GEORGE E. BROWN MEMORIAL LECTURE

Function of Cardiac Receptors


Additional Indexing Words:
Vagal nerves Sympathetic nerves Nerve endings Nerve discharge Atria Ventricles Atrio-venous junction Stretch receptors Afferent fibers Efferent fibers Heart rate Contractility Urine flow Acidosis Peripheral circulation

IT IS A GREAT HONOR to be asked by the American Heart Association to give the George Brown Memorial Lecture. George Brown was Chief of a Section of Medicine at the Mayo Clinic until his untimely death at an early age in 1936. His main topic of interest was the peripheral circulation and he was foremost in joining with others about 40 years ago to form a group within the Heart Association to promote the study of the peripheral circulation. Were he alive today I am sure he would be interested in cardiac receptors because the effects of stimulating cardiac receptors include changes in the peripheral circulation.

Cardiac receptors have been difficult to study because any interference with them, to stimulate them, has resulted in a change in the heart beat which in turn interfered with the stimulus. However there seem to be three broad methods of approach: 1) to examine the tissues histologically; 2) to record action potentials or nerve impulses in nerves from the receptors and then examine different stimuli at the suspected sites of the receptors; and 3) to examine the reflex function of the receptors. I hope to illustrate these three methods of approach in dealing with the receptors in the ventricles and atria.

Over the years various effects and functions have been attributed to receptors in the ventricles and atria. However, it does seem now that some pattern of events is beginning to evolve. Broadly, two groups of effects are obtainable: stimulation of ventricular receptors results in a decrease in heart rate and fall in blood pressure; and stimulation of atrial receptors results in an increase in heart rate and an increase in urine flow.

Ventricular Receptors

One approach to the problem of stimulation of cardiac receptors has been to use chemical substances by application and injection, in order to stimulate receptors in the ventricles of the heart. As long ago as 1867 Bezold and Hirt observed that the injection of veratrum produced apnea, bradycardia and hypotension. Jarisch and his coworkers (e.g., in 1937,2 1939,3 and 19484) confirmed these results and since that time these responses have been known as the Bezold-Jarisch reflex. Dawes5 localized some receptors responsible for the reflex bradycardia and hypotension to the left ventricle and later Dawes and Comroe6 suggested the reflex be called the coronary chemoreflex.

Histology

Numerous investigations have described nerve endings in the ventricular epicardium and myocardium (e.g., King7) but the nomenclature used here is that fully described by Miller and Kasahara.8 Although unencapsulated endings have been reliably demonstrated in the epicardium there are few reliable histological reports of nerve endings in the ventricular endocardium and myocardium. Indeed, Miller and Kasahara stated they were unable to demonstrate sensory terminals ending along myocardial muscle fibers. But they could trace bundles of mixed myelinated and unmyelinated nerves through the connective tissues of the septa between the muscles. They concluded there were no sensory endings in the myocardium—they assumed the

nerve fibers extended ultimately into the endocardium. Thus the commonly held belief that nerves to the ventricle travel only with the coronary vessels is refuted. Evidence in support of this statement is also supplied by Woolard,9 Mitchell,10 and Sleight.11 However, there are no adequate histological techniques with which to define the very small nerve fibers.

Technique

To examine the function of receptors and their discharge it is necessary to dissect the nerves and examine fine filaments as has been described.12 Animals are anesthetized, artificially respired, and the chest opened. The vagal nerves are dissected free in the neck; the sheath is taken off, a slip of the nerve is cut rostrally, peeled off, and placed on electrodes; the resulting changes in potential in the fine slip are amplified, displayed on an oscilloscope, and relayed to a loudspeaker. Action potentials from different receptors are then observed either with a spontaneous cardiac rhythm or with irregular discharges which change their discharge with various stimuli. Drugs can then be injected into each chamber and the response observed; by timing the onset of the discharge some information may be obtained as to which chamber the receptor is in. But probably a better way is to place snares around the aorta, pulmonary artery, and each lung root so that by tightening the snares and differentially raising the pressures in different chambers it is possible to observe the changes in receptor discharge and so make a first guess as to where the receptor is situated.

After obtaining this clue to which chamber contains the receptor it is necessary to attempt to locate the receptor precisely and the following techniques are used in sequence; probing on the outside of the chamber; inserting a probe inside the chamber and probing on the inside; killing the animal by bleeding, opening the heart, sucking away the blood and under direct vision probing the suspected area with a fine glass probe until a high frequency discharge is observed on the oscilloscope and heard over the loudspeaker.

Following this probing one of two further techniques should be used. Either the tissues can be nibbled away until the discharge abruptly ceases—and it is easy to distinguish those receptors in the endocardium from those in the myocardium using this technique—or, a small square of tissue about 1 mm² enclosing the ending can be marked and examined histologically. I cannot agree with Pain-tal13 who stated that it is possible to recognize the chamber and site of organ of receptor discharge without opening the chest and without locating the area precisely in the manner described above.

Receptor Discharge from the Ventricle

Using such techniques Coleridge, Coleridge, and Kidd14 showed there were two types of ventricular receptor, one with a pulsatile discharge in time with the heart beat (as shown in their fig. 4) and one with an irregular discharge as shown in fig. 1. For various reasons little useful comment can be made about those with a cardiac rhythm: they are few in number and little else is known about them. As Pain13 has suggested, the “coronary artery” mechanoreceptors of Brown15, 16 really belong to this group of receptors and are not true “coronary” receptors. However because Brown showed that stimulation of these receptors caused bradycardia and hypotension they can be probably included in the large group of systemic and pulmonary baroreceptors known to have this response.

The second type of ending described by Coleridge et al.14 was characterized by a sparse irregular discharge and is, at the moment, much more interesting. These receptors were stimulated by stroking lightly over an area of the ventricle of about 1 cm² and by various chemicals as shown in fig. 1. Coleridge et al.14 obtained nine single fibers and located all nine receptors in the epicardium. They observed in similar experiments that three single epicardial receptors discharged into non-myelinated small fibers, C fibers, with conduction velocities of about 1 m/sec, totally different from the myelinated fibers from the atrial receptors with conduction velocities of 10–30 m/sec.13

Reflex Response

About the same time Sleight11 and Sleight and Widdicombe17 obtained similar results observing such epicardial receptors to increase their discharge to the topical application of nicotine. Again, in anesthetized and unanesthetized dogs, Sleight11 showed that stimulation of epicardial receptors by nicotine or veratridine did not cause pain but resulted in an average fall in blood pressure of 35 mm Hg and a fall in heart rate of 33 beats/min. The afferent limb of the reflex was shown to be in the vagi.

Further work by Muers and Sleight18, 19 and by Öberg and Thoren20, 21 have increased our knowledge about this reflex response. From their work it is now apparent there are ventricular receptors,
mostly in the left ventricle, which discharge irregularly and sporadically into small nonmyelinated C-fibers in the vagi. They are distributed over the whole left ventricle in both epicardium and myocardium. They are activated by fairly gross changes such as occlusion of the aorta or occlusion of the coronary sinus, causing high pressures, rapid infusions, electrical stimulation of cardiac nerves, intravenous or intracoronary injection of catecholamines, and the injection of drugs such as nicotine, veratridine, capsaicin. However, all these assaults are outside the physiological ranges and provide no evidence yet of the natural physiological stimulus.

The effect of stimulating these receptors is always to cause a reflex bradycardia and hypotension.

Evidence has also been presented that this reflex is responsible for at least part of the bradycardia caused by digitalis glycosides. It is also said to be responsible for the vasodilatation in muscle vessels in dogs caused by the liberation of acetylcholine and cholinergic vasodilatation in muscle vessels are known to occur; these last two investigations require confirmation, particularly because of more recent work. For instance, in attempts to involve ventricular baroreceptors by distension of the ventricles, Mark et al. appeared to produce dilatation in the vessels of muscle (and skin but a smaller effect was observed) whereas coronary occlusion caused vasoconstriction in the vessels of the muscle and vasodilatation in the skin. Neither of these two investigations showed the efferent cholinergic vasodilator pathway to be involved but then neither contained any real evidence that particular receptors were involved. These examples of this type of investigation also suggest that there may be more than one reflex involved and to distinguish which reflexes is a major difficulty of this type of experimentation. Much more and careful work is necessary in this area before a solution to this problem is obtained. It is possible that this reflex is responsible for most of the reflexes coming under the general heading of the Bezold-Jarisch reflex and under the particular heading of "coronary chemoreflex." Lastly, by no means of least importance, Kolatat et al., from experiments in anesthetized dogs, have suggested that the bradycardia and hypotension observed at the time of induced myocardial infarction are brought about reflexly by an increase in discharge from receptors in the infarcted area. This suggestion has been taken recently by Thoren in Göteborg, Sweden. He observed the same reflex bradycardia and hypotension in anesthetized cats when he tied off a major coronary artery. This is the same reflex we are

Figure 1

Multifiber recording from slip of vagus nerve. Each panel contains an electrocardiogram (e.c.g.) and action potentials in the slip of nerve (P). D shows the effect of gently stroking the epicardial surface of the ventricle (at signal). E is recordings when capsaicin 10 µg/mg was injected into left atrium (between arrows). F recorded 5 sec and G, 20 sec, after painting capsaicin (0.001% solution) onto ventricle at site of stroking shown in D. (From Coleridge et al.)
discussing because Thoren also recorded action potentials in small unmyelinated C-fibers. He suggests that the stimulus was a distension of the infarcted area. It is possible to relate these findings to the evidence of Pantridge who studied myocardial infarction in man as early as possible after its onset. It seems that bradyarrhythmia was a fairly common finding within the first hour of a myocardial infarction; in fact, with infarctions of the posterior wall of the left ventricle 61% exhibited brady-arrhythmias.

Even though we must remember there are other causes of brady-arrhythmia it does seem that we ought to ask the question, is the reflex from the left ventricle important in the early stages of myocardial infarction and could it be responsible for some of the early deaths?

Summary

It does seem that it is possible to elicit a reflex from the left ventricle in response to various stimuli, the response to which is a bradycardia and hypotension. The receptors have not been described histologically, the natural stimulus is unknown but the afferent fibers appear to be small, in the C-fiber range. No function is known but suggestions are that the reflex is involved during fainting and myocardial infarction.

It is too early to comment usefully on the claim that there are cardiac reflexes with “sympathetic” afferent fibers and particularly of the suggested cardio-cardiac reflexes where the claim includes a very small response in dP/dt max (maximum rate of change in pressure used as an index of change in contractility or inotropic state of ventricular muscle) of 270 mm Hg/sec (nearly half of which could result from the small rise in systemic pressure) to justify the conclusion that there is a positive inotropic response of the left ventricle. Such a small positive inotropic response should be compared with that of an increase of 10,000 to 14,000 mm Hg/sec in dP/dt max which results from stimulation of the left ansa subclavia under similar circumstances, with the effect of an infusion of isoprenaline causing a change in dP/dt max of about 5000 mm Hg/sec and with the negligible effect (about 200 mm Hg/sec) resulting from the stimulation of atrial receptors (also see below).

More and careful work will have to be produced before these supposed reflexes can be accepted.

Having examined the function of the ventricular receptors we must ask the question, what of atrial receptors?

Atrial Receptors

Here I wish to report the investigations of my colleagues and me in Leeds for the last ten years and to persuade you that stimulation of the atrial receptors results in a reflex increase in heart rate and an increase in urine flow.

Histology

Sensory fibers and their end-organs in the heart have been described histologically since the turn of the century, when in 1895, Berkley first reported an investigation of this problem. At least 25 reports have been made since then of histological investigations into the hearts of puppies, kittens, lambs, dogs, cats, monkeys, and man and a variety of end-organs have been described mainly by free interpretation in drawings from slides. From this mass of data the only certain conclusion is that the endocardium of both atria is the most profusely innervated, and the characteristic features of the atrial endocardium are the wealth and variety of the complex unencapsulated sensory endings found only at the junctions of the superior and inferior vena cava and right atrium, and of the pulmonary veins and left atrium, as described by Nonidez and shown in fig. 2. Following this Paintal showed

Figure 2
Posterior view of the heart of a kitten showing the location of the receptor areas (dotted) at superior (a) and inferior (i) vena caval-right atrial junctions and pulmonary (p) vein-left atrial junctions. (From Nonidez)
CARDIAC RECEPTORS

action potentials in slips of the vagi which originated in receptors in the atria of the cat. In Leeds, a combined physiological and histological study of adult anesthetized dogs was completed which established the presence of atrial receptors at the atrio-venous junctions and that these receptors caused changes in activity in the right and left vagi. More recently Coleridge et al. have given some indication of the relative number of receptors in the two atria in the adult dog (see their fig. 2).

What do these receptors look like? There are two standard methods of staining the receptor endings—with silver impregnation and then a study of subsequent cut sections, or with methylene blue. The most beautiful preparations are obtained when the tissues are soaked in methylene blue and the endings are then viewed from the surface in whole thickness preparations. An example of the receptor endings from a pulmonary vein-atrial junction of the dog is shown in fig. 3. These endings are all in the loose tissue of the endocardium, all have no capsule and obviously will be stimulated by deformation of the wall of the chamber to which they are attached. These stretch receptors were observed in the dog but similar endings have now been observed in the cat and the monkey; Johnston has observed similar receptors in the atria of man. So far, these receptor endings have always, and only, been observed at the junctions of the superior and inferior vena cava and the right atrium, and the pulmonary veins and left atrium.

What Then Is Their Function?

Historically, there has been much interest in the atria and their receptor function since 1915 when Bainbridge observed that giving large infusions of saline or blood to anesthetized dogs caused an increase in heart rate—and Bainbridge claimed that the cause was an increased pressure in the right atrium which stimulated receptors. This response has since been known as the Bainbridge reflex—known to every British medical student as the answer to any question on the circulation, be it to do with exercise or any other stress.

It is important to realize that there is no evidence in his paper from which to draw the conclusion that the right atrium had anything whatsoever to do with this reflex, or combination of reflexes.

Since that time numerous cardiovascular investigators have pursued this holy grail and my colleagues and I have given short reviews of previous work. A survey of the literature in 1964 revealed that the general opinion seemed to be that the response to stretching the heart walls was either no effect or a bradycardia. This opinion was summarized in 1964 by an eminent authority on the subject who rightly concluded “Cardiovascular Reflexes which have been well studied either slow the heart or lower the blood pressure, and do both in response to an increase in pressure, in, or stretch of, the appropriate vessels; this generalization requires the rejection of the Bainbridge reflex.”

I hope, in the remainder of this presentation to refute this statement, and to do this with the evidence from several series of experiments. All the following experiments in anesthetized dogs were completed with my colleagues in Leeds during the last ten years. It was obviously an advantage to us to know exactly where the receptors were, that is, only at the junctions of the veins and atria.
Experiments were therefore designed so that only those areas of atrio-venous wall containing atrial receptors were distended and no changes in atrial pressure or blood flow through the atria were directly caused by the distensions.

Figure 4
Diagram of preparation used to stimulate left atrial receptors. LU = lung; LA = left atrium; RV and LV = right and left ventricles. The diagram illustrates left lung root tied off, small balloons at pulmonary vein-atrial junctions and total venous return passing through right lung. It was possible to distend balloons and stretch junctions without altering flow through the heart or changing atrial pressures. (From Linden†6).

Left Atrial Receptors
The chest was opened in the fifth left interspace and three small balloons, each about 3 mm long, at the end of a short catheter, were placed one in each left pulmonary vein, so that each tip lay at a pulmonary vein-atrial junction. A soft ligature was tied around the root of the left lung immediately behind the catheters so that no blood flowed through the left lung as shown in fig. 4. It was then possible to inject 0.5–1.0 ml of warm saline causing each balloon to expand to a diameter of about 1 cm without causing any obstruction to blood flow through the lungs and atrium and there was no rise in pressure in the atrium.

In one series of experiments action potentials or nerve impulses were recorded in slips of the vagi in the neck and then the balloons were distended. Distension of the balloons in six dogs caused an increased discharge in slips of the vagal nerves and we showed that the only receptors to be stimulated by the balloons were the left atrial receptors. Parts of the records from such an experiment are shown in fig. 5. We were also able to conclude that though this balloon stimulus was so obviously "unphysiological" in one sense, it gave perfectly reasonable physiological effects in the afferent nerves from the atrial receptors—equivalent to a pressure in the left atrium of 10–15 cm H₂O—well within the normal range. Another important observation from fig. 5 is that though the balloon was continually distended for the period of 3 min the discharge of the receptors was pulsatile, exactly as is found if the atrium is distended in the usual way by infusing blood or saline.

In our first investigation in 1964⁶⁹ distensions of the three balloons in the pulmonary vein-left atrial junctions always resulted in an increase in heart rate, an example of which is shown in fig. 6. In 78 distensions on 24 dogs there was a mean increase in heart rate of 24 beats/min (range 2–89) as shown in fig. 7. There was no obvious relationship between the change in heart rate and the small changes in systemic arterial pressure, indicating that the carotid sinus mechanism was not causing the increase in heart rate. In all, our three laboratories in Leeds have published the results of some 310 distensions of the balloons in 109 dogs; heart rate has increased an average of 24 beats/min, and bradycardia never occurred (see references in Furnival et al.⁸⁸).

A criticism of this work might be that we have failed to demonstrate a correlation between the magnitude of the stretch and the increase in heart rate. A possible explanation lies in the peculiar geometry of the vein-atrial junction and the fact that distension of balloons is a crude means of stretching delicate tissue. To date we have found no way of solving this problem which, at the moment, we consider to be solely technical.

This far in the investigation it seemed that we had found a response but required an afferent and efferent pathway to establish a new reflex. By sectioning and cooling the vagi in the chest and in the neck we showed that the afferent pathway was
in the vagi. Because of the slow onset of the response of the increase in heart rate and the even slower decline it was considered that the efferent nervous pathway would be in the sympathetic nerves. The sympathetic nerves to the heart in the dog are all to be found in the left and right ansae subclaviae. In five dogs cutting both ansae subclaviae or using β-receptor blocking drugs to block the efferent sympathetic nerves showed that the efferent sympathetic nerves were indeed involved in this reflex response.40 No efferent vagal response was observed following sympathetic blockade.

In another investigation in which an isolated pouch of the left atrium containing only the atrial receptors was distended by means of pulsatile changes in pressure Ledsome and I52 showed that the same reflex response, increased heart rate, could be elicited. Though high pressures were required in the pouch it was later demonstrated,43 by recording action potentials in slips of vagal nerves and by use of the Law of Laplace, that the tensions in the wall of pouch, and therefore the stretch of the receptors, would be less even though the pressure in the lumen was higher; the pouch had a radius of curvature about four times less than that of the whole atrium. This investigation served to provide more circumstantial evidence that the atrial receptors were involved in this reflex response.

Figure 5

Effect of distension of balloon on discharge of action potentials from left atrial receptor. From above: femoral arterial pressure (Fem. art.) in mm Hg; left atrial pressure (L.A.P.) in cm H₂O; action potentials from slip of vagal nerve; electrocardiogram (e.c.g.); two datum lines. Left panel, before distension of the balloon; right panel, during distension of the balloon with 1 ml of warm saline. Time between vertical lines in each panel is 1 sec. Note (1) the sparse (3–4 impulses/beat) pulsatile discharge in a single fiber with balloon not distended; (2) the great increase (about 20 impulses/beat) in the pulsatile discharge during distension of the balloon. Location of receptor proved at post mortem to be in the endocardium of left upper pulmonary vein-atrial junction.

Figure 6

Effects of stimulation of left atrial receptors on the heart rate in one dog, illustrating, not the best, but one of the better responses. Records, starting at the top: femoral arterial pressure (Fem.) in mm Hg; left atrial pressure (L.A.) in cm H₂O; a datum line; electrocardiogram (e.c.g.). The three panels show records before, during, and 3 min after stimulation of the atrial receptors. The number above the records in each panel indicates the heart rate for that period counted over 1 min. The increase in heart rate (estimated as indicated in legend to figure 7) was 77 beats/min.
Right Atrial Receptors

By a similar technique but with much more difficulty Drs. Kappagoda, Snow, and I\textsuperscript{40, 44} have shown that distension of the junction of the superior vena cava and the right atrium results in a reflex increase in heart rate which is in all respects the same as the one caused by stimulation of left atrial receptors.

It is perfectly reasonable to expect that distension of the terminal balloon which stretched the superior vena caval-right atrial junction would result in discharge of the atrial receptors into the vagal nerves; this was confirmed during two series of experiments. Action potentials were recorded in vagal nerves and the terminal balloon was then distended with varying amounts of warm saline. An example of one record is shown in fig. 8 where an increased discharge of one receptor is shown as a response to increasing distensions of the balloon. A plot of the responses of three receptors is shown in fig. 9 which illustrates that a high discharge of an atrial receptor is not observed until a volume of 8-10 ml of saline had been injected into the balloon, precisely the same volume which had been injected in an earlier investigation in order to obtain the reflex response.

**Figure 7**
The effects of stimulating left atrial receptors: 78 stimulations in 24 dogs. "Change in heart rate" is the heart rate in the third minute (counted for 1 min) of distension minus the average of the rates for the 1 min immediately before distension and the third minute after release of distension (each counted for 1 min). "Change in arterial pressure" was calculated in a similar manner. (From Ledson and Linden.\textsuperscript{39})

**Figure 8**
Effect of stretching the junction between the superior vena cava and the right atrium on a single unit in the cervical vagus. From above down, the superior vena caval (S.V.C.) pressure, right atrial (R.A.) pressure, action potentials from a slip of the right cervical vagus and electrocardiogram (e.c.g.). As the volume in the terminal balloon was increased in increments of 4 ml (i.e., as the superior vena caval-right atrial junction was stretched) the impulse frequency (impulses/beat) increased from 6/beat to 12/beat. The impulse frequency returned to the control value after the release of the distension. This particular single unit showed a discharge during atrial filling and during atrial systole.
of an increase in heart rate. That this order of distension was also within the physiological range was concluded from experiments in which infusions were given until the discharge from the atrial receptors was the same as that obtained by distension of the balloons with 8–10 ml of saline. It was found that a pressure of about 8–12 cm H₂O in the right atrium was required to obtain a discharge equal to that caused by distension of the balloon. Such pressures are well within the physiological range of right atrial pressures and thus the balloon is having an effect well within the physiological range.

As an example of the response of an increase in heart rate part of the record from experiments in which the right atrial receptors were stimulated is shown in fig. 10. A mean increase in heart rate of 25 beats/min resulted.

Sixty-five distensions of the terminal balloon in 16 dogs with an average volume of 8 ml stretched the superior vena caval-right atrial junction and resulted in an increase in heart rate during each distension. The mean increase in heart rate was 17.5 beats/min with a range of 5 to 73. There was no relationship between the small change in arterial pressure and the change in heart rate or between the small change in superior vena caval pressure and change in heart rate. The afferent pathway of the reflex was shown to be in the vasa by cooling each vagus in turn. Sectioning, or cooling both vagi simultaneously is not considered to be a valid test of an afferent pathway such as the one postulated here because a totally different animal base line, which would not be comparable with the previous control periods, is observed after bilateral vagal section. The effect of cooling the right and left cervical vagi on the response is shown in table 1. Cooling the nerve to 6°C blocks conduction in nerve fibers of the size attached to atrial receptors. The response of the increase in heart rate was always less when a vagal nerve was cooled than the response either before cooling or after rewarming the nerve. From these results it is possible to conclude that the afferent pathway of this reflex is at least partly in the vasa.

The results of blocking activity in sympathetic nerves to the heart on the reflex response is shown in table 2. Crushing the right ansa subclavia or blocking the action of the sympathetic nerves with drugs completely abolished the response of an increase in heart rate. Again no bradycardia was observed after sympathetic blockade; the response was solely in the sympathetic nerves.

**Summary**

Thus, from the evidence presented so far, we had discovered a reflex response of an increase in heart rate, involving receptors in both right and left atria, afferent nerves in the vagi and efferent nerves in the sympathetic nerves, and only in the sympathetic nerves.

**Is There a Positive Inotropic Response?**

Stimulation of efferent sympathetic nerves to the heart is known to cause a positive inotropic response as well as an increase in heart rate. It was therefore expected that stimulation of the atrial receptors would also result in a positive inotropic response. We had already shown that dP/dt max in
Figure 10

Effects of stimulating right atrial receptors on tracheal pressure (P) (cm H2O), end tidal (E.T.) Pco₂ (mm Hg), femoral arterial pressure (Fem. P.) (mm Hg), heart rate (beats/min), left and right atrial pressures (L.A.P. and R.A.P.) (cm H2O) and the electrocardiogram. S.V.C.P. = superior vena caval pressures. Records obtained immediately before distension of balloon A (heart rate 97/beats/min), during the distension (heart rate 126 beats/min), and 3 min after removal of the distension (heart rate 106 beats/min). Mean increase in heart rate was 25 beats/min. (From Kappagoda et al.46)

The left ventricle may be used as an index of changes in the inotropic state of the ventricle46 and could denote positive inotropic changes resulting from stimulation of sympathetic nerves.41, 46 Therefore we used dP/dt max as the index of changes in the inotropic state and stimulated the atrial receptors.33

We expected to observe a positive inotropic response; in the event there was no response, only an increase in heart rate.33 The results of 37 experiments in 12 dogs in which the left atrial receptors were stimulated are shown in fig. 11 in which one response (change in dP/dt max) is plotted against the other (change in heart rate). It can be seen that even at the highest increase in heart rate of 90 beats/min in response to stimulation of left atrial receptors there was an increase in dP/dt max of only 276 mm Hg/sec, even less than would be obtained by simple pacing. The mean change in dP/dt max as a result of stimulating the atrial receptors in the 37 experiments was an increase of 193 mm Hg/sec (mean: range 36–828).

Table 1

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Also shown in fig. 11 for comparison is the effect of occluding the carotid arteries in ten experiments and the effect of infusions of isoproterenol. It can be seen that with the increase in heart rate resulting from occlusion of the carotid arteries there is a larger increase in $dP/dt_{max}$; a mean increase of 1263 mm Hg/sec was obtained. The infusion of isoproterenol shows an increase of 3000 mm Hg/sec for an increase of 50 beats/min in heart rate caused by the isoproterenol in a paced denervated heart.32 Each of these larger responses indicates that the technique of recording $dP/dt_{max}$ as an index of the inotropic state is valid in this preparation and that the increase in $dP/dt_{max}$ in response to stimulation of left atrial receptors is negligible.

So we concluded that the reflex involved no concomitant positive inotropic effect—only an increase in heart rate.

In two other series of experiments in our laboratories Drs. Hainsworth and Ledsome47, 48 have shown that stimulation of the left atrial receptors do not affect either respiration or peripheral resistance. The finding of no effect on the peripheral vessels was supported by the work of Karim, Kidd, Malpus, and Penna49 again in our laboratories. They found that there are no changes in activity in efferent sympathetic nerves in the abdominal sympathetic trunk below the origin of the renal artery when the left atrial receptors are stimulated.

But Ledsome and I50 did show that stimulation of left atrial receptors had the added effect of increasing urine flow. Gauer and Henry in 195851 had shown that a large balloon, placed in the left atrium and distended so as to block the mitral orifice and raise the left atrial pressure about 20 cm H$_2$O, would cause an increase in urine flow. Since such an obstruction to the mitral valve causes other effects than stimulation of atrial receptors, we repeated their experiments, adding stimulation of the left atrial receptors. The results of one experiment are shown in fig. 12. Two distensions of the large balloon to obstruct the mitral orifice (B) and two distensions of the small balloons to stimulate only the left atrial receptors (A) were
Although the large balloon also failed to occur (see fig. 12, final distension B). The results of nine distensions of the large balloons and nine stimulations of the left atrial receptors randomly completed in five dogs are shown in fig. 13, and it can be seen that points obtained in both series of experiments appear to belong to the same population.

Thus we can conclude that stimulation of the left atrial receptors causes an increase in urine flow, and although the large balloon caused a larger increase in urine output than the smaller ones, there is no reason to believe that receptors other than the atrial receptors are involved: the big balloon is stimulating over a larger area than the small ones. Recently Drs. Kappagoda, Snow, and Linden reported results of experiments which show that stretching the right atrium without obstructing venous return or altering right atrial pressure also results in an increase in urine flow. Thus we can conclude that right atrial receptors also take part in this reflex.

From other experiments in our laboratory, with innervated kidneys, denervated kidneys, and perfused kidneys, it is possible to conclude that there are two efferent mechanisms involved in this reflex, a blood-borne agent and a nervous one, the latter possibly being the sympathetic nerves to the kidney.

Experiments in other laboratories suggest that the blood-borne agent is antidiuretic hormone, a hypothesis that was revived by Mason and Ledsome last year. They provide a possible explanation of some experiments we completed in 1961 in

Figure 12

Changes in urine flow occurring during one experiment in which atrial receptors were stimulated and in which the mitral valve orifice was obstructed. During A, left atrial receptors were stimulated (small balloons at pulmonary vein-atrial junctions). During B, mitral obstruction was caused by large balloon in the manner of Gauer and Henry. There is a break in the record at “1” where a burst balloon was replaced. At “2,” afferent vagal nerves of the heart rate reflex from the left atrial receptors were sectioned. Note that in this instance sectioning the nerves abolished the diuretic response. L.A.P. = left atrial pressure. (From Ledsome and Linden.)

HEART RATE (beats/min)

L.A.P. (cm saline)

B.P. (mm Hg)

URINE VOL. (ml/min)

Time after operation (hr)
which we believed we had demonstrated that antidiuretic hormone could not be involved in the reflex. More investigations of this aspect of the reflex are required.

However the most interesting observation was made by Karim et al. in our laboratory when they recorded nervous impulses in many sympathetic nerves. On stimulating the left atrial receptors they observed that there was an increase in discharge in the right ansa subclavia (presumably to the sinoatrial node) but a decrease in discharge in nerves to the kidney, and no change in any other sympathetic nerves. This effect on nerves to the kidney is illustrated in fig. 14 where the change in impulse activity in sympathetic nerves as a percentage of control is plotted against a change in blood pressure. There is no obvious relationship between change in efferent activity and blood pressure, indicating no causative relationship resulting from changes in the carotid sinus mechanism. It can be seen from fig. 14 that stimulation of left atrial receptors results in an increase in activity in cardiac efferent sympathetic nerves, a decrease in activity in efferent nerves (presumably sympathetic) to the kidney, and no change in activity in efferent nerves to the spleen and to the lumbar region.

One interesting side point is that if these results are evidence of less activity in sympathetic nerves to the kidney at the same time that activity in

**Figure 13**

Urine volume during period of distension of balloons compared with urine volume during control periods. Open circles, nine tests in five dogs of effects of mitral obstruction (large balloon); filled circles, nine tests in the same five dogs of the effect of stimulating left atrial receptors only (small balloons at pulmonary vein-left atrial junctions). (From Ledsome and Linden.)

**Figure 14**

Relationship between the change in sympathetic efferent impulse activity expressed as a % of control values and the change in mean systemic arterial blood pressure during stimulation of left atrial receptors. Each symbol indicates responses of a group of sympathetic strands; filled circles (○), cardiac; open circles (○), lumbar; crosses (x), splenic; filled squares (●), renal. Note that stimulation of left atrial receptors results in an increase in activity in sympathetic nerves to the heart but a decrease in activity in nerves to the kidney. (From Karim et al.)
sympathetic nerves to the heart is increased, then these results provide yet more evidence to refute Cannon's original hypothesis\textsuperscript{56} that the sympathetic nervous system functions as a whole.

But of interest to us here is the action of the nerves to the kidney as a result of stimulation of left atrial receptors, and we do not know yet what these sympathetic nerves do in the kidney; it is probable they alter blood flow. Skinner and his group\textsuperscript{57} have recently shown that systemic hypotension during bleeding (low left atrial pressure) results in vasoconstriction in the kidney and less blood flow but that systemic hypotension during experimental myocardial infarction (high left atrial pressure) results in vasodilatation. Is it possible the atrial receptors are involved in this response?

Effect of Acidoses

At this stage we asked ourselves why we had found this reflex when others had not? We thought it possible that the fact that we maintained the acid-base state of the animal within normal limits could be an important factor and two pieces of evidence supported this view. Anesthetized animals subjected to surgical interventions are known to become acidotic and Dr. Norman and I\textsuperscript{58} recently showed that an acidemia could abolish a tachycardia of up to 40 beats/min produced by stimulating sympathetic nerves. It is also known from the work of Bendixen\textsuperscript{59} and others that the chronotropic effects of injected catecholamine are reduced by systemic acidemia.

So we set up our preparation again complete with left atrial balloons and elicited control response of an increase in heart rate.\textsuperscript{50, 61} Then we made the animals acidic by the inhalation of CO\textsubscript{2} or the infusion of hydrochloric acid and repeated the distensions. Finally we brought the blood chemistry back to normal again and again repeated the distensions. The results of experiments in five dogs are shown in fig. 15; it can be seen that the lower the pH, the lower the magnitude of the response. At least one conclusion from these experiments was that we should continue to care about the acid-base state of our animals.

Atrial Appendages

But perhaps finally I can reinforce my enthusiasm for the atria and their function if I tell you of a series of experiments Drs. Kappagoda, Saunders, and I\textsuperscript{62} have just reported. Examination of fig. 3 will remind you first of what the atrial receptors look like. There are unencapsulated endings found only at the vein-atrial junctions and a so-called nerve net observed in the endocardium over the whole atrium. May I emphasize that at least two investigations\textsuperscript{8, 37} have stated emphatically that there are no receptor end-organs in the atrial appendages of dog and man, only an end-net as you see in the lower panel of fig. 3.

So we thought we would try to stimulate the end-net. We made a preparation similar to our previous one. Then a small balloon was inserted into each atrial appendage. One small balloon was also inserted into the upper left pulmonary vein-left atrial junction so that control stimulation of the left atrial receptors could be made. Eighty distensions of the atrial appendages in 13 dogs all caused an increase in heart rate; the average increase was 23 beats/min. This could have been a response from the appendages, or we could have been tugging on the atrio-venous junctions which are not far away. So in five dogs, following control distensions of appendages, a clamp was placed for 10 min across each atrial appendage just below the balloon to destroy the veins coming away from the area of

\[
\text{Figure 15}
\]

The relationship between the pH of arterial blood and the increase in heart rate caused by stimulation of left atrial receptors. Each line is computed from the results in one dog. Note that as the blood becomes more acid the magnitude of the increase in heart rate decreases. N = number; R = correlation coefficient. (From Harry et al.\textsuperscript{61}).
the appendage stimulated by the balloon. The response to subsequent distension of the appendages after the clamp was removed was completely abolished in all five dogs, but the response to distension of the upper left pulmonary vein-atrial junction was unaffected, as illustrated in table 3.

Thus the response we observed from the appendages was reflex in nature and the receptors—only the nerve net is there—were in the atrial appendage.

We have also shown that this reflex has the same nervous pathways as the other reflex responses I have already described. The afferent pathway is in the vagi and the efferent solely in the sympathetic nerves. Also, recently we have reported preliminary experiments which show that another result of stretching the atrial appendages is an increase in urine flow.63

As it was possible that we were stimulating not the "end-net," which in some way was acting as a receptor end-organ, but rather unencapsulated endings which existed in the appendage but which have not previously been recognized, Drs. Saunders, Floyd, and I64 have taken numerous atrial appendages and examined them with the methylene blue technique. Each time we examined an appendage we examined a pulmonary vein-atrial junction by the same method. The results we obtained are shown in fig. 16. It is obvious there are perfectly good unencapsulated receptors in the appendages, and from our calculations, about ten receptors per appendage can be estimated.

Thus the whole of each atria seems to take part in this reflex.

Summary

Stimulation of right and left atrial receptors causes an increase in activity in sympathetic nerves to the sinoatrial node resulting in 1) an increase in heart rate, 2) a decrease in activity in nerves to the

Table 3

The Effect of Crushing the Bases of the Atrial Appendages on the Reflex Increase in Heart Rate from Distension of the Atrial Appendages and the Left Upper Pulmonary Vein-atrial Junction (L.U.P.V.)

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Increase in heart rate before crushing appendage (in beats/min)</th>
<th>Increase in heart rate after crushing appendage (in beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>74</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>76</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>77</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>78</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>79</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

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kidney, with an unknown effect, and 3) a diuresis caused by a blood-borne agent which is said by others to be a reduction in the concentration of antidiuretic hormone.

This exciting finding leaves us with many questions both pure and applied. One may be important to us now. Remembering that these receptors have been vividly demonstrated in the atria of man should we not ask, Are these two small chambers not more important in man than commonly appreciated?

Speculation on Function and Dysfunction

This response of an increase in heart rate from left and right atrial receptors has been observed only in anesthetized dogs and its function in the intact animal or man is unknown. But we may speculate, and it is possible to speculate, that this reflex is one of the mechanisms which regulates the size of the heart within narrow limits—first by its effect on the heart rate and secondly by its effect on the kidney and the volume of the extracellular fluid.

It is known that a simple increase in heart rate in dogs and man, by pacing, over the normal range of heart rate of 70–190 beats/min reduces the cardiac output slightly and thus there is a decrease in both end-diastolic volume and stroke volume; that is, a simple increase in heart rate does not increase the cardiac output, only decreases heart volumes.65

It is suggested33 that this reflex maintains relatively constant heart volumes by increasing the heart rate (and thus decreasing each volume—end diastolic, end systolic, and stroke) in response to an increased inflow. The heart volumes are thus maintained at a relatively constant size during the increased flow of blood through the heart, i.e., when venous return is increased.

It is important to remember that because the time of ventricular systole is relatively constant, the rate of change of pressure up to the peak of the "v" wave of the atrial pressure pulse (at end of ventricular systole) is directly related to the inflow into the atrium, i.e., more inflow over constant time causes an increase in the rate of change of pressure. The atrial receptors discharge mainly during ventricular systole. Thus an increased inflow into the atria, particularly during ventricular systole, causes an increased rate of change of pressure in the atria, which in turn causes an increased discharge from atrial receptors and thus an increased heart rate by this reflex: and this increase in heart rate would then reduce the time of filling of the heart and maintain the end-diastolic volume at a relatively constant level despite the increase in venous return.

A corollary of this speculation is that such a reflex mechanism, combined with the other mechanisms determining stroke volume, i.e., the Starling mechanism and sympathetic nerves to the ventricular muscle, would extend the upper limit of obtainable cardiac output in exercise. Again the almost linear relationship between heart rate and cardiac output which has been observed during exercise suggests the existence of a control mechanism relating heart rate to the increase in venous return. It is at least possible that the reflex I have described here will form the basis of the required control mechanism.

Also it is possible to speculate that this reflex mechanism maintains the heart size within narrow limits not only in face of increased venous return but during an increase in extracellular volume. An increase in extracellular volume results in an increase in mean atrial pressure which in turn also causes a greater discharge from atrial receptors. In the short term this increase in discharge of atrial receptors will cause an increase in heart rate and a decrease to normal heart volumes; in the long term the reflex mechanism involving the kidney may adjust the extracellular fluid volume so that the blood volume becomes less and the heart volumes less.

Therefore it is concluded that it is a reasonable speculation that atrial receptors are the first link in a negative feedback mechanism controlling heart volumes, i.e., if the heart volumes get bigger for whatever reason then the heart rate and urine flow increase and the heart volumes become smaller again.

Is it too fantastic to speculate that these mechanisms may be disarranged in disease? In fact J. P. Henry et al.,67 has shown that the atrial receptors discharge less in dogs with chronic heart failure than in normal dogs even though the atrial pressures are higher in the dogs with heart failure. This effect of less atrial receptor discharge may be causative in relation to the known increase in extracellular liquid in heart failure. But it may be a result of the heart failure. These speculations require investigation and evidence.

I am sure that George E. Brown, looking at all this evidence of a reflex response affecting the heart and kidney only, would not rest until he had found some disease which was explained by a disorder of this reflex mechanism.
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References

1. BEZOLD A VON, HIRT L: Unters Physiol Lab Würzburg 1: 75, 1867
2. JARISCH A, HENZE C: Uber Blutdrucksenkung durch
   chemische Erregung depressorischer Nerven. Arch exp
   Path Pharmak 187: 706, 1937
3. JARISCH A, RICHTER H: Die Kreislaufwirkung des
   Veratrine. Arch exp path Pharmak 193: 347, 1939
4. JARISCH A, ZOTTERMAN Y: Depressor reflexes from the
5. DAWES GS: Receptor areas in the coronary arteries and
   elsewhere as revealed by the use of veratridine. J
   Pharmacol Exp Therap 89: 325, 1947
6. DAWES GS, COMMODE HJH: Chemoreflexes from the heart
   and lungs. Physiol Rev 34: 167, 1954
7. KING AB: Nerve endings in the cardiac muscle of the
8. MILLER MR, KASAHARA M: Studies of nerve endings in the
9. WOOLLARD HH: Innervation of the heart. J Anat
   (London) 60: 345, 1926
10. MITCHELL CAG: Cardiovascular Innervation, ed 1.
11. SLEIGHT P: A cardiovascular depressor reflex from the
    epicardium of the left ventricle in the dog. J Physiol
    (London) 173: 321, 1964
12. COLEGERD JCG, HEMINGWAY A, HOLMES RL, LINDEN
    RJ: The location of atrial receptors in the dog: a
    physiological and histological study. J Physiol
    (London) 136: 174, 1957
13. PAINTAL AS: Cardiovascular Receptors. In Enterorecep-
    tors Handbook of Sensory Physiology, edited by
    BERLIN NE. Basel, Springer-Verlag, 1971
14. COLEGERD HM, COLEGERD JCG, KIDD C: Cardiac
    receptors in the dog with particular reference to two
    types of afferent ending in the ventricular wall. J
    Physiol (London) 174: 323, 1964
15. BROWN AM: Mechanoreceptors in or near the coronary
16. BROWN AM: The depressor reflex arising from the left
    coronary artery of the cat. J Physiol (London) 184:
    825, 1966
17. SLEIGHT P, WIDDICOMB JG: Action potentials in
    fibres from receptors in the epicardium and
    myocardium of the dog's left ventricle. J Physiol
    (London) 181: 235, 1965
18. MUERS MF, SLEIGHT P: The reflex cardiovascular
    depression caused by occlusion of the coronary sinus in
    the dog. J Physiol (London) 221: 259, 1972
19. MUERS MF, SLEIGHT P: Action potentials from
    ventricular mechanoreceptors stimulated by occlusion
    of the coronary sinus in the dog. J Physiol (London)
    221: 283, 1972
20. ÖBERG B, THOREN P: Studies on left ventricular
    receptors, signalling in non-medullated vagal affer-
21. ÖBERG B, THOREN P: Increased activity in left
    ventricular receptors during hemorrhage or occlusion
    of caval veins in the cat—A possible cause of
22. SLEIGHT P, LALL A, MUERS M: Reflex cardiovascular
    effects of epicardial stimulation by acetylstrophanthi-
23. BERGEL DH, MAKIN GS: Central and peripheral
    cardiovascular changes following chemical stimula-
    tion of the surface of the dog's heart. Cardiovasc Res
    1: 80, 1967
24. BARCHOFF H, SWAN HJC: Sympathetic Control of
    Human Blood Vessels. London, E, Arnold, 1953
25. MARK AL, HEISTAD DD, SCHMID PC, ABOUB FM:
    Vascular responses to left ventricular outflow
    obstruction in dogs. Circulation 44 (suppl II): II-76,
    1971
26. HANLEY HC, COSTIN JC, SKINNER NS: Differential
    reflex adjustments in cutaneous and muscle vascular
    beds during experimental coronary artery occlusion.
    Amer J Cardiol 27: 513, 1971
27. KOLATAT T, ASCANO G, TALLARIDA RJ, OPPENHEIMER
    MJ: Action potentials in the sensory vagus at the
c    time of coronary infarction. Amer J Physiol 213: 71,
    1967
28. THOREN P: Left ventricular receptors activated by
    severe asphyxia and by coronary artery occlusion.
    Acta physiol scand 85: 455, 1972
29. ADGEY AAJ, GEDDES JS, MULLHOLLAND HC, KEEGAN
    DAJ, PANTERIDGE JF: Incidence, significance and
    management of early bradycardia complicating acute
30. MALLIANI A, PETERSON DF, BISHOP VS, BROWN AM:
31. FURNIVAL CF, LINDEN RJ, SNOW HM: Chronotropic
    and inotropic effects on the dog heart of stimulating
    the efferent cardiac sympathetic nerves. J Physiol
    (London) 230: 137, 1973
32. FURNIVAL CM, LINDEN RJ, SNOW HM: The inotropic
    and chronotropic effects of catecholamines on the dog
    heart. J Physiol (London) 214: 15, 1971
33. FURNIVAL CM, LINDEN RJ, SNOW HM: Reflex effects
    on the heart of stimulating left atrial receptors. J
    Physiol (London) 218: 447, 1971
34. BERKLEY HJ: The intrinsic nerve supply of the cardiac
    ventricles in certain vertebrates. Johns Hopkins Hosp
    Reports 4: 248, 1895
35. NONIDEZ JF: Identification of the receptor areas in the
    venae cavae and pulmonary veins which initiate reflex
    cardiac acceleration. (Bainbridge's reflex) Amer J
    Anat 61: 203, 1937
36. PAINTAL AJ: A study of right and left atrial receptors. J
    Physiol (London) 120: 596, 1953

Circulation, Volume XLVIII, September 1973
40. Kappagoda CT, Linden RJ, Snow HM: A reflex increase in heart rate from distension of the junction between the superior vena cava and the right atrium. J Physiol (London) 220: 177, 1972
44. Kappagoda CT, Linden RJ, Snow HM: The effect of stretching the superior vena caval-right atrial junction on right atrial receptors in the dog. J Physiol (London) 227: 875, 1972
60. Hairy JD, Kappagoda CT, Linden RJ, Snow HM: The effect of acidosis on the increase in heart rate from stimulation of the left atrial receptors in the dog. J Physiol (London) 209: 34P, 1970
61. Hairy JD, Kappagoda CT, Linden RJ, Snow HM: Depression of the reflex tachycardia from the left atrial receptors by acidosis. J Physiol (London) 218: 465, 1971
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