CARDIAC CONTROL IN THE ISOLATED MAMMALIAN HEART.*

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A large number of factors have been implicated in the regulation of cardiac function. Professors Arora, Kapoor and Manchanda have already emphasized the role of the various extrinsic factors in cardiac control. The first part of my discussion aims at cardiac control dependent upon factors operating within the isolated heart, that is independent of the various extrinsic, nervous, physical, chemical or endocrinal factors. The second part comprises of a small feature film illustrating these concepts in an isolated swine heart-lung preparation. The effect of peruvoside an indigenous cardiac glycoside in restoring myocardial contractility in the failing pig heart is also shown. The pigs used—S. scrofa, were obtained from the animal house of the All India Institute of Medical Sciences, New Delhi.

Two fundamental types of autoregulatory responses have been observed in the heart. One type of intrinsic response observed in the isolated ventricles is referred to as homeometric autoregulation. It requires at least a few beats to develop fully after an increase in activity. The ventricle then exhibits its performance characteristics such that its end-diastolic pressure and fiber length tend to be maintained more nearly like that which obtained prior to the activity increase. The increased ventricular activity may be associated with an increase in the aortic pressure (Anrep effect) or the heart rate (Bowditch effect).

The second type of intrinsic response exhibited by the isolated heart is the well-known Frank-Starling mechanism which endows the ventricles with performance characteristics such that the heart ejects whatever volume is put into it. If inflow is augmented and end-diastolic pressure and fiber length are thus increased, the ventricle contracts more forcefully and expels an augmented stroke volume on a beat to beat basis. This regulation is referred to as heterometric autoregulation. A similar mechanism has also been shown to be operative in the atria largely because of the elegant studies of Blinks (1961).

The idea that stretching muscle results in a contraction that is mechanically stronger and releases more total energy than a contraction elicited from an unstretched muscle was established by Fick in 1882 and Blix in 1895.

In 1895, Frank working at the Institute of Physiology, in Munich showed that the length-tension relationship in the frog myocardium correlated well with the well-known responses of skeletal muscle previously established by Fick and Blix. Frank recorded both isometric and isotonic contractions of frog atria and ventricle during various degrees of diastolic filling and

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pressure. He observed that, within limits, stepwise increases in diastolic volume and pressure just before contraction determined the magnitude of the ventricular response i.e. the cardiac response was determined by and large by the hemodynamic events preceding excitation. The findings were independently confirmed by Straub and Wiggers in 1914.

It is well-known that a heart which is deprived of its reflex connections continues to function automatically though it is unable to respond to stress by appropriate changes in rate and force of contraction which result from an interplay between the sympathetic and parasympathetic influences. Nevertheless, such an isolated heart which is independent of hormonal or nervous stimulation has some ability to adjust its performance to various levels of activity. Using his well-known heart-lung preparation Starling (and his co-workers, 1914) illustrated his concept of the law of the heart. He showed that within limits the isolated heart possesses an automatic regulation which depends upon the stretch response. For example, if the load upon the heart is increased by increasing the venous pressure and thus the venous inflow, the heart is filled to a size larger than before and contracts more strongly. Similarly, if the aortic pressure is increased, the heart empties less completely, the residual blood which is added to the diastolic filling causes an increase in diastolic size which in turn enables the heart to do its increased work.

The other explicit propositions made by Starling were: that with increasing fiber length or diastolic volume, the energy of contraction increases, up to a certain optimal length of fiber, but then with further lengthening the energy of contraction diminishes; and that these principles applied basically to the isolated mammalian heart.

Starling's concept won wide acceptance by clinicians who were becoming more interested in physiological mechanisms as playing roles in disease processes. They were familiar with big weak hearts which would improve in performance after venesection. Physiologists, too, were eager to accept Starling's law, because a fundamental concept developed within the laboratory, could explain clinical aspects of circulatory problems in a comprehensible manner. This initial enthusiasm was gradually replaced by growing disillusionment for two reasons: 1) Those who attempted to use this concept did so with inadequate appreciation of the essential operating parameters namely, that Starling's law can be unequivocally demonstrated as a dominant mechanism in cardiac response only when factors like—the physiologic condition of the myocardium, including autonomic hormones, sympathetic nerves, chemical substances in blood and the O₂ supply to the myocardium are kept constant—a condition which is rarely encountered, except in the experimental situation in an isolated heart, and 2) because of the investigations of Wiggers, Katz, Bernell and more recently those of Sarnoff and Rushmer who demonstrated that under certain circumstances the heart could be induced to contract more forcefully and produce more external work even though its end-diastolic volume and pressure were lower i.e. there is a shift in the ventricular function curves as under the influence of epinephrine, sympathetic stimulation or exercise (Reindell et al. 1953)—a concept which was not known during Starling's times.
Apart from the criticisms mentioned above, more recently, it has been argued that various other factors e.g. deficiencies in the methods of recording used by Frank, Starling and Wiggers; depression, distortion or elimination of central cardio-regulatory influences by the use of anesthetic agents; the decrease in size and more complete emptying of the heart after thoracotomy; the influence of experimentally applied loads on the isolated heart etc., should be taken into account before extrapolating the data to intact, close-chested, unanesthetized human beings or animals.

Starling's mechanism unquestionably operates under all conditions, but whether or not it can be identified as a dominant mechanism in cardiac control during spontaneous activity in intact animals and men is a debatable point (Stead and Warren, 1947; Warren et al. 1948; Richards, 1947; Hamilton, 1953; Sarnoff, 1954). That the Frank-Starling mechanism is a dominant mechanism in cardiac control in the denervated transplanted human heart has recently been shown by the studies of Leachman et al. (1969); Glick et al. (1969) and Shaver et al. (1969). The latter workers showed that 18 months after transplantation, the totally denervated transplanted heart was capable of responding to the stress of mild exercise. During the first two minutes of exercise, central filling pressure increased from 0 to 3 mm Hg. The heart rate remained constant over this period and the increase in cardiac output was due solely to a rise in stroke volume by the Frank-Starling mechanism. During the latter three minutes of exercise, stroke volume was further augmented at a constant central filling pressure. This second phase of augmentation was associated with a delayed heart rate response and was probably due to increased levels of catecholamines released by the stress of exercise.

The fact that this small increase in rate was present even after confirmed beta receptor blockade suggests that there may be a second basic mechanism for increasing the heart rate during exercise that is intrinsic to the heart itself — an effect similar to the one described by Blinks (1956) in the isolated mammalian heart.

REFERENCES


