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ACTIVITY OF CARDIAC RECEPTORS DURING EXPERIMENTAL REDUCTIONS IN CORONARY FLOW

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If the primary goal of this Symposium was to convince us that both psychological and neural factors can be importantly involved in cardiovascular diseases, we must agree that the goal has already been achieved. However we also have to recognize that most of these new data still constitute a sort of completely disarticulated knowledge. Indeed no one would doubt that psychic and neural events take place in the same central nervous system: however we can only speculate on whether and how these events may be linked together.

For instance, reductions in coronary flow are known to produce pain [1-3] and nervous reflexes [4, 5]: both types of phenomena being initiated from the heart. We decided therefore to study the activity of different types of cardiac receptors during experimental interruption of left coronary flow in order to see whether they responded homogeneously to this event or whether different patterns of responses might suggest some peculiar role in producing pain and reflexes.

In the laboratory it is possible to perfuse with an extra-corporeal pump the left coronary artery of the cat [6, 7]. If the left coronary flow is stopped, myocardial ischemia follows within 10 sec [6]. After a longer latency (20-40 sec) signs of cardiac failure also become apparent, i.e. systemic blood pressure starts to fall, while atrial and ventricular end-diastolic pressures begin to rise [7].

We shall start by analyzing the behavior of the classical atrial and ventricular cardiac receptors which are those connected to afferent vagal fibers [8]. In Fig. 1a one can see the spontaneous activity of a right atrial receptor. Three minutes after cessation of left coronary inflow (Fig. 1b) a clear increase in discharge of the fiber was present. At that time, arterial pressure was 0 mm Hg, the heart was markedly dilated while its electrical activity was barely discernible. After the pump was turned on, the pattern of discharge of the receptor and all hemodynamic variables returned to normal in about 30 minutes.

Receptors located in each of the cardiac chambers were excited by interruption of left coronary flow, but only when the heart was already failing [9]. This seemed to suggest that the stimulus to these receptors might be more mechanical, due to enlargement of the failing heart, than chemical, due to ischemia. In fact it was constantly found that when the heart was markedly dilated and the receptor discharge highly excited, it was possible to produce an immediate reduction of

such a discharge by emptying the heart manually. In order to distinguish further between possible mechanical or chemical stimuli, we studied the effects of acute, severe hemorrhage on the activity of these receptors. It is known that acute hemorrhage is associated with a marked reduction in coronary flow [10]; however since cardiac filling pressures are reduced [11, 12] and myocardial contractility is sufficiently preserved [13], the heart should not be dilated. If these receptors were similar to chemoreceptors they should be excited by hemorrhage (although the simultaneous reduction in cardiac load makes impredictable the real degree of ischemia).

After an acute hemorrhage of 60 ml of blood (Fig. 1c) the discharge of the atrial receptor was clearly reduced, as already reported by others [14]. The discharge was increased again (Fig. 1d) when blood was reinjected. Therefore these cardiac

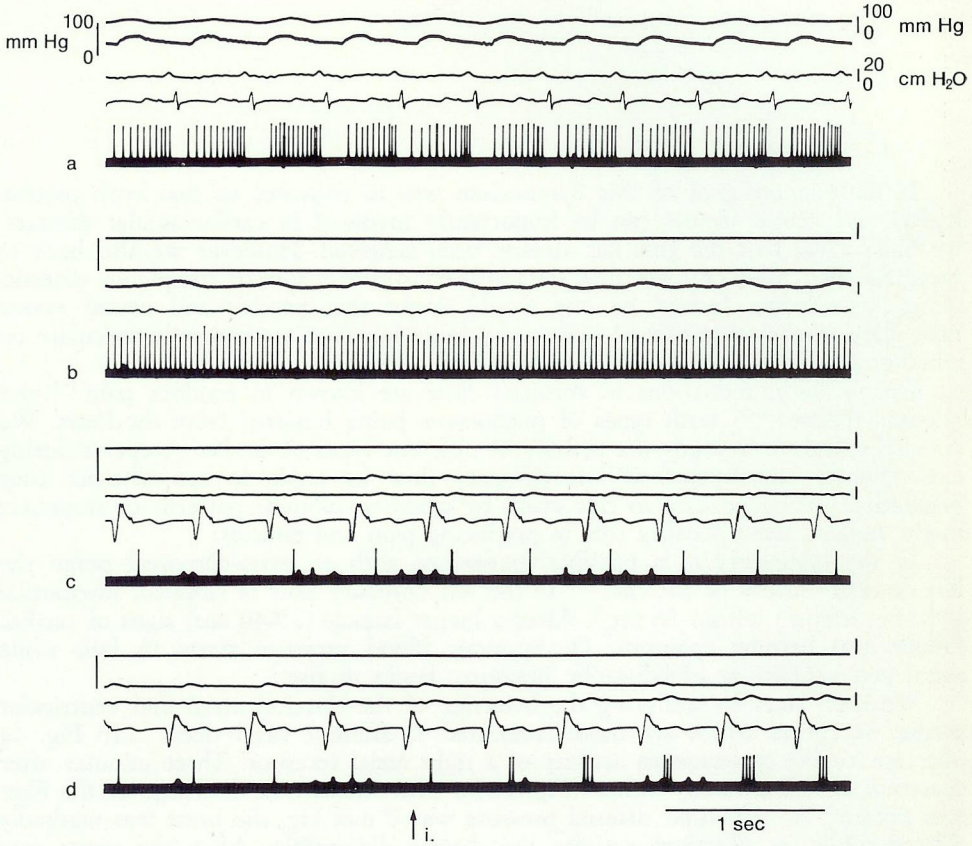

Fig. 1 - Effects of myocardial ischemia (*b*) and hemorrhage (*c* and *d*) on a right atrial vagal receptor. In each panel the traces from top to bottom are: coronary arterial inflow pressure (mm Hg), femoral arterial pressure (mm Hg), right atrial pressure (cm H_2O), E.C.G. and electroneurogram. *a* = control. The fiber discharges during atrial filling and atrial contraction. *b* = begins 180 sec after coronary pump had been stopped. A full recovery of the background neural discharge and of the initial conditions of the cat was then obtained in about 30 minutes. *c* = at this time a bleeding of 60 ml had just been finished (the bleeding had been performed in 6 min). d = re-injection of blood (started at the arrow). During *c* and *d*, coronary pressure was not measured, since the coronary cannula had been withdrawn and the pump used for bleeding the animal. (From Recordati, Schwartz, Pagani, & Malliani [9], by courtesy of Experientia).

vagal receptors behave like pure mechanoreceptors. It is likely that they may be involved in those depressor reflexes which accompany dilatations of cardiac chambers [15-17]. As far as transmission of cardiac pain [1, 2] is concerned, it is well known that afferent vagal fibers only play a minor role, if any, in this fuction.

During the last two years we have found evidence of a new type of atrial and ventricular cardiac receptors characterized by the fact that their fibers run in the sympathetic nerves [18]. They can be functionally and mechanically localized to a definite cardiac chamber: they are also tonically active and extremely sensitive to pressure changes. Fig. 2a shows the spontaneous activity of a sympathetic sensory fiber with a receptive field in the right ventricle. It should be noticed that this spontaneous firing: 1) was constantly in phase with an identifiable part of the cardiac cycle and 2) consisted in no more than one action potential per cycle; however, not all of the cycles were accompanied by a nervous impulse. The spon-

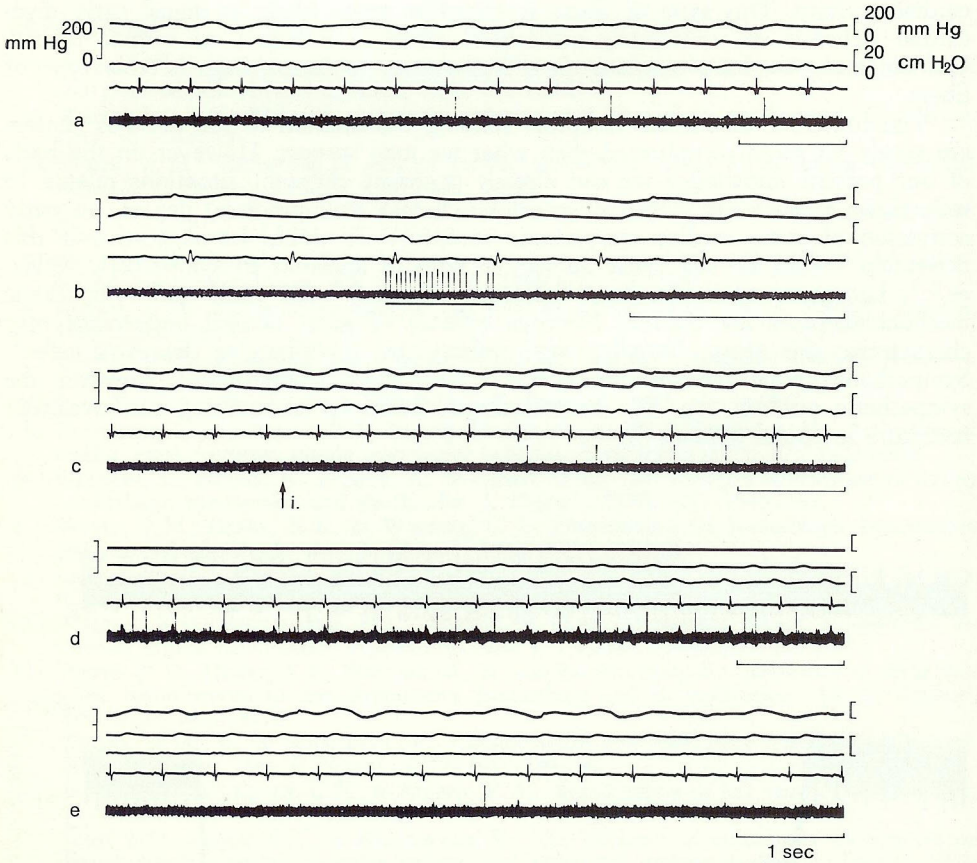

Fig. 2 - Effects of myocardial ischemia (*d*) and hemorrhage (*e*) on the discharge of a sympathetic sensory fiber with a receptive field on the right ventricle (*b*). *a* = control. The fiber discharges during ventricular contraction. *b* = probing of a small area of the right ventricle. *c* = intravenous injection of 2 ml of warm saline. *d* = begins 50 sec after coronary pump had been stopped. A full recovery of the background neural discharge was then obtained in 4 minutes. *e* = at this time a bleeding of 40 ml had just been finished (the bleeding had been performed in 3 min). Traces as in figure 1.

taneous activity of all of these receptors had these same characters. In Fig. 2b the mechanical identification of the receptive field is shown; this maneuver was repeated on the opened heart at the end of the experiment. An injection of 2 ml of warm saline (Fig. 2c) clearly excited the receptor. When the coronary pump was stopped the discharge of the fiber was also increased (Fig. 2d) but only after 50 seconds, at a time when the heart was already failing. This observation was repeated on all of the receptors, atrial and ventricular, studied with the coronary perfusion circuit. During acute hemorrhage (Fig. 2e) the activity of these receptors was markedly decreased. In conclusion, these receptors showed patterns of responses very similar to those of cardiac vagal receptors. These receptors, therefore, do not seem to offer the ideal characters for signalling an early myocardial ischemia, unless accompanied by some degree of mechanical distortion of the cardiac tissues. The reflex effects of the selective stimulation of these receptors is under study.

In the sympathetic nerves we also found [7] afferent fibers which responded with a shorter latency to the interruptions of coronary flow (Fig. 3). These fibers were usually either spontaneously silent or they did not discharge in phase with cardiac activity. This type of fibers is therefore more likely to signal early myocardial ischemia or some early mechanical effect of ischemia on cardiac tissues. Unfortunately we have no data on the responses to hemorrhage of this type of fibers.

The functions of cardiac receptors sending information to the nervous centers are surely far more complicated than what we may suspect. However on the basis of our present knowledge we can already postulate different situations related to reductions in coronary flow. Myocardial ischemia may produce, per se, an early activation of some cardiac sympathetic receptors. It would be suggestive if this activation would already cause subjective pain in addition to sympathetic reflexes [5, 7]. Later on, when the heart becomes enlarged, both vagal and sympathetic mechanoreceptors are excited. Nervous reflexes of great clinical importance may characterize this stage. Usually vagal reflexes are described as depressor ones [4]. Sympathetic spinal reflexes are viceversa very often excitatory [5, 7]; however the sympathetic outflow can also be reflexly inhibited by stimulating cardiovascular receptors in spinal animals [19].

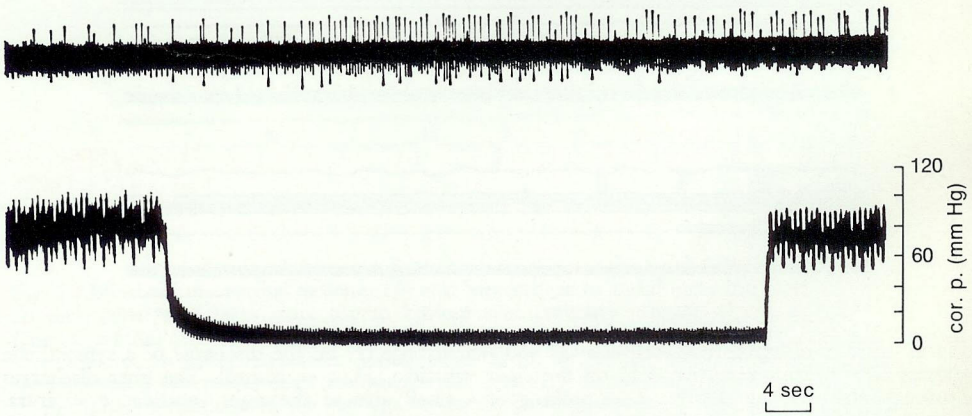

Fig. 3 - Effect of myocardial ischemia on the discharge of a sympathetic sensory fiber isolated from the left inferior cardiac nerve. Upper trace: neural recording; lower trace: coronary artery pressure. (From Brown, & Malliani [7], by courtesy of Journal of Physiology).

It is likely that many independent afferent neural channels are activated by myocardial ischemia and/or by its mechanical effects on the heart. How many of these channels only subserve neural events, such as reflexes, and how many play a role in conscious sensations, such as pain? Moreover, can a neural input which does not reach the consciousness modify the emotional background? In this sense, more than ten years ago [20], we demonstrated that the stimulation of carotid chemoreceptors can produce fits of sham rage in decorticate cats. This was an example of a pure visceral stimulus which was able to affect hypothalamic activity which is still considered a « carrefour » of somatic, emotional and visceral activities. Let's then conclude this report by asking this question: is it possible that a patient may modify his psychological behavior as a consequence of an altered nervous activity from cardiovascular receptors, which does not reach the level of the consciousness?

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