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Vagal effects of the baroreflex on heart rate

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CHAPTER 2

NERVOUS REGULATION OF BLOOD PRESSURE

INTRODUCTION

This chapter will give a general introduction into a few aspects
of the nervous regulation of blood pressure. By nature of the
complexity of the system and the enormous amount of experimental
data available this presentation must be restricted to a personal
choice of the author. I tried to select those concepts and ideas
for the present chapter that serve as a framework of reference
for the chapters to come.

The nervous blood pressure regulating system is divided into 3
sections:
1. Efferent section: the central nervous system (CNS) regulates
pressure by influencing the resistance to flow in the different
vascular beds and it regulates heart rate and stroke volume.
2. Afferent section: this keeps the CNS informed on the degree
of filling of many parts of the circulation. For the present
study we will confine ourselves mostly to the regulation of
pressure in the systemic circulation. In order to regulate this
effectively the CNS should at least receive momentaneous
information on the pressure in one of the central arteries.
3. Integration centre: this processes the different incoming
signals and changes, if necessary, the flow of efferent signals.

This action is not restricted to afferent signals from pressure sensitive elements in the circulation, it can also be evoked by afferent signals from other organs and by the activity of other nervous centres as well.

The efferent part of the system will only very briefly be dealt with in this chapter. A more complete view has recently been presented in ref.136. In the description of the afferent part emphasis will be on the properties of the baroreceptors, on the one hand because of their key-role as pressure receptors in the systemic circulation, on the other hand because the (electrical) stimulation of those afferents is the object of our study. Next a short survey of pressure sensitive receptors in other parts of the circulation will be presented. Finally the integration centre will be discussed, or more precisely: some aspects of central regulation and modulation of blood pressure. It will be argued that the CNS does not aim at the exact maintenance of a given level of blood pressure. Modulation of blood pressure is but one of the many efferent activities of the CNS and should be considered in connection with other phenomena such as emotions and behaviour. The modulations involved are mainly short-term variations around a long-term mean level that seems to escape the control of the CNS (136).

1. EFFERENT SECTION

Blood pressure, as mean systemic arterial pressure, is determined by the product of cardiac output and peripheral resistance. Cardiac output itself is the product of heart rate and stroke volume. Therefore, the efferent part of the blood pressure regulating system has three levers to operate: heart rate, stroke volume and peripheral resistance.

Heart rate can undergo the fastest changes of these three, due to the action of the vagus nerve. Increased vagal activity will decrease heart rate by postganglionic liberation of acetylcholine (ACh), withdrawal of vagotonus accelerates the heart. This action on heart rate is the most important contribution of the parasympathetic system to the control of the circulation. Heart rate can be changed by the action of the sympathetic system as well. Increased sympathetic activity via the cardiac branches will increase heart rate (by the postganglionic liberation of noradrenaline) and vice versa. The same effect can be obtained by the liberation of adrenaline into the circulation from the medulla of the adrenal glands, which are part of the sympathetic system.

Although changes in sympathetic nerve activity can be observed with latencies of around 200 ms after changes of afferent nervous activity to the CNS (77, 111), the reaction time at the catecholaminergic effectors (for adrenaline or noradrenaline) is such that the first change in the function of the end-organ can only be observed after 2-3 seconds (19, 55). The sympathetic system has its influence not only on heart rate, it changes the inotropic state of the myocardium as well. Stroke volume: Suppose the left ventricle ejects an increased fraction of its end-diastolic volume (possibly at a higher heart

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rate), due to an increased sympathetic tone, peripheral resistance and venous return to the left heart remaining unchanged: within a few beats the end-diastolic size of the heart should have diminished and cardiac output should have decreased to its original value. Changes in stroke volume and/or heart rate will only result in changes in cardiac output if they occur in combination with an increased venous return. Of course, since we have a closed circulation, eventually an increased output should result in an increased venous return. However, this supply may lag behind on the demand, e.g. at the onset of sudden exercise. At rest about 50% of the total blood volume is in the veins of the systemic circulation (30), mobilization of venous reservoirs will increase the supply to the right ventricle. This can be achieved (temporarily) by an increase in venomotor tone, since the smooth muscle in the walls of the veins is under the influence of the sympathetic system. Another 25% of the blood volume in the resting state is found in the pulmonary circulation (30). A decrease in size of the large pulmonary vessels will directly supply the left ventricle with an increased inflow. The 'central blood volume' in lungs and heart chambers can act as a buffer volume which is readily available to support an increased cardiac output for some time, awaiting an increased venous return from the working organs.

This part of the blood pressure control machinery: stroke volume, inotropic state of the myocardium and wall tension of the reservoir vessels is solely under the influence of the sympathetic system. Here I neglect the obligatory changes in cardiac inotropism which accompany changes in heart rate (Bowditch (26) and Kruta (87)), or changes in end-diastolic volume (Frank (45) and Starling (134)).

Peripheral resistance is 'the resistance offered to the total

output of the heart by all of the peripheral vascular bed'
(definition by A.C.Burton, 30). Of the total peripheral
resistance 'seen' by the left ventricle about 40% resides in the
arterioles and 30% in the capillaries (ref. 30). Changes in tone
of the smooth muscles in the walls of the arterioles, in the
pre-capillary sphincters and in the arterio-venous anastomoses
will, therefore, have profound effects on the blood pressure as a
whole, and on local flow as well. This smooth muscle tone,
again, is regulated by the sympathetic system. This regulation
is probably highly differentiated in that, depending on the
circumstances, different vascular beds may be 'switched on or
off' (44, 78, 111). Moreover, the local flow in a tissue is to a
large extent under the influence of local metabolic factors, such
as oxygen consumption and metabolites. This autoregulation is
outside the scope of the present paper.
As to the reaction time for a change in peripheral resistance the
above remarks for the catecholaminergic effectors hold true.

2. AFFERENT SECTION

2.1 Pressure sensitive receptors in the systemic arteries

These receptors are commonly referred to as 'baroreceptors'.
They are mainly found in the wall of the aortic arch at branching
points and in the wall of the carotid sinus, the dilatation at
the root of the internal carotid artery (54). Surprisingly these
are the same areas where the peripheral chemoreceptors are found:
the aortic bodies and (bilaterally) the carotid body.
The baroreceptor afferent fibres join different cranial nerves.
The afferents from the carotid sinus area, together with the
chemoreceptor afferents from that same area, form the carotid
sinus nerve (on the Continent named after the discoverer of its
function in blood pressure control: Hering's nerve (53)) which
joins the glossopharyngeal nerve. The afferents from the aortic
arch can form a separate nerve (left and right) which joins the
vagus nerve only high up in the neck, at the branching point of
the superior laryngeal nerve. This is the situation in the
rabbit, where this nerve is known as N.depressor nervi vagi,
shortly depressor nerve, or nerve of De Cyon and Ludwig, who in
1866 gave a description of the anatomy of this nerve and the
reflex effects of its stimulation in the rabbit (34). They
thought of the nerve as being proprioceptive for the heart
muscle, although in their preparation they lost track of the
nerve fibres in the connective tissue between the roots of the
aorta and the pulmonary trunk. The true function of the nerve
was only established in 1903 by Köster and Tschermak (84). In
1883 Wooldridge (142) had stimulated afferent fibres originating
in the aortic arch, resulting in depressor responses. He spoke
of the 'aortic nerve', a name which is still widely in use for

the rabbit's (and cat's) depressor nerve as well. I will use the name 'depressor nerve' in this thesis.

In humans, as in most mammals, we do not find a separate depressor nerve, most of the aortic arch afferents joining the vagus nerve already inside the thorax (105). Figure 1 schematically depicts the human anatomy.
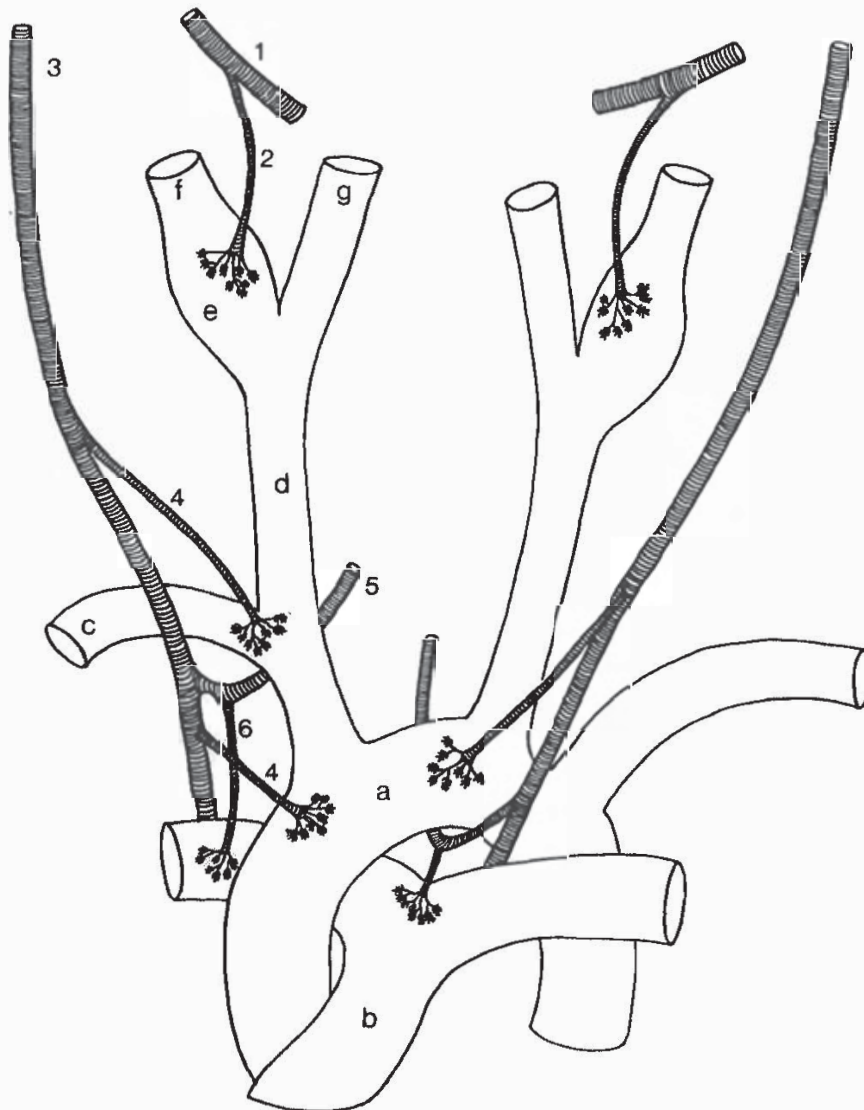

Figure 2.1
Anatomy of the most important vessels having baroreceptors (frontal view).
a: aortic arch, b: pulmonary trunk, c: subclavian artery, d: common carotid artery, e: carotid sinus, f: internal carotid artery, g: external carotid artery.
1: glossopharyngeal nerve, 2: carotid sinus nerve, 3: vagus nerve, 4: cardiac vagal rami, containing afferents from the aortic arch and its branches,
5: recurrent laryngeal nerve, 6: cardiac vagal ramus, containing afferents from the pulmonary trunk and its branches.
(For the sake of clarity numbers and letters have only been placed on the anatomical right hand side).

The pressure sensors are found at the transition of vessel wall media to adventitia (3, 39). The vessels involved are predominantly of the elastic type, but between the elastic lamellae of the media smooth muscle cells are found. The sensors are located in the muscle layers. They are deformation receptors; the adequate stimulus is stretch of the vessel wall. The tight coupling of sensors and muscle layer might constitute a mechanism to adapt the sensitivity of the sensors via regulation of the smooth muscle tone (81, 124). The afferent nerve fibre loses its myelin sheet near to or in the vessel wall, whereafter it profusely ramifies. At the nerve-endings small end-plates are found which show the same onion-like layered structure under the electron microscope as the Pacinian corpuscles. In the case of the baroreceptors, however, the total size does not exceed $5\,\mu$m (39). Impulse activity in a baroreceptor afferent fibre must be caused by deformation of one or more of its sensors. No data are available on static or dynamic behaviour of a separate sensor. Measurements have been performed using single fibre preparations of afferents at different pressure levels inside the vessel.

Figure 2.A schematically shows how impulse frequency varies with the static pressure in the vessel: as long as the pressure stays below a threshold the fibre remains silent. Impulse activity jumps to its threshold frequency as pressure rises just above threshold. As pressure rises further the firing rate increases, until a saturation level is reached. The landmarks in fig.2.A differ among different afferent nerve fibres. Therefore, if we study the compound activity of a nerve bundle (cf. fig.2.B), we will first observe an increase of the number of active fibres as pressure rises, because their respective thresholds are crossed (recruitment). In the range where all fibres are active a rise
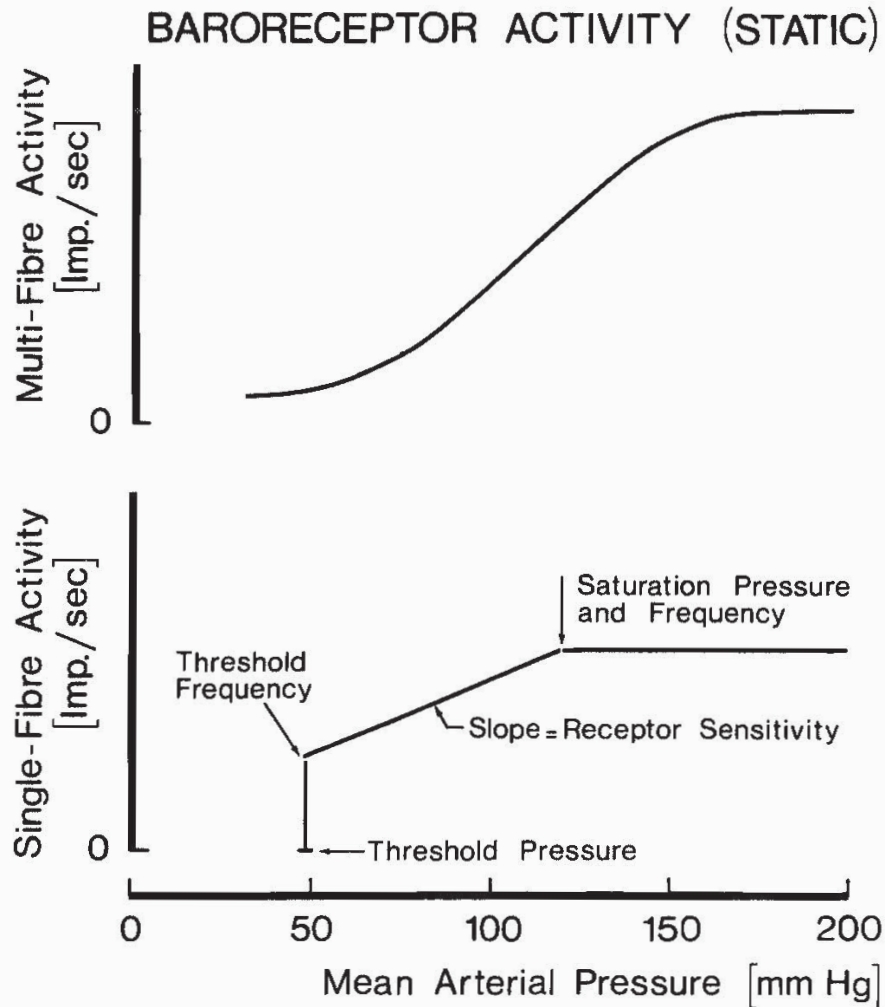
BARORECEPTOR ACTIVITY (STATIC)

Figure 2.2
Impulse activity of the baroreceptors at static pressure loading.
A.(lower panel): single-fibre activity expressed as impulses per unit of time.
B.(upper panel): multi-fibre activity.

in pressure induces a proportional increase in firing rate, until pressure levels are reached where more and more fibres successively reach their saturation level. The resulting curve is S-shaped, as is shown in fig.2.B.

It has been emphasized that this description holds for static, non-varying pressures. In the physiological situation at each heart beat a pressure variation is applied to the sensors, superimposed upon a relatively constant level of blood pressure.
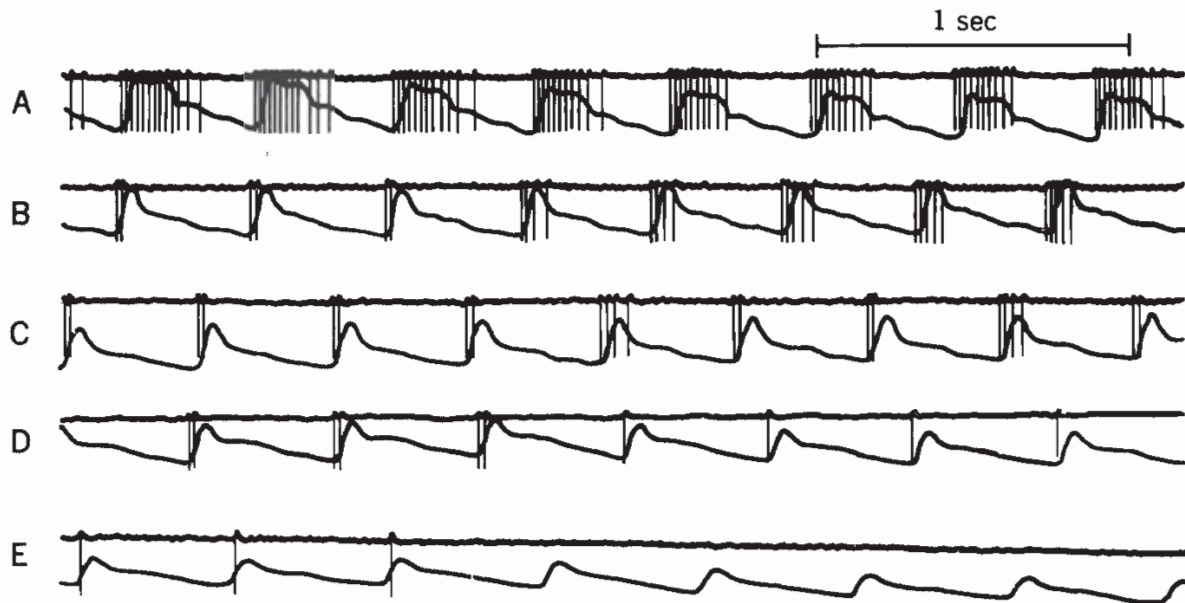
Figure 2.3
Single-fibre activity in a baroreceptor afferent from the aortic arch and blood pressure tracing from the left common carotid artery.
Mean blood pressures: A: 125, B: 80, C: 62, D: 55 and E: 42 mm Hg. From: E.Neil (108).

Figure 3 shows the variations in the firing rate of an aortic baroreceptor afferent fibre during the heart cycle and with changes of mean pressure. Obviously the activity does not simply follow the curve depicted in fig.2: the receptor shows a (non-linear) rate-sensitivity as well. Increasing pressure forces the firing rate to extremely high levels (cf. 90), decreasing pressure suppresses the firing (cf. the work of Franz (46) and Stegemann and Tibes (135), presented at a 1967 symposium on 'Rein control, or unidirectional rate sensitivity, a fundamental dynamic and organizing function in biology'). These two effects together will cause a shift of the static relation between blood pressure and firing rate when a pulsating pressure is applied. Figure 4 depicts this change of the curve. An important point to note is that now the maximal sensitivity for a change in pressure is found at a lower pressure level in comparison to the static case.
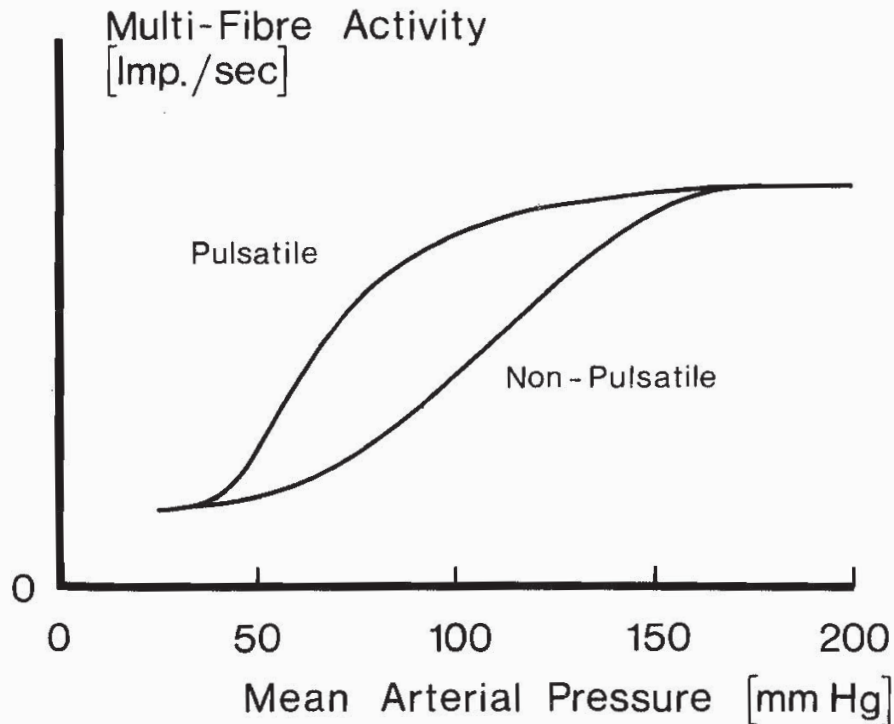
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Figure 2.4
Multi-fibre baroreceptor nerve activity at pulsatile and non-pulsatile pressures.

This phenomenon is not completely explained by the properties of the sensors at varying pressures; one should also consider the visco-elastic properties of the vessel wall in which they are embedded (46, 91). This is illustrated most clearly when the blood pressure-firing rate relationship is tested during an experimentally induced hypertension. The curves of fig.4 are then shifted to the right, i.e. a given firing rate now occurs at higher pressures (McCubbin, 104, and Kezdi, 76). The receptors have adapted to the higher pressure and in the end blood pressure regulation has become possible, again, by increase or decrease of impulse frequency. This is referred to as 'resetting' of the baroreceptors. According to Krieger (86) this resetting will take place within a few hours after the induction of a change in pressure.
It will be clear from these data that the baroreceptors are

unable to protect us from a hypertension that, for instance, is caused by a renal function disturbance. On the contrary, once blood pressure is raised, the baroreflex will counteract a rapid normalization.

After this enumeration of baroreceptor properties it is time we turn to an investigation of the function of these receptors in blood pressure control. Physiology has two classical methods to tackle this problem: (electrical) stimulation of the afferents, or de-afferentation by transection of the nerves. Both methods have been applied to the baroreceptor afferents.
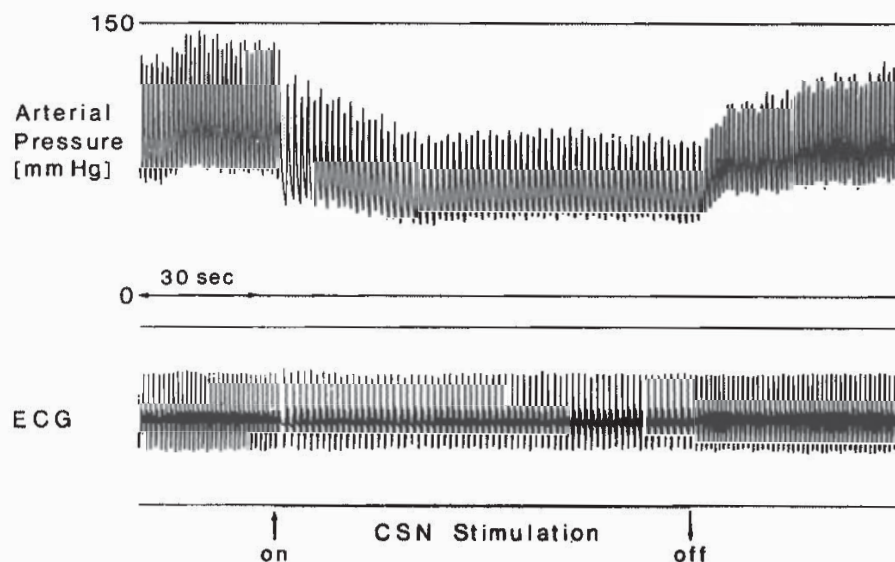

Figure 2.5
Fall of blood pressure and heart rate evoked by electrical stimulation of the carotid sinus nerves (CSN) in man. This patient has implanted electrodes for the alleviation of angina pectoris. Stimulation lasted 90 seconds, frequency was 80 Hz and impulse duration 0.35 ms.

Bilateral electrical stimulation of the carotid sinus nerves has been applied in man (see chapter 1). Figure 5 shows the effect of a 90 seconds' stimulation (at 80 Hz) on heart rate and blood pressure in a patient with coronary heart disease. The mean blood pressure drops considerably, as does the heart rate. The effect on heart rate is most pronounced just after the onset of the stimulation (45% decrease), gradually changing to a 24%

decrease. The time course of this response already suggests that the heart rate changes are chiefly caused by an increased vagal tone and that the lowering of blood pressure originates from a decreased sympathetic tone (cf. 19).

At present the implantation of carotid sinus nerve stimulators is out of use: in hypertension the therapeutically favourable effect on blood pressure obtained by continuous stimulation only lasted a few months, after which the effectiveness gradually declined. For angina pectoris, even if it is caused by multiple stops in the coronary arteries, the bypass operation is nowadays preferred.

Baroreceptor denervation has been performed as well, mainly in animal experiments and a few times in man, for example in an attempt to treat syncope caused by a hypersensitive carotid sinus reflex. In the animal experiments at this moment there is a controversy as to the effect of denervation on the level of mean blood pressure. All research workers agree that blood pressure becomes extremely labile after the denervation procedure. Cowley and collaborators (33) demonstrated an increase in standard deviation around the daily mean level by a factor of 2 as compared to control dogs. The extreme values changed from 80 to 125 mm Hg in control animals to 50-140 mm Hg in denervated animals. However, in their study the mean level of pressure was not altered, neither was the cardiac output or total peripheral resistance. More recently Ito and Scher (63) argued that a really complete aortic denervation in the dog (in their surgery they took extreme measures to make it as complete as possible) will result in a slight (16.7 mm Hg) elevation of the mean level of blood pressure, even with the carotid sinus nerves intact. In a previous study the same authors had shown (62) that transection of the carotid sinus nerves will neither significantly alter the

regulation of blood pressure, nor give rise to an increase in mean blood pressure. In a recent workshop on 'Baroreceptors and Hypertension' (129) the dispute between the most important research groups involved concerning the question whether complete baroreceptor de-afferentation does result in hypertension did not reach a final solution.

In the interpretation of Ito and Scher's experiments it should be noted that in their extensive thorax surgery they cut more than just the aortic baroreceptor afferents. Finally, even if Ito and Scher's interpretation of the data is correct, it is still highly improbable that the long-term regulation of the mean level of blood pressure is governed by the baroreceptor afferents. Their most important function is the instantaneous regulation of pressure.

The general validity of this concept, however, is challenged by a few, though important, communications concerning carotid sinus denervation in man: this could cause a serious, lasting hypertension (16, 128).

2.2 Other pressure receptors in the circulation

The position of the baroreceptors in the places described above seems, at first sight, rather accidental. If we follow the embryonic development, however, the vessels where we find the baroreceptors turn out to be derivations of the branchial arteries. The carotid sinuses are the remnants of the third branchial arteries. The aortic arch and brachiocephalic artery arise from the left and right fourth branchial arteries, respectively. Branchial arteries nos.1, 2 and 5 disappear, no.6 becomes the pulmonary trunk. Muratori (106) has drawn attention to the special wall structure of the derivations of the branchial arteries. They exhibit a transition from the mainly elastic structure of the large (Windkessel) vessels to the muscular structure of the smaller-sized vessels. Right there we find the baroreceptors. Therefore, it is plausible to presume that baroreceptors can be found in the pulmonary arteries as well, as indeed they are (31). The afferents travel in the nerve of the sixth branchial artery: the recurrent laryngeal nerve, a branch of the vagus nerve (see fig.1). However, the physiological response to stimulation of these receptors is obscure: both a decrease of blood pressure in the systemic circulation (32) and an increase (92) have been described.
Bevan (12) argues that the most important effect of stimulation of these receptors is not their influence on blood pressure, but on respiration. Increased pressure in the pulmonary trunk and its main branches would result in a decreased ventilation and a dilatation of the venous reservoir of the systemic circulation. Both these mechanisms decrease the venous return to the right atrium and could, thereby, result in a pressure decrease in the pulmonary trunk.

We made just one step beyond the 'classical' baroreceptors and already the picture of function and meaning of the pressure receptors gets blurred, and even more so, when we start looking for pressure receptors in the heart itself.

More than a hundred years ago Von Bezold and Hirt demonstrated the existence of cardiac receptors by the application of veratrum alkaloids (14). Still, the importance of these receptors in the regulation of the circulation is not established: are they part of an important regulatory mechanism, or just a physiological curiosity? In a recent article by Donald and Shepherd (36) on the receptors in heart and lungs a survey is presented of the research into the adequate stimulus, receptor properties, afferent pathway and possible reflex effects. Since the time of Von Bezold, everywhere in the heart and its large vessels receptors (possibly free nerve endings) have been demonstrated that react to wall-stretch and/or pharmacological agents. In most cases the mean firing rate (1-20 Hz) is much lower than in the arterial baroreceptors. The afferents may be thin, myelinated or unmyelinated fibres, that find their path to the CNS via cardiac vagal or sympathetic branches. Probably the sympathetic afferents are responsible for the pain sensations in angina pectoris. The functional importance for heart and circulation is still subject to speculation.

More is known about the vagal afferents and especially those from the atria (for a review, see Paintal, 115). Two types of atrial stretch receptors have been described, both having myelinated afferents, traversing the vagus nerve. Type A was supposed to be coupled in series with the atrial muscle fibres since they fire during atrial contraction, and type B was thought to be in parallel with the muscle fibres, since they are activated by atrial stretch, as observed during the v-wave of the venous

pulse. More recently this distinction was challenged, when Arndt and coworkers (7) showed that one receptor can exhibit both type A- and type B-responses. Be that as it may, there is sufficient evidence to prove that Gauer and Henry's concept (47) is correct about the influence of atrial receptors on the renal function. Stretch of the atrial wall (in the physiological range) increases diuresis. Both ADH and a thus far unidentified hormone are supposed to be involved. Via this mechanism atrial pressure can play a role in the regulation of the total fluid volume of the circulation. Although this hypothesis is still controversial (for a review, see 49), this reflex could constitute a key-stone in the long term regulation of blood pressure.

In contrast to the atrial receptors, ventricular receptors only show activity under extreme (laboratory ?) circumstances. Activation of unmyelinated parasympathetic afferents in most cases results in a decrease of sympathetic tone and an increase of vagal tone, as already discussed in the classic baroreflex. However: despite the presence of many cardiac receptors, denervation of the heart, as in transplantation, does not lead to a disturbance of blood pressure regulation. The consequences of the absence of efferent innervation in those cases are obvious, e.g. the adaptation to physical exercise is markedly slowed. Finally, receptors have been located not only in the heart and its outflow vessels, but in the inflow vessels as well. Together with atrial- and lung vessel receptors these are referred to as 'low-pressure receptors'. The functional importance of the low-pressure receptors lies in their ability to react to small changes in blood volume, that are not perceived by the arterial baroreceptors. Reflex effects of stimulation of venous receptors should be directed towards the total circulating fluid volume, possibly through changes in renin secretion (52).

3. INTEGRATION CENTRE

In the classical systems analysis this is the black box, which receives as its input the pressure receptor afferents and has output channels to heart rate, stroke volume and peripheral resistance. Here we find the 'deus' of the circulation, who knows which pressure level is desired for the body under different circumstances. Possibly an influence from 'higher centres' on the setting of the deus's reference level is allowed, to accommodate the obvious changes observed during physical exercise, emotional stress, etc. In the classical view we just have to pin-point here the blood pressure regulating centre in the CNS in order to complete our systems description. However, such a blood pressure regulating centre is non-existent. Of course, in specific areas of the medulla oblongata nuclei have been found where pressor effects (increases in blood pressure and heart rate) could be elicited by stimulation, and other areas that result in depressor effects. But those areas are not sharply distinct from one another, there are no well-defined nuclei that can be labelled pressor or depressor. Moreover, evoked pressor effects are combined with other signs of sympathetic excitation, such as pupil dilatation, and changes in bladder tone and spleen size. Mutatis mutandis the same pattern is found for so-called depressor effects. Finally, pressor- and depressor effects are not only elicited from the medulla oblongata, but from many levels of the brain stem.
Notably S.M.Hilton (56, 57) has pointed out two longitudinally organized systems in the brain stem, up to the level of the hypothalamus. One of those two is involved in the so-called defence reaction, where a pattern of sympathetic stimulation is elicited as in generalized alarm conditions: mobilization of

(venous) reservoirs, increases in blood pressure and heart rate, redistribution of the increased cardiac output towards the muscles in particular. This redistribution is reached by a differentiated change in vasoconstrictor tone: increase in some areas, decrease in other areas, among which the skeletal muscles. A parallel system of sympathetic cholinergic vasodilating nerve fibres is supposed to be activated at the same time. These fibres would course from hypothalamic and mesencephalic centres, without relay in the medulla oblongata, direct to the muscle vasculature. Uvnäs in 1971 (140) reviewing the experimental evidence concerning the subject concluded that this active cholinergic vasodilation in muscles probably does not occur in primates. In a more recent review Öberg (114) goes even further in a complete denial of the existence of such a system.

The brain stem's defence system is supposed to dominate, in a more or less differentiated fashion, during many activities. The second longitudinally organized system on the other hand induces rest and depressor effects. This brings us back on a familiar track, because one obvious way to activate this depressor system is stimulation of baroreceptor afferents as described above. The baroreceptor afferents, both from the carotid sinus and the aortic arch have their first synapse in the nucleus tractus solitarii (NTS) in the floor of the fourth ventricle. After this synapse the central 'wiring diagram' becomes very obscure. The eventual result is an inhibition of central sympathetic tone and an increase of activity in the efferent cardiac vagal branches, which have their motor neurones in the nucleus ambiguus. Iriuchijima (60) very elegantly showed the intricacies of this reflex by stimulating the carotid sinus nerve and recording from efferent cardiac vagal fibres. An action potential in the vagal branches was recorded 60 ms after one electrical stimulus applied

to the carotid sinus nerve. Taking the conduction velocities of
the nerves into account this implies a central processing time of
about 50 ms, extremely long for a 'simple' reflex. The
complexity of the reflex comes to light if we repeat the test
several times: the latency may vary from 60 to 120 ms. The
result is even more complex if we simultaneously stimulate the
carotid sinus nerve and an aspecific nerve, such as the brachial
nerve, sciatic nerve or saphenous nerve (skin-afferents): the
reflex response in the vagus nerve disappears. We may conclude
that even the most simple cardiovascular reflex shows a large
extent of central integration.

These experiments were carried out while the experimental animal
(dog) was under anesthesia. We may presume, therefore, that most
central neuronal interactions have been modified by the
anesthetic and by afferents that were stimulated by the induced
tissue trauma. Among others, Kirchheim in a recent review (78)
stresses the importance of carrying out studies on central blood
pressure regulating mechanisms in chronic experiments, in animals
fully recovered after implantation- or other operations and
accustomed to the experimental conditions. A good example of
such experiments is the study by Nathan and Reis (107). In cats
they induced small, well-localized bilateral lesions in the NTS.
This procedure disrupts the baroreceptor afferents and by
consequence we may expect the same kind of unstable blood
pressure as was found in the de-afferentation experiments in dogs
described above (Cowley et al., 33). Cats with NTS-lesions did,
indeed, develop this labile blood pressure, but there were
differences in comparison with the de-afferentation experiments
as well. Mean pressure was definitely increased, especially
during the day-time (on the average 34 mm Hg), when many external
stimuli influenced the animals. During the night the pressure

was, on the average, only slightly higher than in control animals (19 mm Hg) and the variability was not much increased. The authors conclude that on the one hand the NTS-lesion interrupts the baroreceptor afferent information, on the other hand it unmasks the increase of central sympathetic tone that accompanies many forms of spontaneous activity. This sympathetic stimulation is now retraced in the blood pressure of NTS-lesioned animals. A striking example of such activity, where an increase in sympathetic tone is not self-evident is the grooming behaviour of the cat: in the NTS-lesioned animal mean blood pressure rose from about 80 to 130 mm Hg during grooming.

In this short and incomplete description of the nervous regulation of blood pressure I tried to make clear that we are not dealing with a simple control-loop, perhaps somewhat modulated by supramedullary structures. This is underlined by some of our own observations during electrical stimulation of baroreceptor afferent nerves using implanted electrodes, both in humans and in rabbits. We were struck by the fact that not only did the stimulation lower blood pressure and heart rate, but it made patients and experimental animals very quiet, sometimes even doze off.