

Atrial receptor

Two types of atrial receptors located in both atria and veno-atrial junctions have been identified by electro-physiological (1-4) and supported by histological studies (3, 4). These sensory receptors are nerve endings whose afferent fibres travel to the brainstem through the vagi and the spinal sympathetic nerves (5, 6). Atrial type A receptors fire during systole coincident with the "a" wave of the atrial pressure pulse (7-9) and atrial type B receptors are activated during atrial filling and fire a burst of impulses coincident with the "v" wave of the atrial pressure pulse (2, 10-12). Atrial type B receptors are stimulated by mechanical stretch of the atrial wall or venoatrial junctions which is caused by atrial filling. A linear relationship between the receptor activity and amplitude of "v" wave of the atrial pressure waveform (Fig. 1) and "v" wave amplitude being closest index for atrial filling demonstrated that the natural stimulus for the atrial type B receptors is atrial volume reflected in the "v" wave amplitude (13). Unaltered stimulus-response relationship of atrial type B receptors even under various physiological conditions suggests the intact reflex regulatory functions of atrial type B receptors during extreme variations in the experimental conditions (11, 12). The natural stimulus for atrial type B receptors is known to be the pulsatile increase in atrial volume, reflected in the amplitude of "v" wave of the atrial pressure pulse (2, 5, 11, 12). This stimulus response relationship holds good even during acute hypothermic conditions (Fig. 2) with very slow heart rates (11). Hypothermia is known to cause stiffness of the tissue therefore, to resolve the influence of the two factors the stimulus-

response relationship of slower heart rate in the absence of hypothermia could be examined after treatment with propranolol a beta blocker.

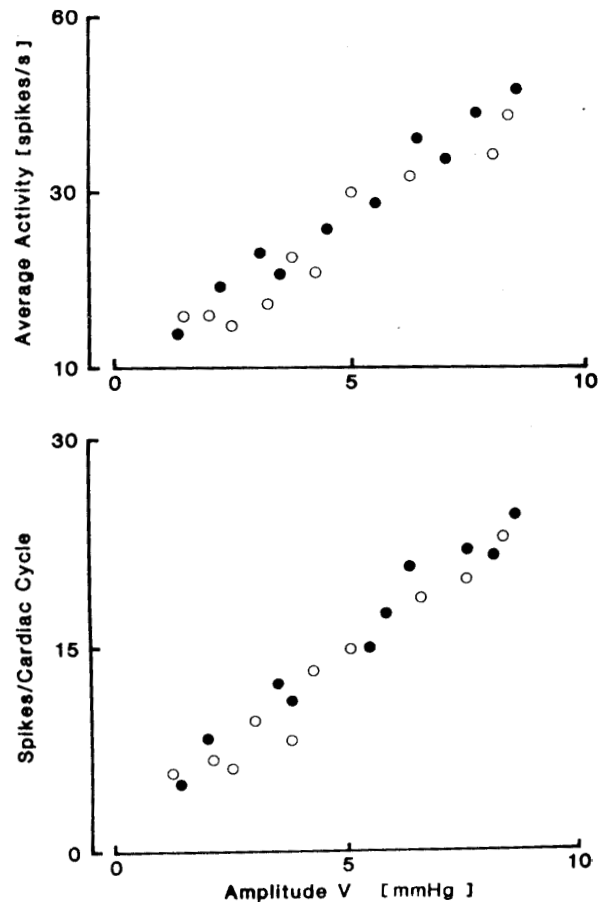


Fig. 1: Response of a left atrial type B receptor to change in "v" wave amplitude of the left atrial pressure waveform. A linear relationship between the left atrial type B receptor activity (spikes per cardiac cycle (lower trace) and average activity of the receptor (upper trace) and amplitude of the: "v" wave was observed with similar slope of the curve for rise (•) and fall (o) in amplitude of "v" wave.

Stimulus-response relationship of atrial B receptors

The stimulus-response relationships of type B receptors have been studied extensively in the dog (3, 4, 11, 14) and the

cat (1, 2, 12, 15, 16). It has been reported that these receptors respond primarily to atrial filling and show closer relationship to the amplitude of the "v" wave of the atrial pressure waveform rather than to the peak "v" wave pressure or mean atrial pressure both in cats (2) and dogs (11). However, in another study when the amplitude of "v" wave of atrial pressure pulse was plotted against receptor discharge per cardiac cycle, hysteresis was present (14). By studying the responses of the left atrial type B receptors in the isolated in-situ left atrium of cat it has been demonstrated that these receptors were slowly adapting receptors stimulated by increased atrial filling (1). This was confirmed by similar experiments in dogs (3, 17) and with graded distension of the left atrial balloons (18, 19). This led to the conclusion that the normal stimulus for the type B atrial receptors is increased atrial filling (2, 5). According to this view, the receptor discharge starts when the filling threshold of the receptor is attained during the rise of "v" wave and it falls when the atrium empties after the opening of the "a-v" valves on the down slope of the "v" wave. Since the atrial type B receptors show activity only during the "v" wave of the atrial pressure waveform and not during "a" or "c" wave when the pressure of "a" or "c" wave may be same or more than the "v" wave further supports the view that these receptors are primarily stimulated by atrial filling and not due to atrial pressure *per se*.

It is conceivable, however, that the results obtained under unusual conditions as with isolated in-situ atria may not be applicable under normal conditions and it is therefore necessary to get records of receptor activity simultaneously with

records of phasic changes in atrial volume. This is not possible at present because there is no reliable method of recording phasic changes in atrial volume. It is therefore not possible to correlate the intensity of the natural stimulus with the activity of the receptors in normally beating intact hearts. It was pointed out that the "v" wave of the atrial pressure pulse reflects the increase in atrial volume (and consequently atrial stretch) as a result of atrial filling (1, 20). This assumption was reasonable because, firstly, pressure in the atrium is linearly related to atrial volume within normal limits of filling (21, 22, 23, 24), and secondly, it can be assumed that the compliance of the atrium does not change appreciably during diastole (1, 20). Accordingly, the amplitude of "v" wave of the atrial pressure pulse serves as a convenient quantitative index of the atrial filling during atrial diastole. Such a relationship has been confirmed in the intact left atria of dogs (13). In our studies also the activity of left atrial type B receptor showed a linear relationship with the amplitude of the "v" wave and other covariant parameters of the "v" wave in dogs (13) and cats (12).

Intravenous propranolol slows the heart rate and the average activity of atrial type B receptors is significantly reduced although there is no significant change in the receptor activity per cardiac cycle. A linear relationship between the activity of type B atrial receptors and the "v" wave parameters is still maintained, however, the slopes of the curves are significantly reduced for the activity per cardiac cycle as well as average activity following propranolol. Our results are not in agreement to an earlier study (14) where a larger dose of propranolol was

used to depress the atrial contractility and the slope of stimulus-response relationship remained unaltered. The possible explanation could be that in our case smaller doses of propranolol acted primarily as a beta blocker whereas, in their study atrial myocardium was depressed due to high dose of propranolol which increased the basal activity of the receptors.

Influence of propranolol on stimulus-response relationship of left atrial type B receptors.

Infusion of saline produces an increase in the activity of atrial type B receptors with a corresponding increase in the intra-atrial pressure with the result that mean left atrial pressure, peak pressure of "v" wave and the amplitude of "v" wave of left atrial pressure waveform increase and during blood loss the activity of these receptors is reduced with a fall in these covariant factors of the left atrial pressure waveform. Left atrial type B receptors show a fairly linear relationship with the changes in the left atrial pressure. Intravenous administration of 1 mg/kg propranolol produces a decrease in the heart rate and no significant change in the receptor activity per cardiac cycle. However, the average activity of the receptor decreases significantly by propranolol. In propranolol treated animals, although the linear relationship between the receptor activity and the left atrial pressure is maintained, the slope of the curves are significantly reduced.

Effect of veratrum alkaloids on atrial receptor activity

Veratrum alkaloids are known to stimulate different types of visceral sensory

receptors (10, 12, 25–30), however, the mechanism of stimulation of these sensory receptors by the alkaloids of veratrum is not fully understood. Intense stimulation of the sensory receptors by veratrum alkaloid is also coupled with desensitization of the receptors (30) which has not been either noticed or explained by many investigators. Calcium chloride blocks the stimulatory effect of veratrum alkaloids on atrial and pulmonary stretch receptors (30). An alteration in the permeability of the membrane (31, 32) by the alkaloids which may enhance the local receptor potential has been proposed. The second explanation is supported by the view that veratrum increases the negative after potential in nerve fibres (33). We observed that the effect of veratrum alkaloid is also dependent on the plasma calcium level in the dose-dependent manner. When 125 μM calcium chloride solution is infused through femoral vein at a rate of 1 ml/min, the same dose of veratridine which causes marked stimulation of left atrial receptor before infusion of calcium chloride, produced significantly attenuated response. The effect of same dose of veratridine is completely blocked during infusion of 250 μM calcium chloride solution. A higher dose of veratridine can stimulate the atrial receptor even during infusion of 250 μM calcium chloride solution. Therefore, a possible explanation for the reduced responsiveness of the atrial receptors to veratrum alkaloids could be altered membrane permeability as calcium alone does not produce any significant change in the basal activity of the atrial receptors. These observations also favour the speculation of depolarization of the receptors by altering the permeability of the membrane (31, 32) by veratrum alkaloids.

Atrial receptors are markedly stimulated and desensitized by veratrum alkaloids injected intravenously or into the right atrium (10, 12, 17, 29, 30, 34, 35). Based on the effect of veratrum alkaloids on nerve and muscle (36), the mechanism of action of alkaloids and their derivatives on cardiac receptors has been attributed to changes in sodium permeability (34). Intravenous injection of calcium reverses the stimulatory effect of veratrum alkaloid on sensory receptors (34). The digitalis alkaloids commonly used in the treatment of heart failure are known to increase the sensitivity of aortic and carotid chemoreceptors to their natural stimulus (37–39) and increase the activity of those left ventricular receptors which have nonmyelinated vagal afferents (40). Changes in the extracellular Na^+ and K^+ are known to alter the sensitivity and functions of mechanoreceptors (12, 30–32, 41–43). Intravenous administration of acetylstrophanthidin octahydrate produces an increase in left atrial receptor activity in anaesthetised dogs and no significant change in heart rate, left atrial pressure on mean atrial pressure occurs, and the sensitivity of left atrial receptors to volume expansion is increased (44). Similar effect of cardiac glycosides on cardiac receptor activity was observed on intracoronary injection or epicardial application of acetylstrophanthidin (45). It has been believed that the stimulation of cardiac receptors by veratrum alkaloids is due to increased sodium permeability (34). If this is true then the relative sensitivity of atrial receptors to veratrum alkaloids or to the natural stimulus could be altered by varying the Na^+ flux across the receptor membrane using cardiac glycosides because of their ability to inhibit $\text{Na}^+\text{-K}^+$ adenosine

triphosphate activity (46–48). It is also known that blocking of the electrogenic sodium pump can unmask the membrane depolarising effect of monensin a sodium ionophore (49). This was further substantiated by increase in sensitivity of atrial type B receptors to veratridine following treatment with acetylstrophanthidin (12). Acetylstrophanthidin did not sensitize the type B atrial receptors to their natural stimulus (12).

Effect of veratridine on left atrial type B receptors at normal and elevated plasma calcium levels.

Veratridine produces stimulation of the atrial receptors in the form of continuous spikes (Fig. 3). With an increase in the duration of continuous neural activity increase in average discharge and peak frequency of discharge occurred following infusion of $125 \mu\text{M CaCl}_2$, on administration of same dose of veratridine as injected earlier during control observation, the left atrial receptors were stimulated. The duration of continuous activity increased from 0.11 ± 0.02 to 5.1 ± 0.91 sec, average activity of atrial receptors from 20.25 ± 3.7 to 105.00 ± 4.02 impulses per sec, and peak frequency of discharge increased from 120.75 ± 7.14 to 167.60 ± 7.59 impulses per sec. The increase in all the three parameters of the receptor activity was significantly less than that produced by the same dose of veratridine at normal plasma calcium level. On increasing plasma calcium level further by infusion of $250 \mu\text{M CaCl}_2$ there was no significant change in basal level of activity of left atrial type B receptors. Values being average activity 21.25 ± 3.31 impulses per sec and peak frequency of discharge 118.25 ± 7.23 impulses per sec before

veratradine and there was no significant change in the receptor activity on injection of same dose of veratridine which produced significant increase in the receptor activity at normal plasma calcium level. After administration of veratridine, duration of continuous discharge was 0.12 ± 0.04 sec average activity 22.2 ± 3.51 impulses *per sec* and peak frequency of discharge 117.50 ± 5.90 impulses *per se*. These values were not significantly different from the corresponding values before veratridine.

Reflex regulatory function of atrial receptors

The type B atrial receptors are believed to play an important role in the reflex regulation of body fluid volume in cats (50, 51), and dogs (3, 18, 52). Cardiovascular receptors are also known to play vital role in the regulation of the heart rate. Stimulation of these receptors by distension of small balloons in the pulmonary vein-atrial junction and distension of a left atrial pouch in the dog also caused a reflex increase in the heart rate (53–57). The afferent pathway for this reflex is reported to be in the vagi and the efferent pathway entirely in the cardiac sympathetic nerves (55, 57). However, in cats, Hakumaki (16) found an inhibition of the cardiac sympathetic efferent nerve activity following stimulation of type B atrial receptors.

Stimulation of left atrial receptors by distending left artial or venoatrial junction balloons elicited a tachycardia response in anaesthetized cats and dogs. Contrary to earlier reports in our study the tachycardia response was not due to an increase in the cardiac sympathetic nerve activity as the increase in the heart rate was not affected

by beta blockade with propranolol (Fig. 4). The attenuation of atrial receptor mediated chronotropic response by peridural procaine indicates the involvement of spinal sympathetic afferent nerves in this reflex effect. The major component of the tachycardia response on atrial receptor stimulation is blocked by atropine or bilateral vagotomy (Fig. 4, 6), suggesting that the reflex increase in heart rate is mediated mainly by inhibition of vagal efferent activity (Fig. 4) with afferent fibres

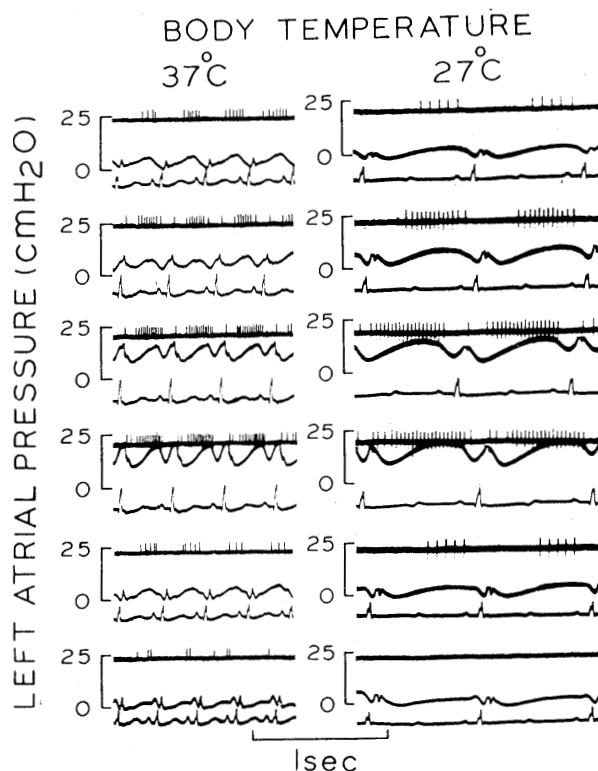


Fig. 2: Response of a left atrial type B receptor to changes in left atrial pressure due to infusion of normal saline and haemorrhage at (a) normal body temperature, 37°C and (b) during hypothermia, 27°C. In each record upper trace shows the activity of the left atrial type B receptor; middle trace left atrial pressure and lower trace ECG. At both the temperatures, records from top to bottom are control, 50 ml, 100 ml and 150 ml saline infusion, 50 ml and 100 ml withdrawal of blood respectively.

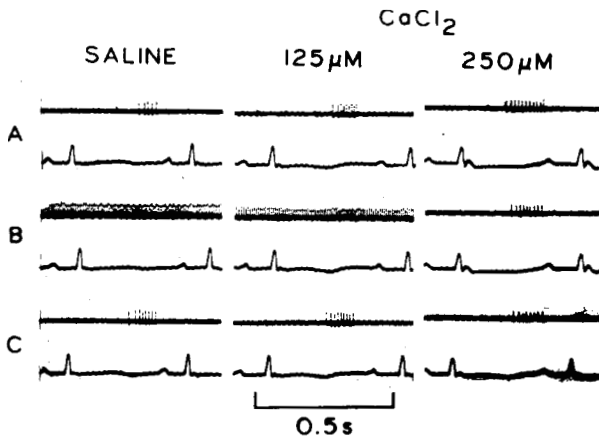


Fig. 3: Effect of intravenous administration of Veratridine (50 $\mu\text{g}/\text{kg}$) on the activity of a left atrial type B receptor (upper trace in each record) and ECG (lower trace in each record) in animals infused saline (left column), 125 μM CaCl_2 (middle column) or 250 μM CaCl_2 at a rate of 1 ml/min. In each record row A: shows activity of the receptor before Veratridine, row B: on injection of 50 $\mu\text{g}/\text{kg}$ Veratridine and row C: recovery from Veratridine.

in vagi and spinal sympathetic nerves. Inhibition of vagal efferent nerve fibre activity during tachycardia response on atrial receptor stimulation further confirmed the significant role of vagal efferents in the heart rate response. The precise function of type A atrial receptors is not yet clearly established. It has been suggested that in cats the type A atrial receptors might signal heart rate (9). However, the electrophysiological studies have revealed that there are few type A atrial receptors in dogs (5, 58) and monkeys (59) which reduces the significance that these receptors are specific for signalling heart rate.

The mammalian heart is innervated from the sympathetic and parasympathetic divisions of the autonomic nervous system, and these nerves modulate cardiac activities

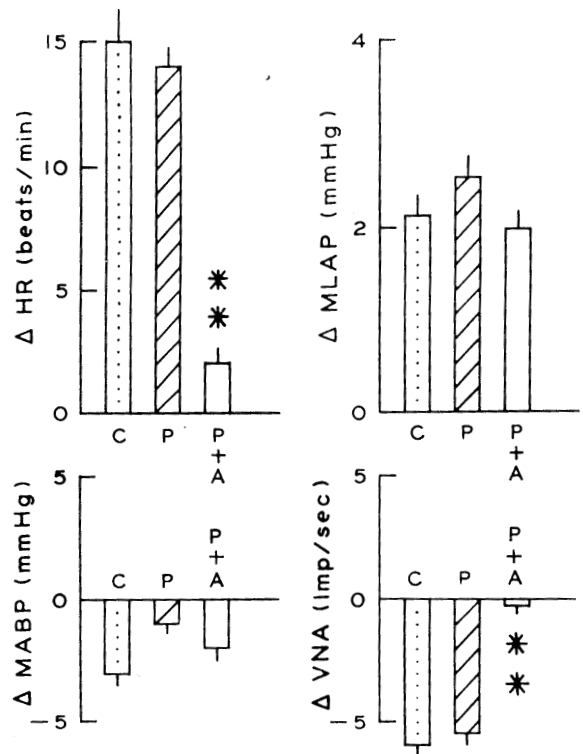


Fig. 4: Influence of propranolol (P) and propranolol plus atropine (P+A) on the effects of left atrial/pulmonary vein-left atrial junction balloons distension on the change in the heart rate (ΔHR), change in mean left atrial pressure (ΔMLAP), change in mean arterial blood pressure (ΔMABP) and change in vagal efferent nerve activity (ΔVNA). C: Control ** $P < 0.01$.

by acting simultaneously in varying degrees (60). The reflex chronotropic effects of sympathetic afferents are well documented (6, 61–63) and an interaction between inputs from various cardiovascular afferents which regulate the autonomic output has been suggested (63). These studies indicate involvement of vagal and spinal sympathetic afferents and their influence on the parasympathetic and sympathetic cardiac efferent outflow resulting in the reflex tachycardia response on stimulation of cardiopulmonary receptors. However, these studies do not provide direct evidence of the

precise contribution of afferent inputs and parasympathetic and sympathetic cardiac efferent nerves outflow in this reflex chronotropic response elicited by stimulation of left atrial receptors.

In our investigation, a selective block of the autonomic nervous system atrial receptor stimulation is mainly through the vagus system (Fig. 4–6). Administration of peridural procaine produces a reversible complete block of cardiac sympathetic nerve activity in the animals. Following peridural procaine the reflex tachycardia response to left atrial receptor stimulation is slightly reduced (Fig. 5). As cardiac sympathetic efferent nerve activity does not show a clear relation to the reflex effect, a possible explanation for the attenuation of the reflex responses could be the block of spinal afferents along with sympathetic efferents. The role of sympathetic afferents in the reflex chronotropic effect is now well established (61–63). The possibility of a contribution of sympathetic afferents to the reflex chronotropic effect of left atrial receptor stimulation is supported by our observation on animals treated with propranolol. Intravenous administration of propranolol (1 mg/kg) which blocks the cardiac sympathetic efferent nerve activity does not affect the magnitude of the reflex increase in the heart rate during left atrial receptor stimulation (Fig. 4) and the decrease in the cardioinhibitory vagal efferent nerve activity is also unaffected by the beta blocker (Fig. 4).

Administration of procaine in the pericardium would result in a denervated heart preparation, hence, none of the animals in our investigation showed any

response to left atrial balloon distension following pericardial procaine (Fig. 5). Pericardial procaine also has a direct effect on heart muscle besides blocking the nerves, in a separate series of experiments, atropine was given to eliminate the contribution of cardiac vagal efferent nerves to the reflex tachycardia response. Atropine abolishes the reflex tachycardia response to stimulation of left atrial receptors (Fig. 4, 6), with no change in cardiac sympathetic efferent nerve activity. Thus this reflex chronotropic effect during stimulation of left atrial receptor is resulting from the corresponding withdrawal of the vagal tone. It is well known that the anaesthesia inhibits vagal tone (64, 65), because the efferent limb of the reflex tachycardia response to left atrial receptor stimulation is mainly through the vagus system, therefore, the magnitude of the response will depend on the existing vagal tone. It has already been shown that following the anaesthesia and surgery there is very little tonic cardiac vagal restraint in cats (65), while it could be a possible reason for relatively smaller tachycardia response in cats on stimulation of left atrial receptors (66). Our observation clearly demonstrated the significant role of vagal efferents (66) in the reflex increase in the heart rate on stimulation of atrial receptors contrary to earlier reports (55, 57). We found that the role of sympathetic efferent nerves in this reflex response is negligible (Fig. 6, 8) and the reflex increase in the heart rate during atrial receptor stimulation is primarily due to withdrawal of vagal tone (Fig. 7). It is known that changes of pulse pressure which do not alter mean arterial blood pressure can alter the baroreceptor input resulting in baroreceptor mediated reflex changes in the heart rate (67). The

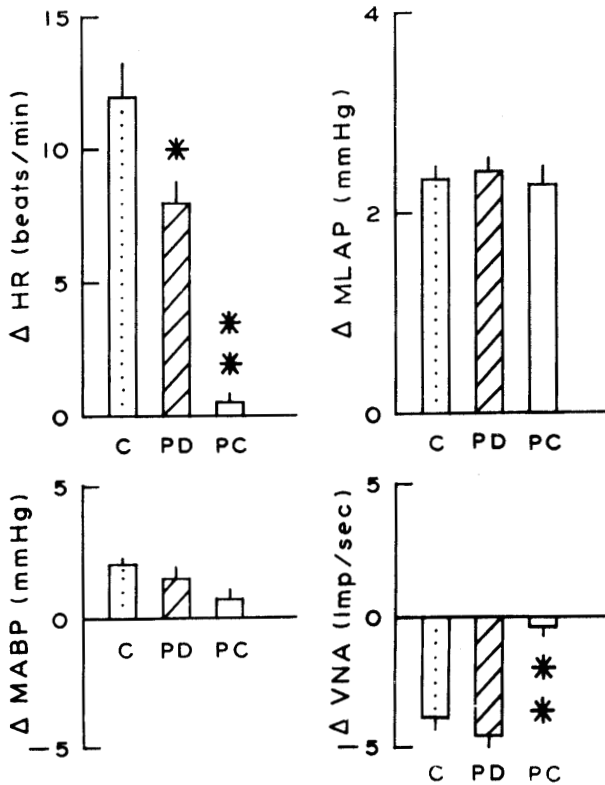


Fig. 5: Effect of peridural procaine (PD) and pericardial procaine (PC) on the left atrial receptor stimulation mediated changes in the heart rate (Δ HR), mean left atrial pressure (Δ MLAP), mean arterial blood pressure (Δ MABP) and vagal efferent nerve activity (Δ VNA). C: Control ** $P < 0.01$.

observations also indicate that during left atrial balloon/pulmonary vein balloons distensions, even in the absence of any significant change in the mean arterial blood pressure, a small fall in pulse pressure due to distension of balloon can cause significant change in the sympathetic cardiac efferent nerve activity and consequently producing a tachycardia response. Therefore, it is possible that the increase in the cardiac sympathetic efferent nerve activity during distension of pulmonary vein balloons observed by Karim et al (55) could be due to small fall in the

pulse pressure. In our study the distension of balloons was so controlled that there was no change in mean arterial pressures (Fig. 8). Involvement of vagal afferents and the cardiac sympathetic efferent nerves in the reflex tachycardia response to distension of pulmonary vein- left atrial junction balloons has been reported by other investigators (53, 56) as well. Later Burkhardt and Ledsome (68) showed that this reflex response contained contribution also from efferent vagus nerves. Contrary to the sympathetic excitatory effect reported by these workers, our observations showed a small inhibition of the cardiac sympathetic efferent nerves during the left atrial receptor stimulation supporting the results of an earlier study where atrial receptor stimulation by infusion of fluid in cats caused a decrease in cardiac sympathetic efferent nerve activity which did not show any correlation to the reflex response. Variations in the cardiac sympathetic efferent nerve activity could be attributed to the small changes in systemic blood pressure.

Therefore, the tachycardia elicited by left atrial receptor stimulation may be due to a reflex with its afferent pathway in the vagi and spinal cord and its efferent pathway in the vagus nerves.

Role of cardiovascular receptors in reflex control of circulation

The cardiovascular sensory receptors play an important role in the regulation of cardiovascular system (7, 64, 66, 69, 70, 71). The arterial baroreceptors located in the aortic arch and carotid sinus region regulate the arterial pressure by reflex changes in

heart rate and vascular tone (39, 64, 71–76). Atrial type B receptors located in veno-atrial junctions and the atria are known to be involved primarily in reflex regulation of blood volume (7, 52, 77–79). Stimulation of cardiopulmonary receptors also produces reflexly induced positive chronotropic effect (66, 69, 78, 80). Therefore, both arterial baroreceptors and cardiopulmonary receptors reflexly influence the cardiovascular system and are involved in blood pressure, heart rate and volume control (79, 81–89). The modulatory role of one type of receptors on the reflex regulation of cardiovascular parameters by other types is well documented (79, 82, 86, 90–92).

A number of stress-induced disturbances alter blood flow to various organs resulting in production of a chronotropic effect and changes in cardiac output. The cardiovascular responses produced by a particular disturbance are usually specific, resulting from interaction between various cardiovascular sensory receptors and their reflex autonomic effects. The effects could also be nonautonomic, humoral and direct on the heart and blood vessels (Fig. 9). The autonomic nervous system (ANS) mediated circulatory responses to stress involve changes in sympathetic and parasympathetic neural activity to various organs, with increased vascular constrictor tone in some areas and decreased tone in other vascular beds (66, 69, 93). Sympathetic neural discharge is known to be influenced by emotional stimuli and by muscle exercise (Fig. 9). Besides aortic arch and carotid sinus arterial baroreceptors, other main cardiovascular receptors which influence heart rate, blood pressure and peripheral resistance, include atrial receptors and

ventricular receptors (5, 7, 56). Since heart and peripheral vessels of several regions are connected in series and parallel, any circulatory disturbance will tend to alter pressure in different regions of the body by changing inputs from various cardiovascular sensory receptors to the central nervous system (CNS). The resulting autonomic effector response will depend on the interactions among the contributions of various sensory receptors (Fig. 9). It is likely that depending on the circulatory disturbance at a particular time, one

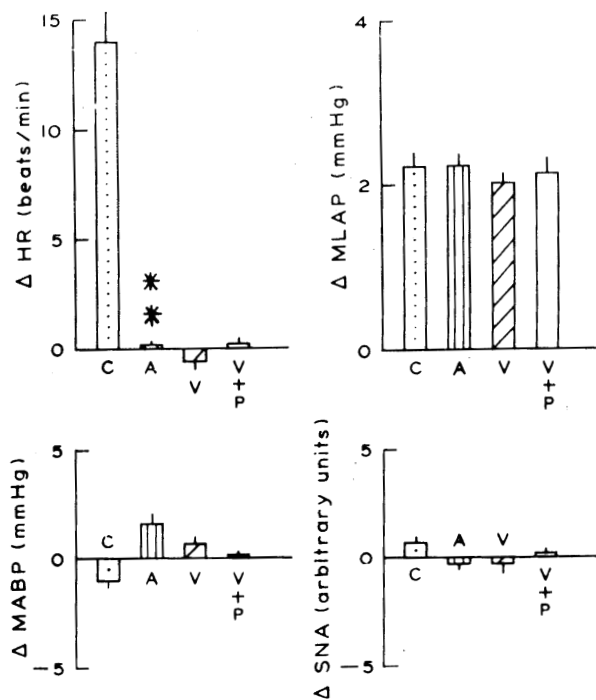


Fig. 6: Showing atropine abolishes increase in heart rate (Δ HR) resulting from left atrial/pulmonary vein-left atrial junction balloons distension by atropine (A) in dogs. Change in mean left atrial pressure (Δ MLAP), change in mean arterial pressure (Δ MABP), change in sympathetic efferent nerve activity (Δ SNA), change in vagal efferent nerve activity (Δ VNA), in control condition (C), following atropine (A), bilateral vagotomy (V), and vagotomy plus propranolol (V+P) **P<0.01.

type of receptor may play a dominant role compared to others in bringing cardiovascular changes through autonomic effectors. The possibility of sensory receptors other than cardiovascular receptors affecting circulatory parameters under certain environmental changes, also exists. Chemoreceptors, pulmonary stretch receptors and receptors located in skin and muscle are known to modulate the reflex cardiovascular effects of arterial pressure changes. Possible sensory inputs to the CNS during circulatory disturbance and contributing autonomic effectors are illustrated in Fig. 9.

Arterial Baroreceptor reflex

The role of arterial baroreceptors in the regulation of arterial pressure by reflex chronotropic effect and vasoconstriction is well established (39, 64, 69, 71–76).

Arterial baroreceptor reflex :

Increase in arterial pressure stimulates the arterial baroreceptors located in the aortic arch and carotid sinus regions. This leads to reflex inhibition of sympathetic efferent nerve activity (69) and excitation of parasympathetic efferent nerve activity (Fig. 10, 12) (69) resulting in a fall in the heart rate and during hypotension (Fig. 10, 11, 13) there is an increase in sympathetic efferent nerve activity and inhibition of vagal efferent nerve activity causing reflex tachycardia response (Fig. 10, 12). A change in relationship between arterial pressure and heart rate or sympathetic resetting of the baroreflex occurs (71). The resetting of baroreceptor reflex may occur at the peripheral level, which is called peripheral

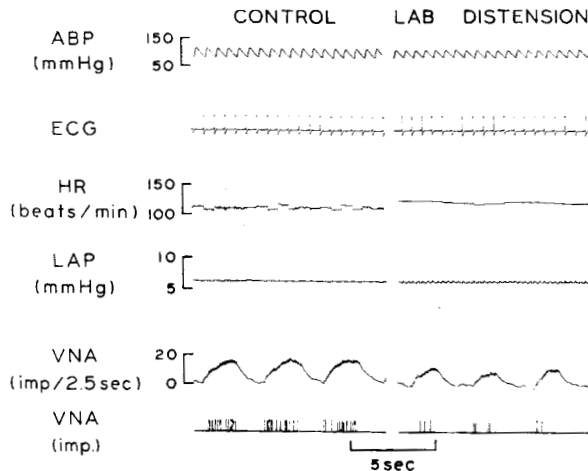


Fig. 7: Original tracing showing increase in heart rate on distension of left atrial balloon (LAB) with a fall in vagal efferent nerve activity. From above downward: arterial blood pressure (ABP), electrocardiogram (ECG), heart rate (HR), left atrial pressure (LAP), integrated vagal efferent nerve activity (VNA) and single vagal efferent fibre activity (VNA imp).

resetting, resetting within the CNS is known as central resetting.

Peripheral resetting of baroreflex :

An increase in the arterial pressure causes an increase in the threshold pressure required for activation of the baroreceptors (39, 43). This is accompanied by rightward shift in the arterial pressure-baroreceptor activity relationship which is known as resetting. It increases the threshold level for stimulation of arterial baroreceptors and maintains the arterial pressure at an elevated level. The slope of the pressure - response curve may decrease and there may be a decrease in maximum activity of the baroreceptors. In baroreceptor resetting, lower activity of arterial baroreceptors at an equivalent pressure may reduce the strain on the blood vessel, or a fall in

activity may produce unaltered or even greater deformity of the blood vessel. However, the baroreceptors also reset during hypotension, i.e. threshold pressure of arterial baroreceptors is decreased on exposure to low pressure and arterial pressure-receptors activity curve is shifted to the left (94); generally, peripheral resetting of arterial baroreflex occurs under conditions of sustained change in arterial pressure, e.g. chronic hypertension, but there may be acute resetting of the reflex also. There are three types of peripheral resetting (i) **Instantaneous resetting**: Fall in receptor activity during diastolic phase of the cardiac cycle at the same pressure is known as instantaneous resetting (95). (ii) **Acute resetting**: Acute resetting of baroreceptors occurs within a few cardiac cycles after change in pressure and stabilizes at changed pressure level in minutes, (iii) **Chronic resetting**: Decreased vascular compliance could cause a fall in arterial baroreceptor activity during chronic hypertension and could produce less strain on arterial baroreceptor endings. Chronic hypertension produces a sustained increase in strain on arterial baroreceptor endings. This changes the diameter of the aorta and carotid sinus regions which then remain stable. The baroreflex sensitivity is decreased and the resetting of arterial baroreceptors at the new threshold stimulus is complete.

Central resetting of baroreflex

When the efferent sympathetic activity is significantly different for the same level of baroreceptor input it is called central resetting of the baroreflex. Central resetting is also influenced by other neural reflexes

and /or humoral agents (71, 96) in certain conditions, e.g. during exercise and hypoxia. It is suggested that neurons involved in central inhibition of sympathetic efferent activity may be less sensitive to increase in the arterial baroreceptor input.

The resetting of baroreceptors mediated reflex plays an important role in the cardiovascular regulation in physiological and pathophysiological conditions. Central resetting of baroreflex under certain conditions, e.g. severe hypoxia, may involve baroreflex -dependent changes as well as baroreflex-independent changes (71). Central resetting of the baroreflex may involve both suprapontine and bulbospinal pathways in autonomic regulation of cardiovascular system.

Acute baroreflex resetting during hypotension

Ajmaloon (Hamdard, India), a preparation from *Rauwolfia serpentina* and certain herbs reduce blood pressure in humans and animals in a dose-dependent manner (97). Intravenous administration of 100 mg/kg Ajmaloon in anaesthetized rabbits and monkeys produced significant fall in arterial blood pressure (Fig. 15), with no significant change in heart rate. The systolic arterial pressure heart rate curve shifted to the left following the intravenous injection of Ajmaloon and at the same pressure, heart rate was lower and thus showed an acute resetting of the baroreflex (Fig. 16). Loss of tachycardia response to fall in arterial pressure in Ajmaloon-treated animals suggests a sympathetic excitatory influence in response to hypotension. It also suggests a significant fall in baroreflex sensitivity at the lower arterial pressure caused by the drug.

Baroreflex response during acute hypoxia

It is well known that in animals respiratory status affects the autonomic vaso-constrictor response (98). In mild hypoxia there is a slight and gradual rise in total peripheral resistance, and during severe hypoxia where arterial PO_2 falls below 35mmHg rise in autonomic effect on total peripheral resistance is abrupt. Abrupt rise in peripheral resistance of PO_2 below 35 mmHg is attributed to stimulation of chemoreceptors. Due to increase in ventilation during exposure to hypoxic breathing, the pulmonary stretch receptors are also stimulated. This also modulates the peripheral resistance. The ratio between the activity of pulmonary stretch receptors and chemoreceptors reflects the magnitude of the rise in total peripheral resistance through the ANS due to hypoxia. The pulmonary stretch receptor mediated inhibitory effects on peripheral resistance are known to be cortically -mediated. Heart rate response mediated through the ANS is also altered during hypoxic breathing. Mild hypoxia causes increase in heart rate, but severe hypoxia produces increased bradycardia.

During hypoxia sustained bradycardia occurs in animals with intact CNS and in pontine (intracollicular decerebration) animals there was an increase in heart rate at all levels of hypoxia. In suprapontine preparations of thalamic animals only, bradycardia occurs even at a mild level of hypoxia. It has been suggested that the tachycardia response to hypoxia is mediated through bulbo-spinal regions. Thus bradycardia response to hypoxia is due to stimulation of the chemoreceptors and

suppression of cardiac slowing during mild hypoxia caused by stimulation of the pulmonary stretch receptors due to hyperventilation. Magnitude of inputs from two sets of receptors (chemoreceptors and pulmonary stretch receptors) to the autonomic centres determines the autonomic effector response during respiratory disturbance (hypoxia). This in turn triggers the CNS to modulate the respiration in order to meet the demands of oxygenation of arterial blood during any kind of respiratory stress. In humans, hypoxia with hypocapnia, produces tachycardia without any significant change in blood pressure or in baroreflex sensitivity. During exercise the changes were similar except that baroreflex sensitivity is depressed more than what was expected by exercise alone.

Baroreflex response during acute experimental anaemia

While in hypoxia PO_2 falls, in haemodilution the PO_2 may be normal but the oxygen-carrying capacity of the blood is reduced in proportion to the reduction in hematocrit (99). Acute haemodilution in dogs produces increase in cardiac output (Fig. 8) and fall in total peripheral resistance. The magnitude of these effects depends on the degree of haemodilution. It was observed that in dogs with a low control heart rate (60–80 beats/min) with intact autonomic innervation and following beta blockade, the increase in cardiac output was almost entirely owing to an increase in heart rate (Fig. 9). Whereas, in dogs with high basal heart rate following (i) cholinergic blockade, (ii) or bilateral vagotomy, and (iii) or bilateral vagotomy plus beta blockade, cardiac output increased

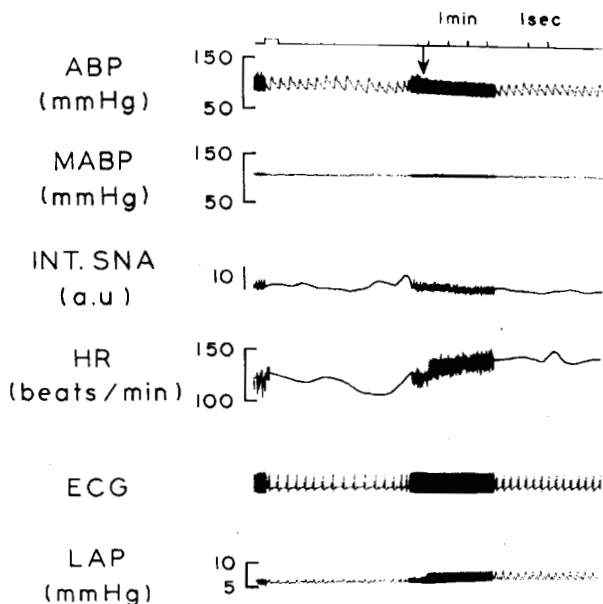


Fig. 8: Original tracing showing the tachycardia response during stimulation of left atrial receptors by inflating pulmonary vein-left atrial junction balloons started at arrow (\downarrow) shown on the top. From above downward: arterial blood pressure (ABP), mean arterial blood pressure (MABP), integrated sympathetic efferent nerve activity (INT. SNA), heart rate (HR), electrocardiogram (ECG), and left atrial pressure (LAP).

solely due to an increase in the stroke volume (Fig. 10). Thus the tachycardia response to haemodilution is primarily mediated through the efferent vagus nerves, and the efferent sympathetic nerves do not make any significant contribution in the reflex regulation of acute fall in the oxygen-carrying capacity of the circulating blood (Fig. 18). In another study on anaesthetized cats, the increase in cardiac output (Fig. 17) on acute haemodilution was largely due to an increase in stroke volume (Fig. 19) with small increase in heart rate (100). This could be due to low vagal tone in the anaesthetized cats. Haemodilution attenuates the excitatory effects of phenylephrine and

other cardiotoxic agents. The reduced sensitivity of the drug under such condition could be due to reduced myocardial oxygen supply, suppression of the excitatory effects by local vasodilating agents and certain other factors which control vascular responsiveness to drugs. Baroreflex (systolic pressure-heart rate relationship) is not altered by haemodilution. However, at the same level of systolic pressure, heart rate showed an increase corresponding to the degree of haemodilution and reset itself at that level. The sensitivity of baroreflex tachycardia response to hypotension is attenuated only during severe (HCT-14%) haemodilution.

Baroreflex response during coronary artery occlusion

Acute coronary artery occlusion causes myocardial ischaemia which induces autonomic adjustments in the cardiovascular system. Excitation of cardiac afferent nerves produces reflex which is cardioinhibitory and vasodepressor response with a fall in sympathetic tone (45, 101). The vasodepressor response is abolished in acute myocardial infarction due to the interruption of vagal afferent (102). Inactivation of the ventricular sensory nerve endings, due to chronic myocardial infarction as well as by impairment of cardiac reflexes in response to changes in cardiac filling is known to occur (103). In clinical studies the status of autonomic reflex control has been used for assessment of degree of risk for sudden death, because baroreflex-mediated changes in heart rate can provide a useful criterion to assess autonomic neural control of the heart (81). Acute coronary artery

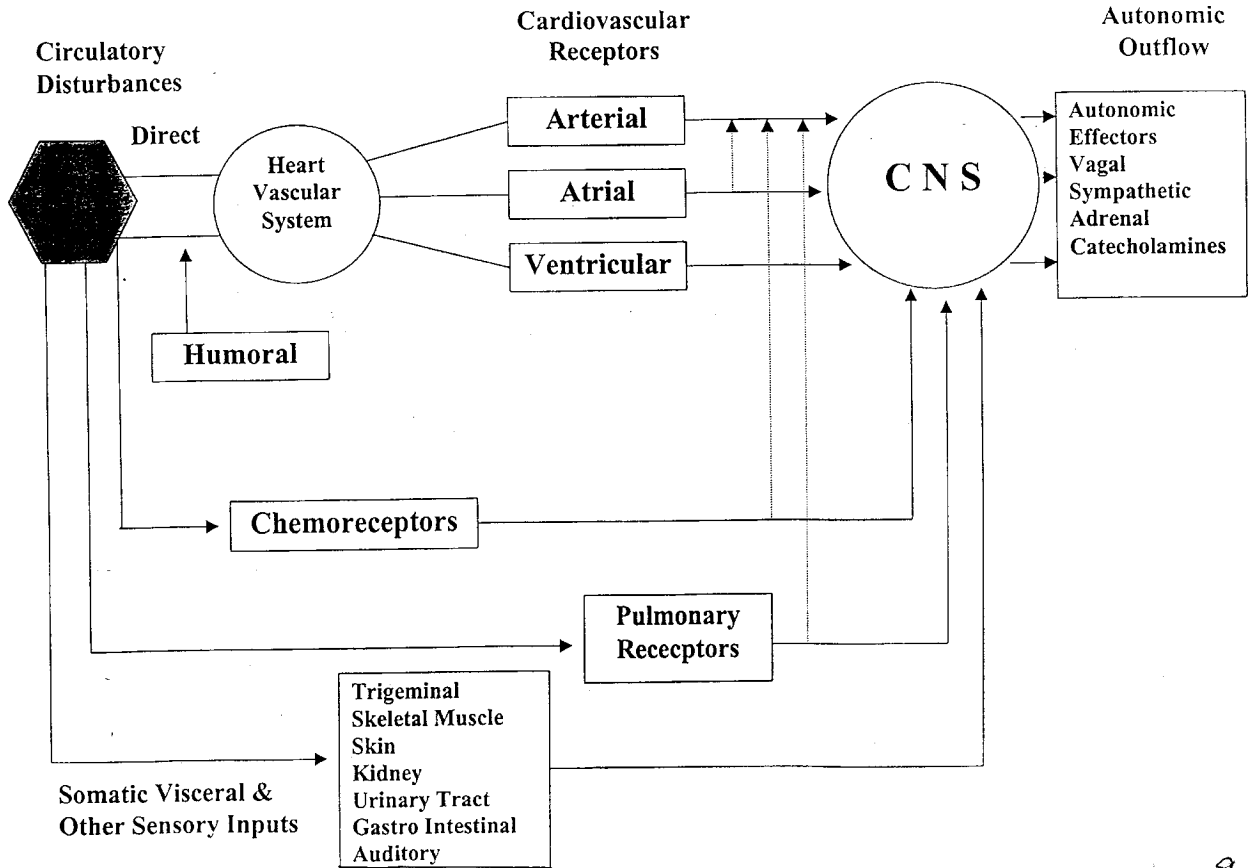


Fig. 9: Illustration of various possible sites of the integrated baroreflex regulatory control. Any circulatory disorder directly affects the heart and the vascular beds, changes vascular pressure and changes input from various cardiovascular receptors to the central nervous system (CNS). Autonomic effectors include vagal and sympathetic efferents and release of adrenal catecholamines. Arterial baroreflex activity is modulated by other cardiovascular receptors, chemoreceptors, pulmonary receptors and other somatic, visceral and sensory inputs.

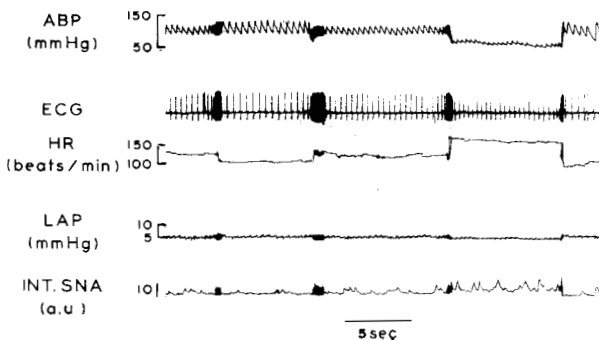


Fig. 10: Original tracing showing the bradycardia response during increase (↑) in arterial blood pressure (ABP) and tachycardia during fall (↓) in ABP. From above downward: ABP, electrocardiogram (ECG), heart rate (HR), left atrial pressure (LAP), integrated sympathetic efferent nerve activity (INT. SNA).

occlusion attenuates baroreflex control of heart rate in response to an increase in arterial pressure (91, 104).

In dogs the tachycardia response was related to the duration of coronary artery occlusion with intact ANS as well as after beta blockade, indicating inhibition of vagal efferent nerve activity. Heart rate response in dogs to coronary artery occlusion is abolished following atropine injection (i.v) or bilateral section of vagus nerves. In normal dogs, the sensitivity of baroreflex tachycardia response to fall in arterial

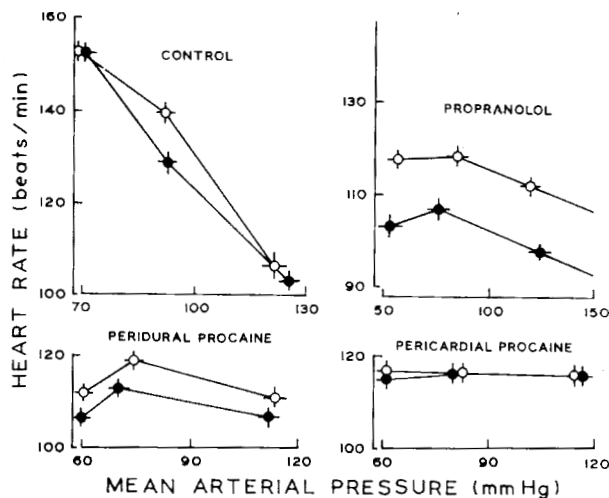


Fig. 11: Mean curves representing the baroreflex mean arterial blood pressure-heart relationship for the peak effects before (•) and during (◊) left atrial receptor stimulation in seven dogs following administration of intravenous propranolol, peridural procaine and pericardial procaine. All values are mean \pm SEM.

pressure and the bradycardia response to rise in pressure, was attenuated four hours after acute occlusion of left anterior descending coronary artery (LAD). In beta-blocked animals, tachycardia response after the occlusion of LAD was almost abolished. Atropinization or vagotomy attenuated the peak sensitivity of baroreflex-mediated bradycardia response, whereas, the peak sensitivity of baroreflex tachycardia response is increased after bilateral vagotomy. The bradycardia response is enhanced after beta-blockade. Thus acute myocardial ischaemia attenuates arterial baroreflex control of heart rate. The fall in baroreflex sensitivity following LAD occlusion involves parasympathetic efferent nerves (104). In another study the cardiovascular reflex effects of intravenously administered phenylephrine and sodium nitroprusside were attenuated after

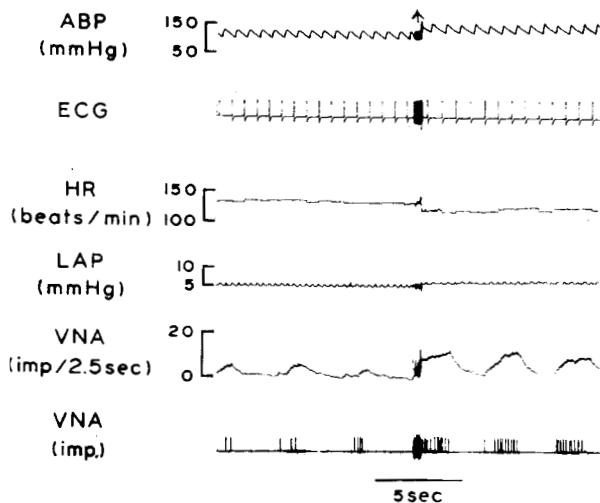


Fig. 12: Original record showing a fall in heart rate (HR) and a rise in parasympathetic activity (VNA) during increase (↑) in arterial blood pressure (ABP). From above downwards: ABP, electrocardiogram (ECG), HR, left atrial pressure (LAP); integrated vagal efferent nerve activity (VNA impulses per 2.5 sec), single vagal efferent fibre activity (VNA imp.).

occlusion of LAD (105). Acute LAD coronary artery occlusion produced a fall in arterial pressure (Fig. 20) and stroke volume (Fig. 21). It also produced a rise in cardiac output (Fig. 21) due to increase in heart rate. The baroreflex dysfunction is suggested to be due to the abnormality in the afferent limb rather than the central or efferent limbs of the reflex arc.

Influence of other cardiac sensory receptors on the arterial baroreceptor-mediated reflex responses

Left ventricular receptor stimulation by intracoronary infusion of veratrine attenuates arterial baroreflex control of heart rate. The fall in sensitivity of the reflex and the heart rate is mediated by parasympathetic motoneurons common to both reflex arcs (70). Further, the resetting

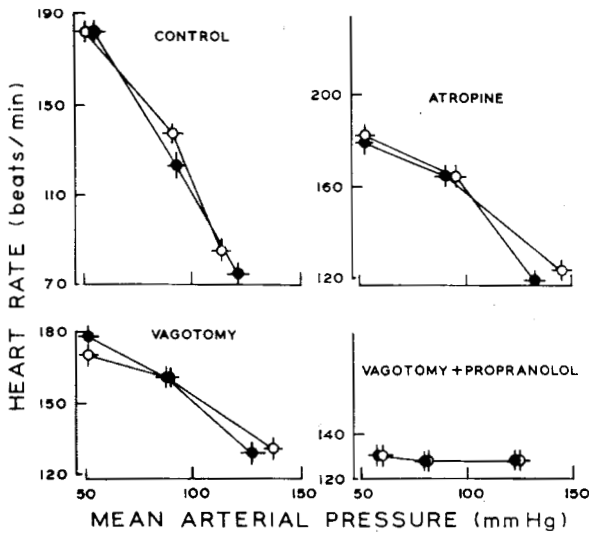


Fig. 13: Mean curves representing the baroreflex mean arterial blood pressure-heart rate relationships for peak effects before (●) and during (○) left atrial receptor stimulation following atropine injection, bilateral vagotomy and administration of propranolol in vagotomised animals. Values are mean \pm SEM from five dogs.

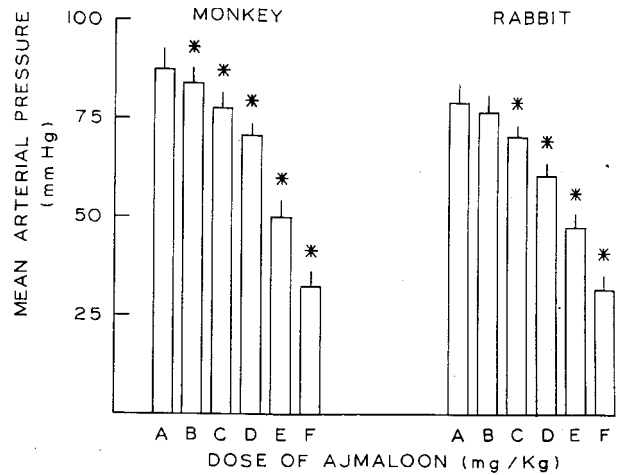


Fig. 15: Histograms showing the effect of varying doses of intravenous Ajmaloon on mean arterial pressure in anaesthetised monkeys and rabbits. In each set A: control before Ajmaloon, B, C, D, E, F: after intravenous administration of 25, 50, 100, 200, 300 mg/kg Ajmaloon respectively.

Interaction between atrial receptors and arterial baroreceptors in the reflex control of heart rate

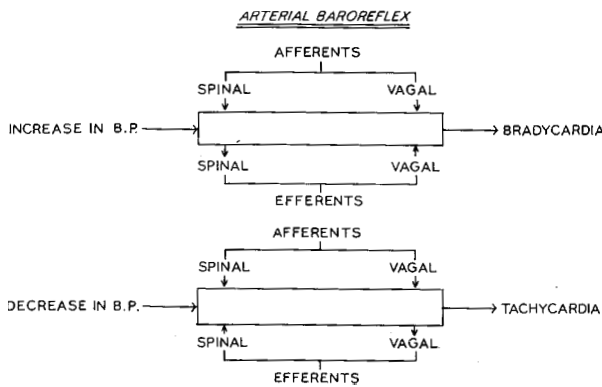


Fig. 14: Block showing involvement of vagal and spinal afferents and efferents in the reflex regulation of blood pressure through changes in the heart rate.

of the reflex to a lower operational set point is suggested to be mediated by cardiac sympathetic motoneurons common to both the reflex arcs (70).

The atrial type B receptors or cardio-pulmonary low-pressure receptors are known to participate primarily in reflex regulation of blood volume. In dogs, localized stimulation of atrial receptors produces a reflex tachycardia response. Since arterial baroreceptors are known to regulate arterial pressure by reflex changes in the heart rate and by vasoconstriction, it suggests that these two sets of sensory receptors reflexly influence both the cardiovascular system and the autonomic efferent output. Roddie et al. (79) suggested that excitation of cardio-pulmonary receptors inhibits the arterial baroreflex through a central mechanism. Interaction between two groups of cardiovascular sensory receptors has also been observed by other investigators. The cardiovascular reflex

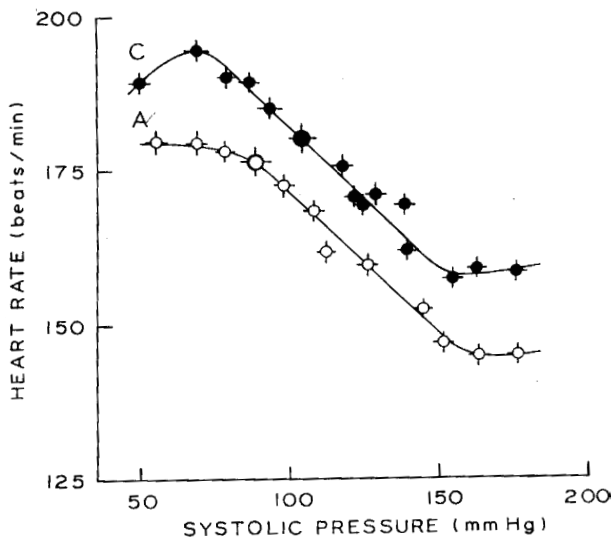


Fig. 16: Mean curves representing baroreflex systolic arterial pressure-heart rate relationship before (●) and after (○), 100 mg/kg intravenous Ajmaloon. Larger circles are the resting values. The values are mean \pm SEM from five monkeys.

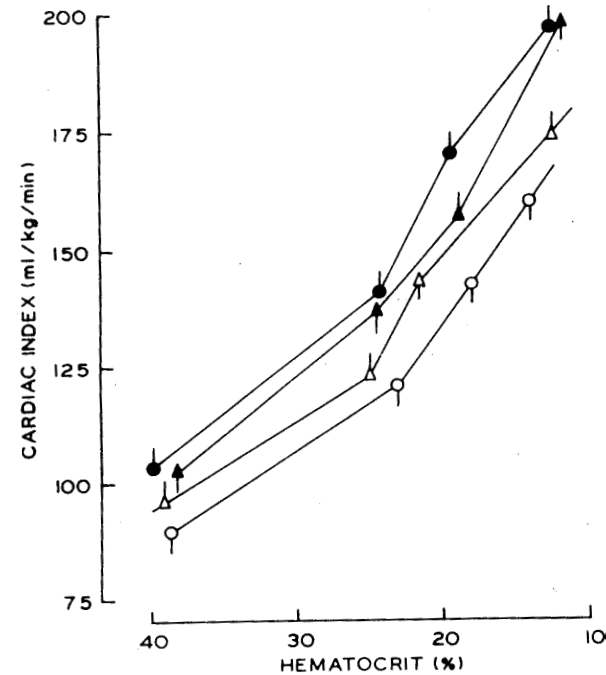


Fig. 17: Increase in cardiac index with fall in hematocrit due to graded normovolemic haemodilution in control (●), beta blocked (○), vagotomized (▲), and vagotomized beta blocked (Δ) dogs.

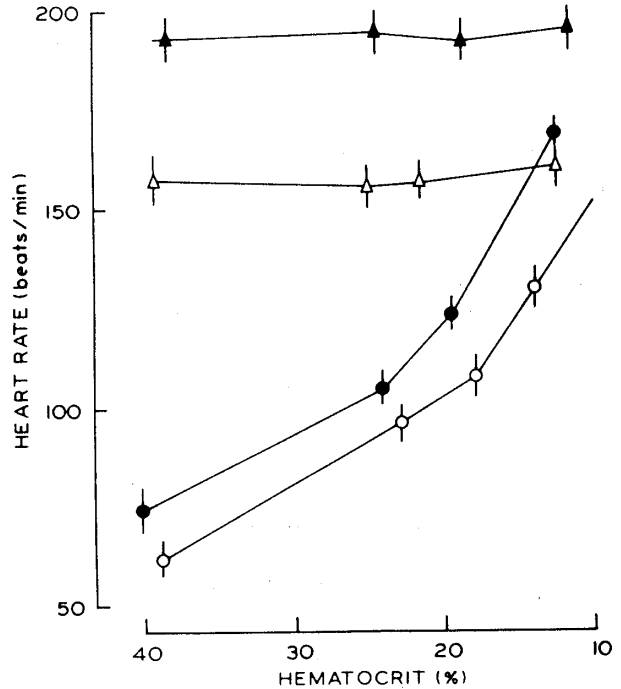


Fig. 18: Heart rate changes with fall in hematocrit due to graded normovolemic hemodilution in control (●), beta blocked (○), vagotomized (▲), and vagotomized beta blocked (Δ) dogs.

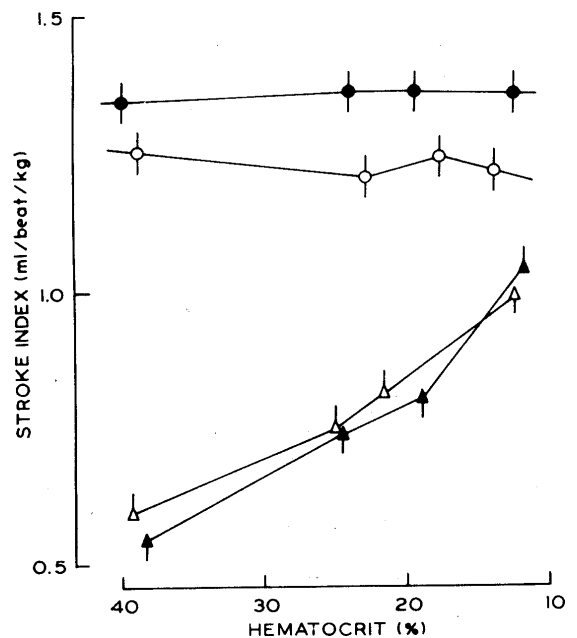


Fig. 19: Changes in stroke index with fall in hematocrit due to graded normovolemic hemodilution in control (●), beta blocked (○), vagotomized (▲), and vagotomized beta blocked (Δ) dogs.

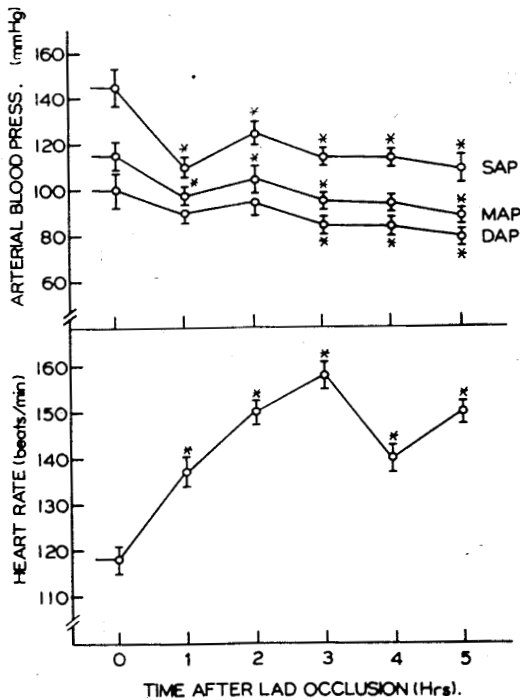


Fig. 20: Changes in arterial blood pressure and heart rate after complete occlusion of left anterior descending artery (LAD). SAP: Systolic arterial pressure; MAP: Mean arterial pressure. All values are mean \pm SEM from data on ten dogs. * $P < 0.01$ as compared to basal values at 0 time on the X-axis.

effects produced by arterial baroreceptors and atrial receptors involve both vagal and sympathetic efferents and afferents. In one of our studies (69) on anaesthetized cats and dogs we recorded the sympathetic cardiac efferent nerve activity and cardioinhibitory vagus efferent nerve fibre activity on stimulation of the arterial baroreceptors, atrial receptors or both types of receptors simultaneously. Arterial baroreceptor-mediated chronotropic effect involved both sympathetic and parasympathetic limbs of the autonomic nervous system (Fig. 14). However, cardio-acceleration produced by localized stimulation of the left atrial

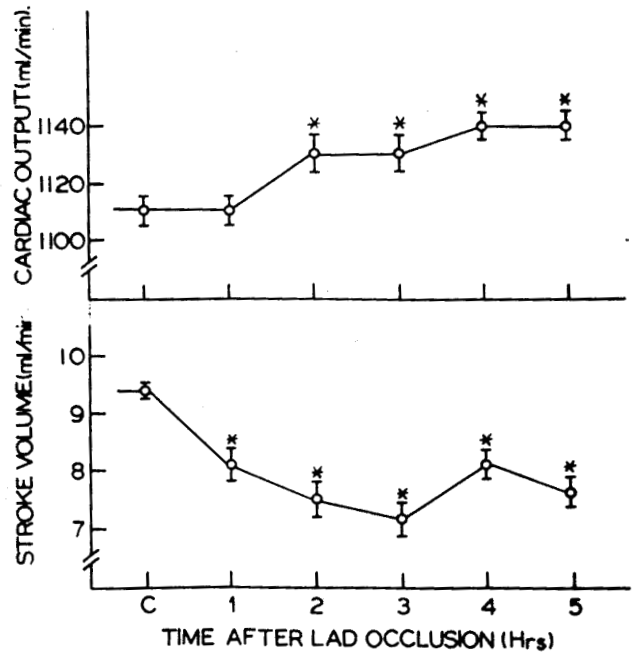


Fig. 21: Changes in Cardiac Output and stroke volume after complete occlusion of left anterior descending coronary artery (LAD). All values are mean \pm SEM from data on ten dogs. * $P < 0.01$ as compared to basal values (C) before occlusion of LAD.

receptors was mainly due to withdrawal of parasympathetic tone and not by excitation of sympathetic efferent (69). On stimulation of both types of cardiovascular receptors simultaneously, net result was a slight inhibition of the baroreflex tachycardia response to hypotension and an augmentation of baroreceptor mediated bradycardia response to the increase in arterial pressure. Thus atrial receptors modulate the arterial baroreceptor-mediated chronotropic response to change in arterial pressure. The arterial baroreceptors and atrial receptors during sustained change in their natural stimulus reset the reflex chronotropic response.

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