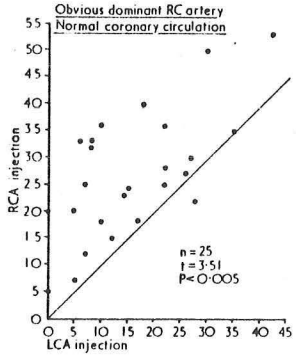

Figure 41. Decrease of sinus rate during injection of the right coronary artery (RCA injection) and of the left coronary (LCA injection) in 25 cases with an obvious dominant right coronary artery (Perez-Gomez and Garcia-Aquado, 1977).

Although the above studies suggested that the bradycardia and systemic vasodilation response to injection of contrast dye into the coronary arteries was a reflex, definite proof has come from Zelis et al (1976). These investigators have demonstrated a reflex cholinergic vasodilation in the forearm during contrast dye injection into the left coronary artery (Figs. 42, 43).

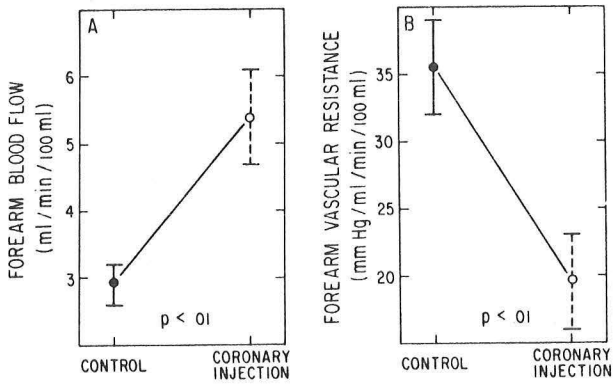

Figure 42. Mean changes in forearm in forearm blood flow (A) and forearm vascular resistance (B) induced by the injection of contrast dye into the left coronary artery. Control values are indicated by filled circles and those following coronary injection by open circles. Brackets indicate standard error of the mean (Zelis et al, 1976)

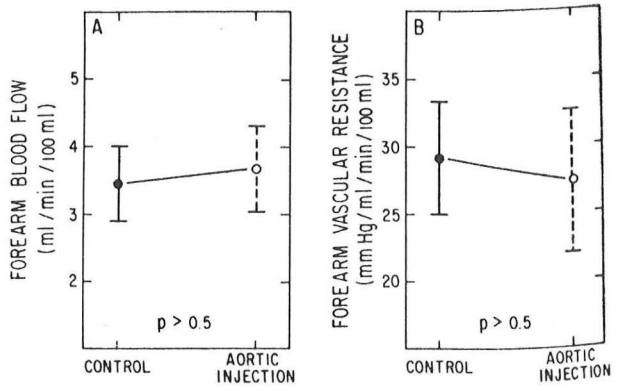

Figure 43. Changes in the forearm blood flow (A) and forearm vascular resistance (B) induced by the injection of 8cc of contrast dye into the ascending aorta above the coronary ostia (Zelis et al, 1976).

3. Arrhythmias

Atrial fibrillation results in an increase in left atrial pressure and a stimulation of the type B receptors by 25-30%. The increased receptor discharge occurs in an asynchronous pattern (Zucker and Gilmore, 1973) (Fig. 44). This situation could result in erroneous information being sent to the central nervous system and might result in an inappropriate diuresis (Fig. 45). Such a situation has been postulated to occur in humans (Wood, 1963). In fact, polyuria tends to occur with many forms of paroxysmal tachycardia lasting over 20 minutes particularly if the associated heart rate is greater than 110/min (Table III).

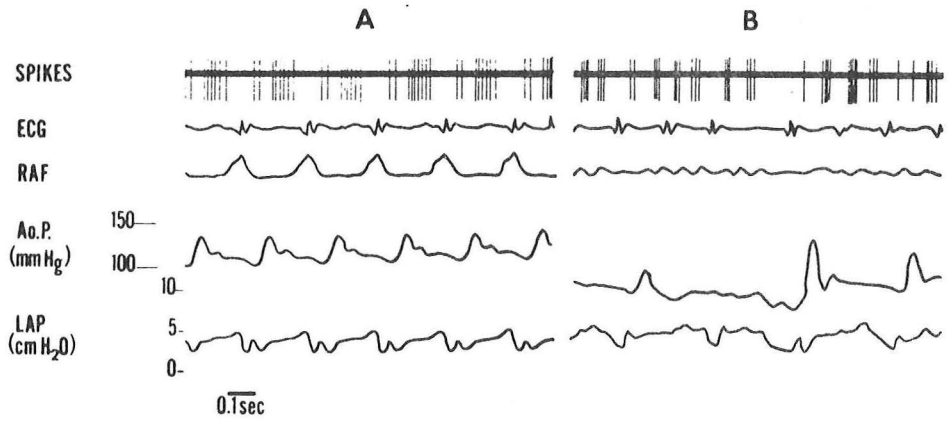

Figure 44. Recording of activity from a type B left atrial receptor during atrial fibrillation. SPIKES, neurogram; ECG, electrocardiogram; RAF, right atrial force; Ao.P., aortic blood pressure; LAP, left atrial pressure. All recordings were made during expiration. A: control. B: atrial fibrillation (Zucker and Gilmore, 1981).

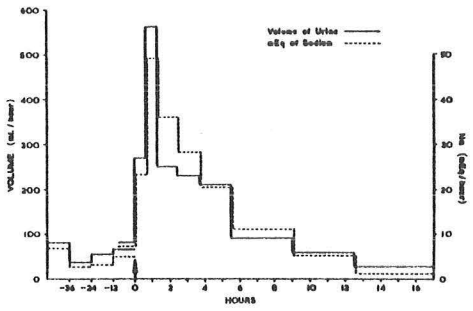

Figure 45. Chart showing the increased volume of urine per hour and the increased output of sodium during an attack of paroxysmal atrial fibrillation that lasted 18 hours: the onset is indicated by an arrow. The increases started within 5 to 10 minutes, as was usual with this patient, and were considerable for 5½ hours, with a peak at about 1 hour. The urine had been measured and analysed for 48 hours, a week before this attack, and this is shown on the chart before the attack, as a control. From a woman, aged 60, with hypertension and a cardiomyopathy (Wood, 1963).

Table III Incidence of Polyuria in Various Paroxysmal Arrhythmias

Nature of arrhythmia	No. of cases	No. with polyuria	Percentage
Atrial fibrillation	19	13	68
Atrial flutter	8	5	63
Atrial tachycardia	8	2	25
Nodal tachycardia	2	0	--
W.P.W. syndrome	6	3	50
Uncertain	16	8	50
Ventricular tachycardia	5	2	40
Total	64	33	51.5

(Wood, 1963)

In contrast to the situation with paroxysmal atrial tachycardias and atrial fibrillation, sinus tachycardia usually results in a decreased receptor discharge because of a decrease in left atrial filling (Zucker and Gilmore, 1973). Further, patients with mitral stenosis usually do not develop a diuresis when they go into atrial fibrillation probably because of the hypotension that results from the almost immediate decrease in cardiac output causes an increase in aldosterone secretion. The increase in aldostrone secretion will antagonize the decrease in ADH and decrease in renal flow which would result from an increased left atrial distension consequent to the atrial fibrillation (Wood, 1963).

The possibility of cardio-cardiac reflexes also may be important in the genesis of ventricular arrhythmias. For instance, cooling or ablation of the left stellate ganglion increases the ventricular fibrillation threshold. On the other hand, cooling or ablation of the right stellate ganglion decreases the ventricular fibrillation threshold (Schwartz et al,

1976b) (Fig. 46). The effect of raising the ventricular fibrillation threshold with left stellate ganglion cooling holds true for both the anterior part of the right ventricle as well as the posterior part of the left ventricle. Schwartz concluded from these studies that left stellate ablation decreases the temporal dispersion of refractory periods whereas right stellate ablation increases dispersion of refractory periods. This finding is consistent with observations by other investigators that the cardiac sympathetic nerves and the left stellate ganglion in particular is more important than the right stellate ganglion in producing arrhythmias (Armour et al, 1972; Hagman et al, 1973; Schwartz et al, 1975). It is also consistent with the observation that bilateral stellectomy increases the ventricular fibrillation threshold (Kliks et al, 1975). Whether or not these studies can be extrapolated to man is somewhat questionable since very high heart rates induced by pacing were used (heart rate = 213 beats/min). In addition, the animals were vagotomized to inhibit any tonic parasympathetic activity. This maneuver was performed because it is known that an increase in vagal tone can alter the ventricular fibrillation threshold (Kent et al, 1973). Nevertheless, the high heart rates and vagotomized state removes the applicability of these animal studies from the situation in man, particularly the neurally intact man with heart rates between 60 and 100 beats/min.

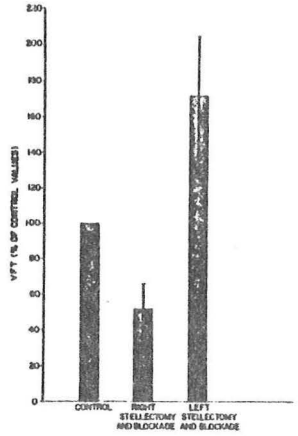

Figure 46. Effect of unilateral stellectomy and blockade on ventricular fibrillation threshold (VFT). Right stellectomy and blockade (11 animals) lowered the ventricular fibrillation threshold by 48 ± 14 percent compared with control values ($P<0.001$), left stellectomy and blockade (9 animals) raised the threshold by 72 ± 33 percent compared with control values ($P<0.001$) (Schwartz et al, 1976b).

Since the above studies did not prove whether the effect of stellectomy was due to interruption of an afferent or an efferent pathway, Schwartz et al (1976a) performed further studies designed to examine these possibilities. To do this, they briefly occluded (5-90 sec) a coronary artery of vagotomized dogs and cats both before and after transection of the dorsal roots C_8-T_5. They noted a decrease in the absolute number of ectopic beats by 63% with dorsal root section. They concluded that there was an excitatory reflex mediated by sensory fibers which traveled with the sympathetic nerves and that excitation of these fibers led to increased efferent sympathetic tone and the production of arrhythmias during coronary

occlusion (Figs. 47, 48). A similar type of reflex may be operative for the digitalis-induced arrhythmias since these compounds are also known to excite cardiac receptors (see below).

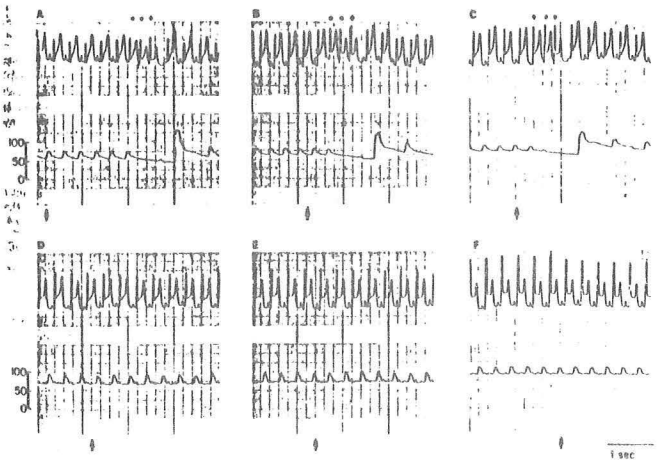

Figure 47. Vagotomized dog. Upper trace: ECG (limb lead II). Lower trace: aortic blood pressure (mmHg). Arrows indicate release of 60 second occlusions of both circumflex and left descending coronary arteries. A, B, and C show three consecutive coronary artery occlusions performed in control condition. A brief episode of nodal tachycardia (3 consecutive nodal beats marked by asterisks) follows release of occlusion. D, E, and F are three consecutive coronary artery occlusions performed after dorsal root section: episodes of nodal tachycardia are no longer present. Low level of blood pressure was produced by coronary artery occlusions (Schwartz et al, 1976a).

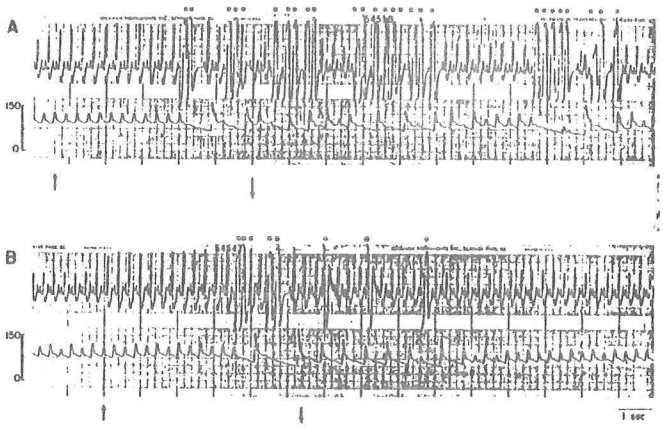

Figure 48. Vagotomized dog. Tracings as in Fig. 47. Arrows indicate a 5 second occlusion of left descending coronary artery. In A, a coronary artery occlusion during control conditions produces a large number of premature ventricular beats, marked by asterisks, which result in runs of ventricular tachycardia. In B, same occlusion after dorsal root section produces only a few ectopic beats (Schwartz et al, 1976a).

4. Congestive Heart Failure

As discussed above, vagal afferent nerves from the heart may play an important part in the control of plasma ADH, renal nerve activity, and plasma renin activity. It has been demonstrated that patients with heart failure have high left atrial pressures and high ADH levels (Stein et al, 1954; Yamane, 1968). The inappropriately high ADH levels may contribute to the peripheral edema, ascites, and hyponatremia that is often seen in patients with heart failure (Zucker et al, 1977) (Fig. 49). Although the ADH levels would be expected to be decreased with increased stretch of the left atrium, it is possible that the left atrial receptors may adapt when they are subjected to chronic stretch (Greenberg et al, 1973; Aujuchovskij et al, 1976; Zucker et al, 1977). These investigators have demonstrated in several animal models using tricuspid insufficiency combined with pulmonary stenosis (Greenberg et al, 1973) or an A-V fistula (Zucker et al, 1977) that the phenomenon of atrial receptor adaptation is reversible.

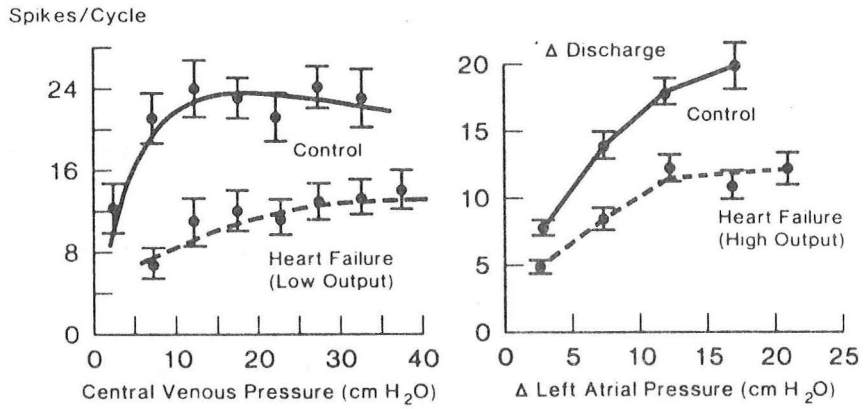

Figure 49. Decreased activity of cardiac vagal afferent fibers in two different animal models of heart failure (Adapted from Greenberg et al, 1973 and Zucker et al, 1980).

Acute depression of left atrial contractility with propranolol does not cause resetting of the receptor discharge (Gilmore and Zucker, 1974). The difference between acute propranolol administration and chronic congestive heart failure is a decreased compliance of the atrium which occurs only in the latter situation (Zucker and Gilmore, 1981). With a decrease in compliance there is actually less atrial distension for any given increase in pressure.

In addition to an altered left atrial compliance, there may be abnormalities of the axons which terminate in the left atrium. These have been shown to be diffuse and fragmented (Zucker and Gilmore, 1981). Unfortunately it is not known if these histological abnormalities are truly abnormal since in normal animals there are a variety of different types of endings and the diffuse fragmented endings observed in heart failure animals may be simply one end of this spectrum.

Approximately 50% of the vagal C-fibers increase their discharge rate following the epicardial application of acetylstrophathidin (Sleight et al, 1969). Further, cooling the vagus blocks the reflex hypotension and

bradycardia response to epicardial application of this digitalis glycoside. Unmyelinated ventricular receptors with a sparse resting discharge are not only stimulated by digitalis glycosides but are sensitized by these drugs so that they respond more vigorously to aortic occlusion (Oberg and Thorén, 1972). The response of the ventricular receptors to the digitalis glycosides is similar to the response that has been observed with the arterial baroreceptors (Quest and Gillis, 1971).

Not only is the discharge of receptors with unmyelinated ventricular afferent fibers increased, but the discharge of atrial receptors is enhanced by cardiac glycosides (Zucker et al, 1980). The enhancement of the atrial receptor discharge by these drugs occurs over a broad range of left atrial pressures and occurs in the absence of any changes in heart rate or mean arterial pressure (Fig. 45). This heightened sensitivity of the left atrial receptors applies to those with a type B discharge pattern, i.e., firing during the left atrial v wave (Zucker et al, 1979).

The reflex responses from either intracoronary or epicardial administration of acetylstrophanthidin is a bradycardia and vasodepression and a decrease in renal efferent sympathetic nerve activity (Thames, 1979). The reduction in renal nerve activity persists with volume loading (Thames et al, 1980). It has been postulated that digitalis, by the mechanisms mentioned above, may reduce plasma ADH and restore renal function in patients with congestive heart failure (Fig. 50). This response may also explain why patients with heart failure who receive digitalis demonstrate a vasodilation rather than a vasoconstriction, the typical response in subjects without heart failure (Mason and Braunwald, 1964).

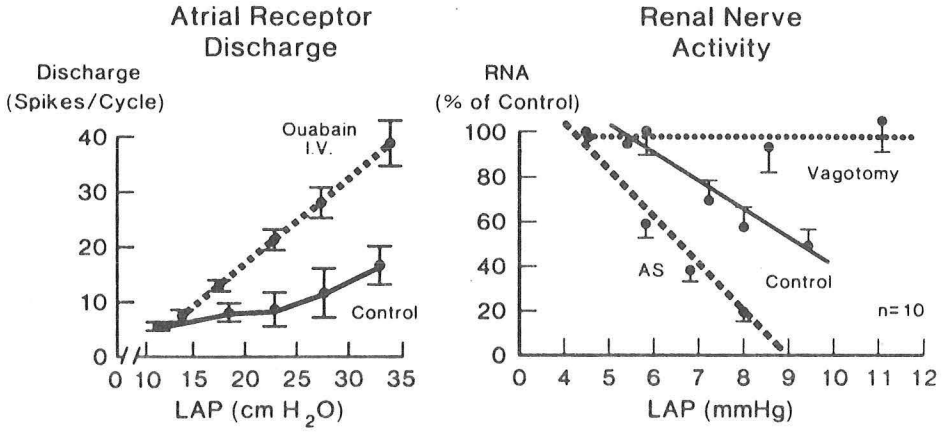

Figure 50. Effects of intravenous ouabain (left) and intracoronary acetylstrophanthidin (AS; right). LAP, left atrial pressure (Thames et al, 1980 and Zucker et al, 1980).

Dogs with chronic (15-23 months) mitral stenosis develop fibrosis and calcification of the left atrium and less of an increase in ADH in response to a 5 or 10% hemorrhage (Zehr et al, 1971). However, the left atrial pressure never falls below 15 mmHg in these animals so that there may not be a significant reduction in the receptor discharge from the left atrium during hemorrhage. Stimulation of the left atrium in the opposite direction, i.e. increasing left atrial pressure by 10-15 mmHg, with a

concomitant decrease in mean arterial pressure by 10 mmHg causes an increase in urine flow and free water clearance in normal but not in heart failure dogs (Fig. 51). Although renin activity is increased in the heart failure dogs it does not change in either normal or heart failure animals with balloon inflation (Zucker et al, 1979). This data contrasts with that of Zehr et al (1976) who demonstrated a suppression of renin release in response to hemorrhage. Possible differences between these two studies are different modes of stimulation of the left atrium, distension vs. contraction with hemorrhage, and differences in methods of measurement of plasma renin. Heart failure dogs demonstrate greater plasma ADH levels at rest. Left atrial balloon distension decreases plasma ADH levels in both heart failure and normal dogs but, because the ADH starts from a higher level in the heart failure animals, it is still high enough to maintain an antidiuretic state even after balloon distension of the left atrium (Fig. 52). It is unclear why ADH still decreases significantly in heart failure animals if there is a decreased receptor activity resulting from a decrease in atrial compliance. Also, it is not clear if the receptors recorded in dogs represent those which mediate a change in ADH during atrial stimulation. Finally, it is possible that balloon distension of the left atrium could stimulate receptors in areas other than the left atrium such as the pulmonary veins and pulmonary arteries.

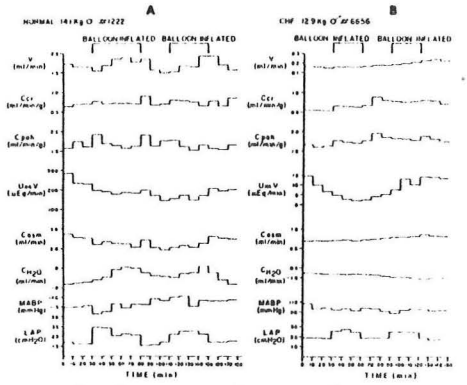

Figure 51. Time course of changes in various parameters in response to left atrial balloon distension in a normal dog (A) and a dog with congestive heart failure (B) (Zucker and Gilmore, 1981).

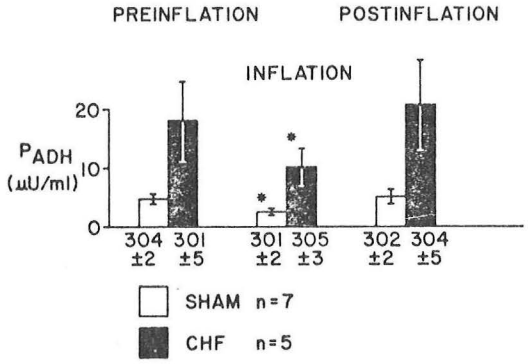

Figure 52. Plasma ADH concentrations in normal dogs and dogs with congestive heart failure before, during, and after inflation of balloon in left atrium. Data are means ± SE. *Values are statistically significant from those for pre- and post-inflation periods. Numbers below bars are corresponding plasma osmolalities (Zucker and Gilmore, 1981).

There may be an increase in activity of the cardiac afferent nerves during the early hypervolemic phase of heart failure (Watkins et al, 1976). This may result in a decreased neurohumoral drive to the circulation. In chronic heart failure there may be a decreased cardiac afferent nerve activity resulting in an increased neurohumoral drive with associated vasoconstriction, sodium retention, and augmentation of certain excitatory reflexes (Abboud et al, 1981). In humans this would be manifest by the increased circulating norepinephrine, increased plasma renin activity, and increased angiotensin (Chidsey et al, 1962; DeChamplain et al, 1963; Genest et al, 1968; Levine et al, 1980). The improvement with digitalis, diuretics, and sodium restriction may restore the cardiac afferent nerve stimulation, thereby inhibiting the prevailing neurohumoral excitatory state of heart failure. The result may be a peripheral vasodilation, naturesis, and diuresis and a decrease in the afterload presented to the heart.

To partially verify the above hypotheses, Thames and Abboud (1979) have demonstrated that vagotomy abolishes the decrease in renal nerve activity occurring with expansion of blood volume (Fig. 53). Also, they have shown that vagal cooling causes an increase in the plasma ADH at any given carotid sinus pressure. This effect is most pronounced at lower carotid sinus pressures (Thames and Schmid, 1979). Finally, vagotomy has been shown to release the tonic inhibition of plasma renin and prevent the increase in response to hemorrhage (Mancia et al, 1975a; Thames et al, 1978; Thames and Schmid, 1979). Thus, in general, a reduction in the cardiopulmonary afferent vagal discharge facilitates the neurohumoral excitation of the cardiovascular system. However, these experiments do not prove that the atrial receptors or even the heart is the receptive area mediating this neurohumoral drive.

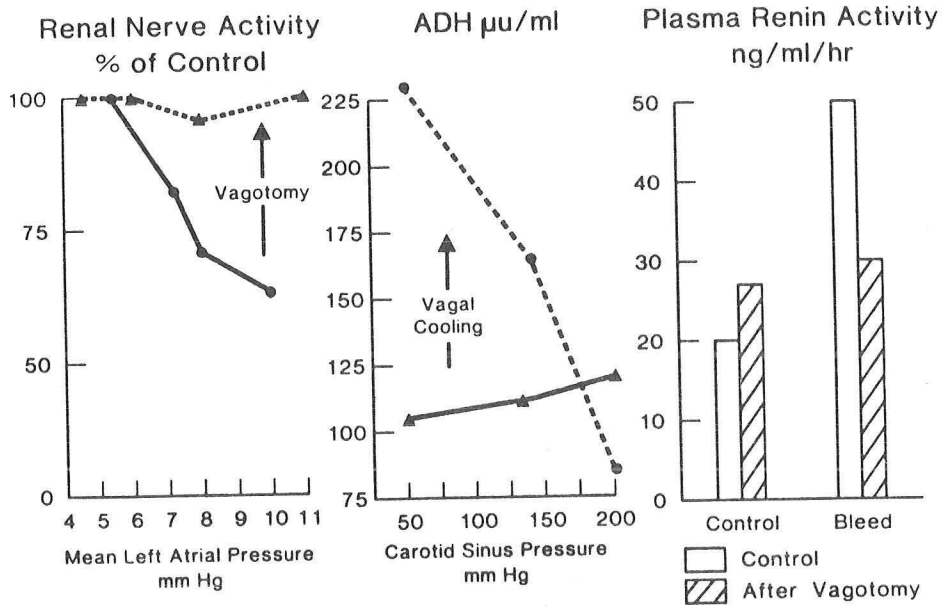

Figure 53. Influence of vagal afferent nerves on renal sympathetic afferent activity, antidiuretic hormone (ADH), and renin (Thames and Schmid, 1979, Thames et al, 1978, 1980).

There is enhanced sympathetic drive during exercise in patients with heart failure as compared to normal subjects. This is manifested by the much larger increases in circulating plasma norepinephrine in heart failure as compared to normal subjects who are exercising (Chidsey et al, 1972). Additionally, patients in congestive heart failure have larger increases in plasma venous tone as compared to patients who have recovered from the heart failure (Wood, 1962). Patients with congestive heart failure also have less vasodilation in their exercising extremities compared to normal subjects (Zelis et al, 1974; Longhurst et al, 1976). Part of the diminished active hyperemia is due to decreased compliance of the vessels and part is due to an excessive neurogenic vasoconstriction interacting with the metabolic vasodilation (Zelis et al, 1974).

Patients with heart failure do not decrease their systemic vascular resistance during exercise as do normal subjects. This may result from the excessive vasoconstrictor activity or perhaps the less compliant vessels which do not have the ability to dilate in response to a metabolic stress (Zelis et al, 1974; Longhurst et al, 1976; Thadani and Parker, 1978).

The reflex renal vasoconstriction elicited by somatic afferent nerve stimulation is inhibited by volume loading and is enhanced by vagotomy in dogs (Thames and Abboud, 1979). This data suggests that there is an interaction between somatic afferent-induced renal vasoconstriction and cardiac afferent-induced renal vasodilation. However, a major problem with this type of experiment is that sciatic nerve stimulation is very dissimilar to exercise.

Unloading the cardiopulmonary receptors with lower body negative pressure during handgrip static exercise in humans causes an exaggeration of the pressor response as well as an exaggeration of the vasoconstrictor response in the non-exercising forearm (Walker et al, 1980). This experiment is much more conclusive in demonstrating the interaction of skeletal muscle and cardiopulmonary afferents. However, it suffers from the limitation that it does not localize the cardiopulmonary receptors to the heart since pulmonary baroreceptors also may be unloaded by this maneuver.

In congestive heart failure there is renal cortical vasoconstriction in dogs (Barger, 1966; Sparks et al, 1972) and in humans (Kilcoyne et al, 1973). This regional renal vasoconstriction may be responsible for the decreased sodium excretion during heart failure in dogs (Barger, 1966) and in humans (Brod, 1972). During exercise the renal vasoconstriction is further enhanced in dogs (Millard et al, 1972).

There are no studies of the cardiac C-fibers in congestive heart failure. However, Thorén and Ricksten (1981) believe that the atrial C-fibers are probably reset in a manner similar to the myelinated atrial afferent fibers, due to the altered compliance of the left atrial wall. The decreased contractility resulting from propranolol may also decrease C-fiber discharge from the atria. Although there is no information on the renal effects of cardiopulmonary activation in patients with heart failure, Thorén and Ricksten (1981) speculate that an impaired activation of the cardiopulmonary receptors may contribute to the abnormal control of renal function in heart failure. Acute myocardial infarction and heart failure

can cause an increase in renal flow, sodium output, and glomerular filtration rate despite the presence of hypotension (Bennet et al, 1977). It is possible that activation of the cardiac C-fibers from an increase in left atrial pressure or a wall motion abnormality may reflexly inhibit the renal sympathetic outflow.

5. Hypertension

In the spontaneously hypertensive rat there is a resetting of the atrial receptors so that there is less discharge for any given left atrial pressure (Thorén et al, 1979a, b) (Fig. 54). This situation will actually increase renal efferent sympathetic discharge (Ricksten et al, 1979). The mechanism for the reduced receptor response is a reduced distensibility of the left atrium in hypertensive rats in response to a rapid, but not to a slow infusion (Thorén and Ricksten, 1981) (Fig. 55). Despite the reduced left atrial receptor sensitivity in the hypertensive rats, the mean left atrial pressure is much higher in these animals compared to normotensive controls (Fig. 56). This increase in left atrial pressure offsets the reduction in receptor sensitivity so that there is actually a greater inhibition of splanchnic (and possibly renal) efferent sympathetic discharge in response to a volume infusion in the hypertensive animals (Ricksten and Thorén, 1981). The reduced receptor sensitivity in the hypertensive animals may prevent the efferent sympathetic discharge from becoming inordinantly increased and compromising the function of one or several regional circulations.

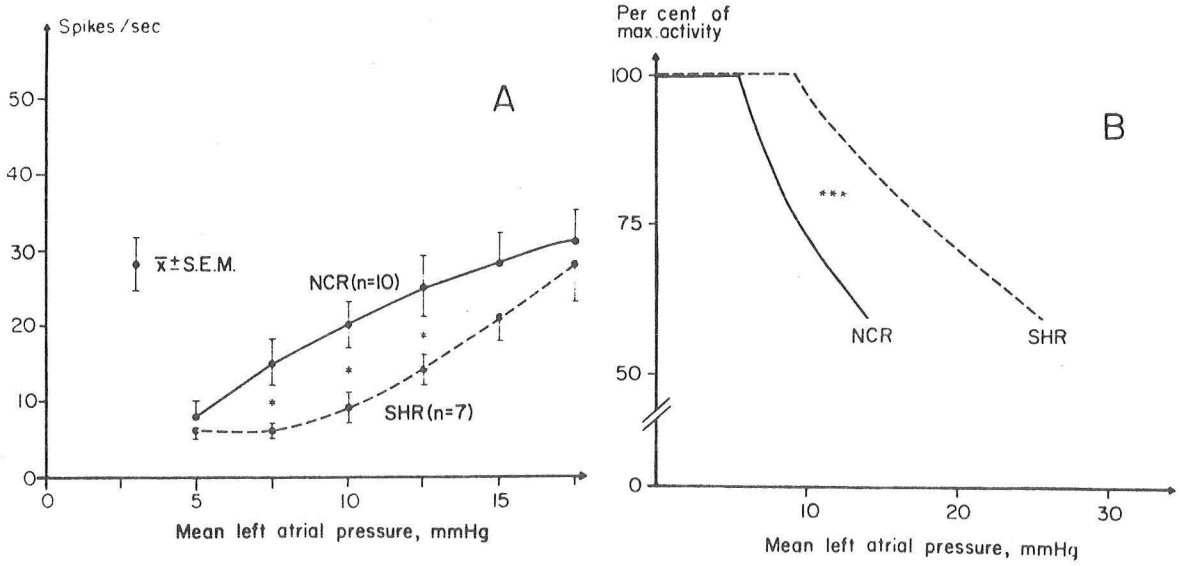

Figure 54. A: mean activity in left atrial C-fibers plotted against mean left atrial pressure for 10 receptors in normotensive rats and 7 receptors in hypertensive rats. Thresholds for C-fiber endings in normotensive rats are around 9-10 mmHg. From 5 to 12.5 mmHg there is a significant difference between the 2 groups of animals (*P<0.05). B: relation between mean left atrial pressure and reflexly induced inhibition of renal sympathetic outflow for 6 normotensive and 6 hypertensive sinoaortic-denervated rats. Activity in renal nerves is inhibited at considerably higher pressure levels in hypertensive animals (***P<0.001) (Thorén, 1979).

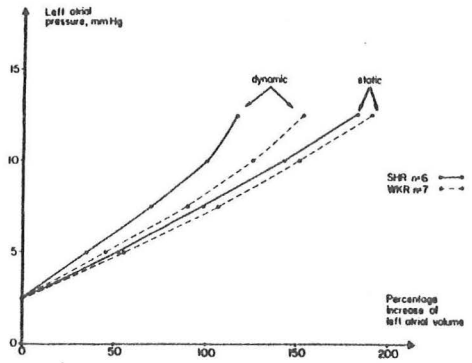

Figure 55. Average pressure-volume curves from spontaneously hypertensive rats (SHRs) and Wistar-Kyoto rats (WKRs) when left atrial pressure was increased either slowly (static distensibility) or rapidly (dynamic distensibility) in the same experiment. There was no difference in static distensibility between the 2 groups. However, there was a difference in dynamic distensibility ($P<0.01$) (Thorén and Ricksten, 1981).

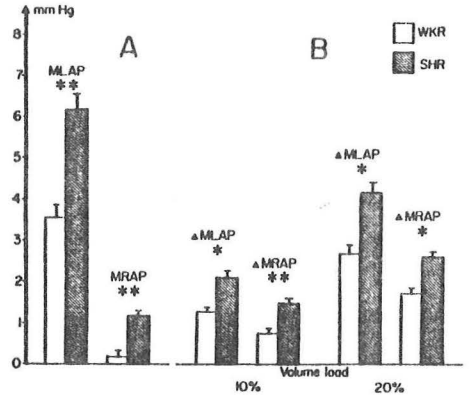

Figure 56. A: mean left atrial pressure (MLAP) and mean right atrial pressure (MRAP) in Wistar-Kyoto rats (WKRs) and spontaneously hypertensive rats (SHRs) measured in awake animals. B: change in MLAP and MRAP on volume load with blood corresponding to 10% and 20% of total blood volume (Thorén and Ricksten, 1981).

It may be possible to extrapolate the above animal data to the human counterpart. Thus, patients with mild hypertension and low renin have a 30% increase in central blood volume but a normal total blood volume (Willis et al, 1976; Julius and Esler, 1977). The increased central blood volume may reflexly inhibit the release of renin through stimulation of the cardiopulmonary receptors (Thorén et al, 1979c). Other patients with hypertension and a mild high or borderline elevated plasma renin have increased sympathetic efferent discharge. They do not have an increase in their central blood volume (Esler et al, 1977). Still other subjects with chronic and more severe hypertension do not demonstrate an inverse relationship between central blood volume and plasma renin activity (London et al, 1977). It is possible that the increased central blood volume in these patients does not suppress renin because the cardiac receptors have been reset.

6. Aortic Stenosis

Patients with severe aortic stenosis quite commonly experience syncope. It has been thought that the syncope results from a sudden failure of the myocardium resulting in a decreased cardiac output and decreased cerebral blood flow which leads to a loss of consciousness. However, Mark and co-workers (1973a) demonstrated that patients with aortic stenosis and syncope show a significant decrease in their forearm vascular resistance during exercise (Fig. 57). Patients with aortic stenosis who had not experienced syncope did not change their vascular forearm resistance during exercise. A decreased or unchanged vascular forearm resistance during bicycle exercise is the exact opposite of normal subjects who increase their forearm vascular resistance with exercise. An increased vascular forearm resistance and increased resistance to other inactive organs during exercise helps to maintain blood pressure and redistribute blood flow towards the exercising extremities. Apparently, patients with aortic stenosis, particularly those who experience syncope, are unable to vasoconstrict these non-essential or inactive regional circulations. It is likely that the forearm vasodilation is caused by an excessive increase in left ventricular systolic and end-diastolic pressures stimulating the cardiac receptors to reflexly decrease vascular resistance and blood pressure. Certainly this response may explain some of the cases of syncope in patients with aortic stenosis particularly those which occur during exercise.

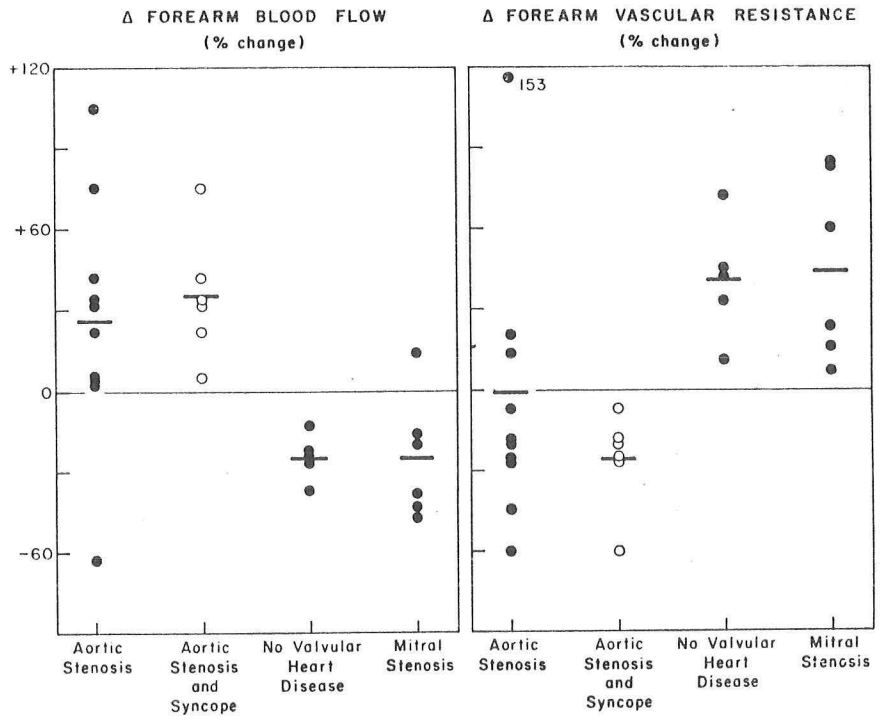

Figure 57. Percent change in forearm blood flow (left) and forearm vascular resistance (right) during the second minute of exercise. Dots represent responses in individual patients. The horizontal lines indicate means of response in each group (Mark et al, 1973a).

These investigators also demonstrated in an animal model that stimulation of the cardiac receptors caused a withdrawal of alpha-adrenergic tone to the muscles and to a lesser extent the skin (Mark et al, 1973b).

7. Vasovagal Syncope

A rapid and severe hemorrhage in cats causes a reflex bradycardia that is triggered by the cardiac receptors with vagal afferents (Oberg and White, 1970). There is an increased activity of the left ventricular receptors during hemorrhage but no change in the activity of the atrial type A or type B receptors (Oberg and Thorén, 1972). Thus, the natural stimulus for the receptors seems to be a distension of the left ventricle due either to aortic occlusion or alternatively to contraction around an empty chamber. One difficulty with this study is that only 20% of the receptors which responded to aortic occlusion could be excited by rapid hemorrhage. It is apparently necessary for a strong inotropic influence to combine with the poor diastolic filling to cause the receptor activation and result in a reflex bradycardia (Oberg and Thorén, 1972). It is possible that vasovagal syncope may be caused by a decrease in diastolic filling in a situation where there is intensified sympathetic stimulation such that, due to the squeezing effect, there is a sudden activation of the ventricular receptors. Telelogically one might speculate that a reflex bradycardia would allow for better diastolic filling of the heart and improve myocardial pump performance.

An alternative explanation for vasovagal syncope has been demonstrated in the dog. In this animal, chemical stimulation of the epicardium with nicotine causes a reflex sympathetic cholinergic vasodilation that is quite similar to that which occurs with vasovagal syncope (Bergel and Makin, 1967).

8. Drugs

As mentioned above, digitalis glycosides have a strong effect of stimulating the cardiac receptors. In addition to these agents, several other drugs including clonidine, sodium chromoglycate and propranolol can be demonstrated to affect cardiac receptors.

Clonidine is thought to have primarily a central nervous system action causing a decrease in sympathetic outflow, perhaps through a facilitation of the inhibitory baroreceptor effect. Recently it has been suggested that the bradycardia induced by clonidine may be dependent upon intact cardiac receptors in addition to the arterial baroreceptors. When clonidine is administered it causes a transient vasoconstriction. This may increase preload and afterload and perhaps stimulate the cardiac mechanoreceptors by this mechanism (Lisander and Wennegren, 1979). Unfortunately, the studies that have been conducted have not carefully eliminated afferent from efferent neural effects with the nerve transections that have been performed.

Sodium chromoglycate is used in the treatment of asthma to prevent bronchoconstriction. The major mechanism of action of this drug is to stabilize cell membranes in the lung and prevent the release of substances

which lead to bronchoconstriction. It has been previously suggested that this drug may reverse the action of lung irritant receptors. However, there is apparently little data to support this contention (Dixon et al, 1979). When injected into the dog, this agent causes hypotension and a bradycardia that is mediated by cardiac afferent nerves since the reflex can be blocked by locally instilling an anesthetic into the pericardium (Dixon et al, 1979). When this drug is allowed to exert its effect on the cardiac receptors, it reverses the bronchoconstriction induced by inhalation of aerosolized histamine (Dixon et al, 1979). The major problem with this study is that sodium chromoglycate is always given as an aerosolized preparation rather than injected into the blood stream. At the present time there is insufficient evidence to prove that significant amounts of chromoglycate are absorbed into the blood stream to cause a similar effect in humans as can be shown with intravenous injection in animals. Also, this drug is usually used as a prophylactic measure prior to any acute asthmatic attack in humans. In this regard, the drug manufacturers recommend that it not be given during the acute asthmatic attack since it may actually increase the severity of the bronchoconstriction. Thus, it is unlikely that the effect on cardiac receptors is an important mechanism for determining this drug's prophylactic benefit in humans.

The discharge of type B atrial receptors is increased because of an increase in left atrial pressure by propranolol (Gilmore and Zucker, 1974). The discharge of atrial type A receptors is decreased by propranolol probably because of the decreased heart rate (Recordati et al, 1976). The discharge of unmyelinated atrial receptors are not affected by propranolol (Thames, 1980). Unmyelinated vagal afferents from the left ventricle of cats are markedly attenuated in their response to a graded aortic occlusion following the injection of propranolol (Thorén, 1977). The effect of propranolol apparently results from its beta-adrenergic blocking activity rather than its membrane stabilizing properties (Thames, 1980). Thus, the effect of propranolol on the reduction of afferent activity from the left ventricle is apparently due to its reduction of ventricular contractility.

9. Zero Gravity and Prolonged Bedrest

Zero gravity is experienced by the astronauts and cosmonauts involved with the manned space flight missions that have been and are currently being mounted in the United States and Russia. The hemodynamic effect of zero gravity is very similar to that which occurs with patients who are put to prolonged bedrest. In both situations the hydrostatic gradients which are present in gravity and in the normal upright position are abolished. This results in a shift of the blood volume towards the heart and lungs (Blomqvist and Stone, 1982). It has been demonstrated that, consequent to the central blood volume translocation, there is a several kilogram weight loss averaging 3-4 kg or approximately 4% of the total body weight (Thornton and Ord, 1977; Thornton et al, 1977). The plasma volume contraction begins to occur as early as six hours after initiating the bedrest and continues for the first three days (Vogt et al, 1967; Johnson et al, 1971; Chobanian et al, 1974; Greenleaf et al, 1977). There may be a slow progressive fluid loss thereafter up to approximately 12% at 120 days (Pak et al, 1973). With the shift of blood volume centrally, there is an

activation of the low pressure cardiopulmonary baroreceptors (Gauer and Henry, 1976). This reflex causes an inhibition of ADH and a water diuresis (Epstein and Saruta, 1971; Epstein et al, 1975; Epstein, 1978). Changes in plasma osmolarity and renal hemodynamics do not play a role in this response.

Zero gravity is somewhat different than bedrest in that there is a decrease in fluid intake rather than a diuresis (Leach and Rambaut, 1977). After 24 hours there is a reduced blood volume, central venous pressure, and stroke volume. To maintain a constant cardiac output and blood pressure in both situations, heart rate is increased and plasma ADH tend to rise above normal (Blomqvist et al, 1980). This secondary adaptation may again be the result of cardiopulmonary receptor stimulation. Thus, there may be either a decreased stimulation or alternatively a reduced sensitivity.

The consequences of the hypovolemia (and perhaps the altered venous compliance and baroreceptor dysfunction, see Blomqvist and Stone, 1982 for review) is a reduced capacity to deal with the gravitational-induced fluid shifts which occur when subjects return to earth and assume the upright position.

Several types of prophylactic countermeasures have been used to prevent this orthostatic intolerance. These include exercise, intermittent assumption of an upright position, and re-expansion of the blood volume with 9-alpha-fluorohydrocortisone. Dynamic exercise does not help prevent orthostatic intolerance (Brannon et al, 1963; Birkhead et al, 1964; 1966; Miller et al, 1965; Lancaster and Triebwasser, 1971; Stremmel et al, 1976). However, static exercise has provided some favorable results (Stremmel et al, 1976). Standing daily for three hours or eight hours of quiet sitting prevents the development of orthostatic intolerance with bedrest (Birkhead et al, 1964; 1966). Administration of mineralocorticoids does not prevent the orthostatic intolerance (Stevens and Lynch, 1965; Stevens et al, 1966).

IX. CONCLUSIONS

Cardiac receptors include both mechanically and chemically sensitive receptors located in the atria and in the ventricles. These receptors appear to have major importance with volume control, particularly with regard to these atrial receptors innervated by myelinated afferents which course with the vagal efferent nerves. Ventricular receptors, when stimulated, may elicit either a reflex bradycardia and hypotension or alternatively an excitation of the cardiovascular system. The former response is mediated by afferent nerves which are located with the vagal efferents while the latter is mediated by afferent nerves which are located with the sympathetic efferents. Under normal circumstances, the cardiac receptors may sense changes in wall motion or diastolic pressure and perhaps allow for fine tuning of the cardiovascular system. However, it can be demonstrated that under certain pathological conditions such as coronary ischemia, which causes the release of substances such as bradykinin and prostaglandins, that there may be an exaggerated response of the ventricular receptors to cause a reflex depression of the cardiovascular system which includes renal vasodilation. This circumstance may be protective of the heart and kidney by lessening the myocardial oxygen

requirements and increasing renal blood flow. In the setting of heart failure and perhaps hypertension, both the atrial and the ventricular receptors may be reset and provide for an exaggerated neurohumoral discharge which can accompany these conditions. In the setting of aortic stenosis there may be an exaggerated response from the left ventricular receptors to cause reflex vasodilation and syncope. Finally, after prolonged bedrest the normal response of these receptors to the increased central blood volume results in a diuresis and loss of plasma volume and may cause significant orthostatic hypotension upon reassuming the upright position.

In the future, I am sure that we will learn more about the influence of these cardiac receptors in both health and disease. However, it will be necessary for future scientists to focus on the mechanisms of excitation of these cardiac receptors particularly with regard to mechanisms that may occur in physiologically or pathophysiologically relevant conditions. It will not be suitable for us to use stimuli that have little if any relevance to what might potentially occur in both health and disease. A better understanding of the mechanisms involved with the stimulation of cardiac receptors will provide for new approaches to prevent the harmful reflexes or alternatively to augment the benefical reflexes that can result from stimulation of these receptors.

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