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THE ROLE OF THE HEART IN THE REGULATION OF THE CIRCULATION

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In WEBSTER's dictionary (1966) circulation is defined as: "the state of being circulated", while to circulate is defined as: "to go around a specified course and return to the starting place, as the blood circulates".

It seems a fair assumption that the heart is the starting place for the circulating blood and indeed without a beating heart the blood does not move. The opposite, however, is far from true; the beating of the heart is more or less independent of whether or not blood is being circulated.

In the intact organism almost every intervention, imposed to study the circulation, will have an effect on the heart and almost every intervention, applied to study the heart, will have its effect on the circulatory system. It is still not known which circulatory parameter is most representative for the contractile behaviour of the heart. For that reason it is difficult, if not impossible, to evaluate quantitatively the function of the heart, using circulatory parameters. The title of this paper is therefore misleading, since the role of the heart cannot be evaluated quantitatively (KAVALER, 1967). Therefore extrapolation from isolated heart- or isolated myocardial strip studies can hardly be avoided. The mechanical activity of the (isolated) heart can be influenced by a number of factors which also seem to regulate the force of the heartbeat in the intact organism. For the sake of briefness only the most important of these factors will be listed:

1. Sympathetic- and/or parasympathetic (adrenergic- or cholinergic) nerve stimulation (CYON and CYON, 1867; WEBER, 1845).
2. Hormonal influence such as epinephrine, norepinephrine and acetyl-choline (EVANS and OGAWA, 1914; LOEWI, 1921).

a smaller contraction. This shortened interval not only gives rise to a small beat directly following that short interval, but also to a number of enlarged contractions afterwards. This phenomenon is known as "postextrasystolic potentiation" (HOFFMAN *et al.*, 1956; MEIJLER *et al.*, 1962). The effect of one interposed longer interval is just the opposite. It enhances the first contraction ("rest contraction") (ROSIN and FARAH, 1955), but the beats coming thereafter are somewhat smaller than the controls ("depotentiation") (KATZ, 1967).

With these rather simple examples it may become clear that in the intact organism, in which two RR-intervals are seldom identical, the influence of the interval-contractility relationship on the overall mechanical activity of the heart becomes rather complicated. This holds for instance especially for the contractions of the heart in patients with atrial fibrillation. It was found that the RR-intervals of patients with atrial fibrillation are randomly distributed (MEIJLER *et al.*, 1968). When we knew this, the effect of random rhythms on the contractile behaviour of isolated perfused rat hearts was studied. By means of crosscorrelation techniques it was found that there was also a close relationship between the RR-interval(s) and the height of the contraction(s) during random beating (MEIJLER *et al.*, 1968). These and other studies (KRUTA and BRAVENY, 1968; MEIJLER and DURRER, 1965) demonstrate that a direct influence of rate and rhythm on the contractile behaviour of the heart may indeed play an important role in the regulation of the circulation. During every day activities the heart constantly changes its rate and rhythm and thus its RR-intervals. For example during exertion the heart rate increases. This increase in rate enables the heart to expel more blood in a shorter time. Substantial evidence has been presented that the calcium ion, via the excitation-contraction coupling (NIEUWENDIJK, 1966; ZIMMERMAN, 1966; NIEUWENDIJK *et al.*, 1967), translates the duration of the RR-interval in a more or less forceful contraction.

From the list of 9 factors I have focused attention only on factor 8, which, via intermediate mechanisms, influences the mechanical activity of the heart. At the same time, it should be realized that although the factors are listed separately, they all influence each other and may even act via each other. For instance the positive inotropic action of an increase in heart rate may be expressed by

a shift from one so-called Starling-curve to another (SARNOFF, 1955) and the effect of a rise in temperature seems to make use of an increase in heart rate (KNOWLTON and STARLING, 1912).

Once more it should be stated that the evaluation of any pharmacological intervention on the contractile behaviour of the heart is only allowable if the intervention took place during a fixed and controlled heart rate.

The boundary between knowledge and ignorance of myocardial contractile behaviour has reached the subcellular level (SONNENBLICK, 1968). In our country academic pharmacology is 60 years old. Maybe in the coming decades the iron curtain of our ignorance will be removed from the molecular site, where, most probably, the contractile force of the myocardial cell is regulated. The role of the heart in the regulation of the circulation may then be completely understood.

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[1] These references are only a few from the vast amount written on this topic. Special attention has been paid to classical papers and Dutch papers or monographs.

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