Activation of Cardiac Vagal Receptors During Myocardial Ischemia[1]

The effect of myocardial ischemia produced by experimental coronary occlusion on the discharge of cardiac vagal receptor fibers is unknown. However, it has been reported[2] that destruction of ventricular muscle by hexachlorotetrafluorobutane excites some vagal ventricular receptors. It has also been suggested that excitation of afferent cardiac vagal fibers may be responsible for depressor reflexes associated with myocardial ischemia in humans[3] and experimental animals[4,5]. Therefore, we performed experiments to determine 1. if cardiac vagal receptors were excited during myocardial ischemia, and 2. whether the stimulus responsible for excitation of these receptors was mechanical or chemical.

26 experiments were performed on cats anaesthetized by i.p. injection of pentobarbital sodium (35 mg/kg). The animals were paralyzed with gallamine triethiodide and artificially ventilated. Polyethylene catheters were inserted into: 1. a femoral artery, 2. the left atrium through the atrial appendage, 3. the right atrium through the external jugular vein, and 4. a femoral vein. Threads were passed loosely around the main left coronary artery, thoracic aorta, pulmonary artery and veins, and inferior vena cava. The ends of the threads were pulled through rigid polyethylene tubes whenever the vessels had to be occluded. The main left coronary artery was perfused with a pump in 19 experiments[6,7]. Pressures in the inflow coronary arterial line, femoral artery, and both atria were registered with Statham strain gauges (P23 Dc and De). These variables, together with ECG (lead 1), heart rate, and respiratory movements were recorded on a multichannel ink-writer polygraph (Grass P7).

Afferent nervous activity was recorded from filaments isolated under a dissecting microscope from the right

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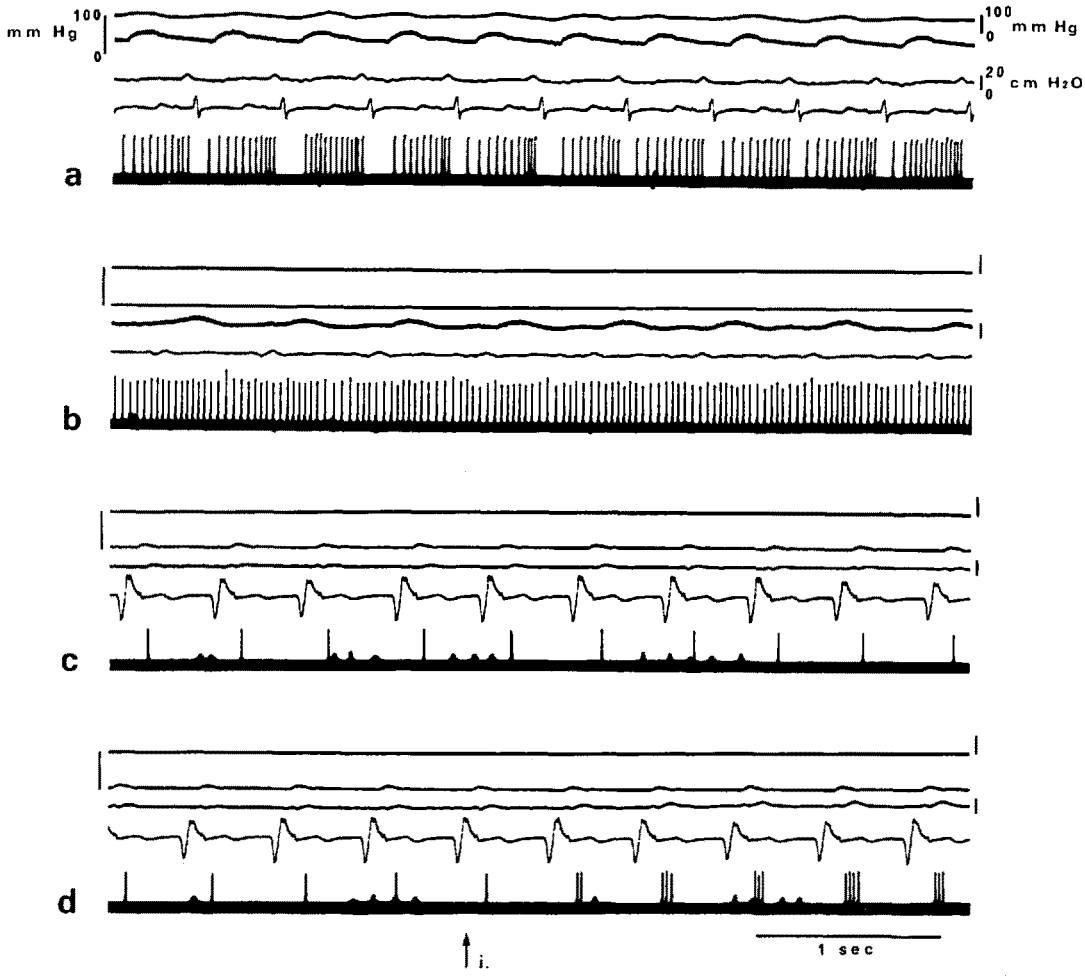

Effects of myocardial ischemia (b) and hemorrhage (c and d) on a right atrial receptor. In each panel the traces from top to bottom are: coronary arterial inflow pressure (mm Hg), femoral arterial pressure (mm Hg), right atrial pressure (cm H_2O), E.C.G., and electroneurogram. a, control. The fiber discharges 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 min. c, at this time a bleeding of 60 ml had just been finished (the bleeding had been performed in 6 min). d, reinjection 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.

cervical vagus. Platinum electrodes were connected to AC preamplifiers (Grass Model P511) with a band width of 10 c/s to 10 Kc/s. Nervous activity and all variables recorded on the polygraph were fed into a tape recorder (Hewlett-Packard 3900). Five of these variables could also be photographed from a slave cathode-ray tube arranged in parallel with a Tektronix 565 oscilloscope.

We isolated 31 afferent cardiac vagal fibers which were excited during ischemia produced either by stopping the coronary inflow pump or by transient occlusion of the main left coronary artery using a snare (Table). The receptors were identified as atrial or ventricular according to their pattern of discharge[8,9]. They were judged to be either in the left or right heart by their response to separate occlusions of pulmonary artery and aorta. They were further localized by direct probing of the cardiac chamber in which they were thought to be located. As shown in the Table receptors from each cardiac chamber were activated during ischemia (69 trials, 31 fibers, 100% success rate).

The discharge of a right atrial receptor is shown in Figure a. 3 min after cessation of left coronary inflow, the arterial pressure fell to 0 mm Hg, the heart was markedly dilated and contracting weakly, while its electrical activity was barely discernible (Figure b). A clear increase in disharge of the receptor was then present. If at this time the heart was manually emptied by cardiac massage, a temporary reduction or cessation in discharge occurred. After the pump was turned on, the pattern of discharge returned to normal in about 30 min.

When the coronary pump was stopped, the mean latency for excitation of all fibers was about 42 sec. At this time, aortic pressure had begun to fall, atrial pressures were rising, and the heart was failing. The stimulus to these receptors might therefore have been mechanical due to enlargement of the failing heart, or chemical due to ischemia. The reduction in discharge produced by emptying the heart manually indicated that the stimulus to these receptors was mainly mechanical although a chemical component due to ischemia could not be ruled out.

To distinguish further amongst these possibilities, we attempted to produce myocardial ischemia by acute, severe hemorrhage since this event is associated with a marked reduction in coronary flow[10]. In this case atrial pressures are reduced[11,12], while myocardial contractility is still relatively well-preserved[13]. Therefore, any possible myocardial ischemia that may occur would not be associated with an increase in cardiac size. However, these experiments suffer from the limitation that ischemia is probably both general and regional. In Figure c, the discharge of the fiber was clear reduced following removal of 60 ml of blood. The ECG was markedly altered, and the arterial pressure had fallen to about 20 mm Hg. When the blood was reinjected, the discarge increased as the atrial pressure began to rise (Figure d). 4 atrial and 2 ventricular fibers that were excited during myocardial ischemia produced by reduction of coronary flow were inhibited during acute hemorrhage (14 trials, 100% success rate). A decrease in firing of vagal atrial receptors during hemorrhage has already been reported[14].

Cardiac vagal receptors located in each of the cardiac chambers were activated during myocardial ischemia produced by reduction of left coronary flow. The effective stimulus to these receptors is likely to be the attendant increase in heart size while ischemia per se seems to be of little or no importance. This would account for the excitation of right atrial receptors whose blood supply is probably largely independent of left coronary flow. Such receptors are known to be highly responsive to changes in atrial volume[8,14]. By contrast, cardiac receptors whose afferent fibers run in the cardiac sympathetic nerves respond to myocardial ischemia after a much shorter latency (10–20 sec) and ischemia appears to be the effective stimulus[7].

It is reasonable to speculate that excitation of cardiac vagal receptors may initiate depressor reflexes[4,5] when myocardial ischemia is accompanied by cardiac failure.

Résumé. La décharge de fibres vagales d'origine cardiaque est augmentée au cours d'une réduction du flux sanguin dans l'artère coronaire de gauche. Toutefois cette excitation n'a lieu que lorsque le coeur est déjà défaillant à cause de l'ichémie. La stimulation effective paraît être de nature mécanique.

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Summary of afferent cardiac vagal fibers excited during myocardial ischemia

Method used to produce ischemia	No. of fibers	Location of the receptors R.A.	R.V.	L.A.	L.V.
Cessation of pump inflow	21	13	–	4	4
Transient occlusion by snare	10	4	2	4	–

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Periodic Depression by N-Methyl-N-nitrosourea of Electrocortical Activity in the Cat Brain

N-Methyl-N-nitrosourea (MNU) is an alkylating agent which has been widely used in the experimental production of brain tumors[1,2]. Early biological effects of MNU include methylation of nucleic acids[3], inhibition of DNA synthesis[4] and pathological changes in proliferating cells. Recent observations of episodes of tonic seizure activity after systemic application in mice suggest that MNU also exerts an acute neurotoxic effect[5].