Clinical Relevance of Postextrasystolic Potentiation

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The significance and clinical relevance of postextrasystolic potentiation resides in the fact that any change in duration of the cardiac cycle results in a change in the contractile behavior of the heart. Since neither a normal nor a diseased heart ever beats strictly regularly, postextrasystolic potentiation is continuously operative, and all hemodynamic or circulatory data obtained in the intact organism are affected by it. This means that postextrasystolic potentiation should be taken into account when cardiovascular clinical data are analyzed and subsequently used for diagnosis or treatment. Postextrasystolic potentiation used as an intervention for the evaluation of residual viable myocardium in scar tissue areas in patients with coronary heart disease may contribute to our insights in the prognosis of and therapeutic judgments in those patients. Postextrasystolic potentiation is a fundamental physiologic property of all myocardium under all circumstances and as such does not allow for integrating or averaging data obtained during more than one cardiac cycle, if cardiac rhythm has not been strictly regular. This fact is insufficiently appreciated in nuclear cardiology and two-dimensional echocardiography.

Few concepts in clinical cardiology are so loosely applied and so often ignored as postextrasystolic potentiation. First of all, the term "postextrasystolic potentiation" should be properly defined. We propose to use the term in each instance of RR interval-dependent changes in contractility of the myocardium. Frequency-force relation, frequency potentiation, paired (pulse) stimulation, electro-augmentation, rest contractions, and so on, all result from the same basic physiologic mechanism—that any change in rate or rhythm of the heart affects its forthcoming contraction(s).

In 1965 Cranefield[1] wrote an excellent, though brief, historical review called "The force of contraction of extrasystoles and the potentiation of force of the postextrasystolic contraction." The year 1965 was the pinnacle of clinical interest in postextrasystolic potentiation, because at that time paired stimulation was thought to be useful for the temporary treatment of therapy-resistant tachycardias[2-4] and intractable cardiac failure.[5-7] However, paired stimulation gave rise to an unexpectedly high myocardial oxygen consumption,[5,7] and since patients with coronary heart disease are the most apt to get life-threatening tachycardias or cardiac shock, the interest in postextrasystolic potentiation by clinical cardiologists was followed by an almost total neglect. There was a weak attempt to revive this interesting area in a monograph edited by Cranefield and Hoffman.[8] From a clinical point of view, the field of postextrasystolic potentiation was almost completely deserted until the rediscovery of the fact that coronary artery occlusion results in segmental myocardial disorders.[9-12]

Dyke and associates[13,14] were the first to demonstrate that in patients and dogs, postextrasystolic potentiation could help to identify viability in acutely ischemic heart muscle. Recently, Azancot and associates[15] demonstrated in patients that postextrasystolic potentiation is effective in

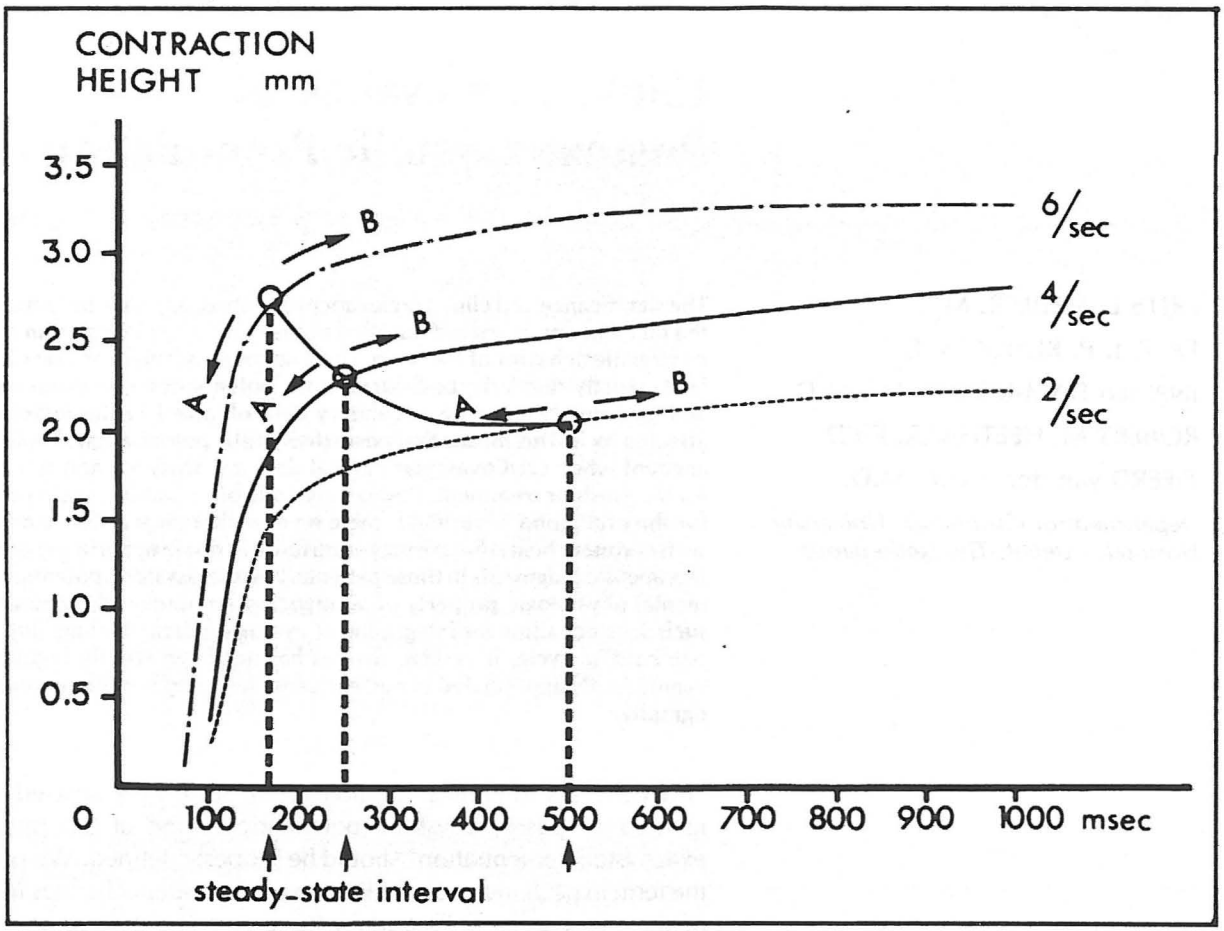

Fig. 1. Restitution curves of an isolated rat heart at three different steady-state heart rates. The "A" part of each curve is the "premature beat part," the "B" part "the rest contraction part." The open circle on each curve represents the contraction height at the steady-state frequency. The line connecting these three circles represents the relationship between heart rate and contractility at the steady state. (From Meijler and associates.[25] By permission.)

allowing discrimination between potentially reversible ischemic areas and definitely jeopardized areas of the myocardium. The clinical significance of such information is evident, since it is of value for prognostic reasons as well as for major therapeutic decisions such as coronary artery bypass surgery. Apart from true postextrasystolic potentiation, there have been other tests, such as atrial pacing, based on the same physiologic principle, to evaluate residual myocardial contractile capabilities.[16-18] All of those tests or interventions are based on the potentiating effect of a shortened RR interval or an increased heart rate (or both) on the contractile behavior of the heart. However, the clinical relevance of postextrasystolic potentiation exceeds by far the opportunity it offers to enhance segmental or global myocardial contractile function.

(PATHO-)PHYSIOLOGIC CONSIDERATIONS

The groundwork for an understanding of postextrasystolic potentiation was laid in the mid 1930's by the Czechoslovakian physiologist Kruta.[19] He was the first to use programmed stimulation to analyze the phenomenon in a quantitative way. He demonstrated the so-called S-shaped relationship between steady-state stimulation rate and myocardial contractility.

The second principle, which is related to the previous one, was his concept of "restitution,"[20] based on the direct relation between the preceding cardiac cycle and the directly following contraction during an otherwise regular rhythm. He found that each contraction after a cycle shorter than the basic (steady-state) cycle length is weaker than the control beat, and each contraction following a cycle longer than the control beat is stronger than the control beat.

A beat occurring after a shortened cycle is an extrasystole, and a contraction occurring after a longer (than basic) cycle is called a "rest contraction."[21-23] Since contractility is, up to a certain maximum, related to

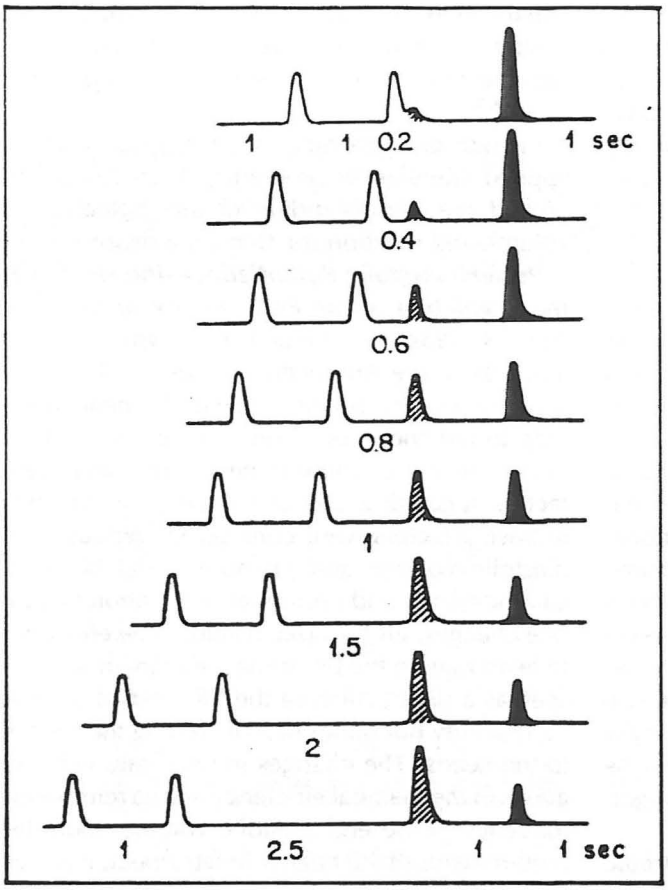

Fig. 2. The effect of a change of one single interval on the immediate *(shaded area)* and following *(black area)* contraction, showing the reciprocal development of contractility of these two neighboring beats in respect to the steady state *(unshaded)*. Redrawn from a representative experiment on guinea pig atrium at 32°C and 60-per-minute stimulation (isometric recording). (From Kruta and Braveny.[26] By permission.)

steady-state frequency—the higher the rate, the stronger is the contraction, and vice versa—different restitution curves can be produced at different heart rates (Fig. 1). At a higher heart rate, restitution is faster. This implies that the strength or size of an extrasystole depends not only on its coupling interval but also on the strength of the preceding control beats.[24] Thus, interval-dependent myocardial contractility can, at any particular moment, be expressed in the form of a restitution curve.

Since an extrasystole can be looked at as the first beat of a higher heart rate, it follows that the restitution curve after even one extrasystole is steeper than before; but after a rest contraction (the first beat of a lower heart rate) restitution is less steep than that in the control situation. This means that an extrasystole is followed by a stronger contraction (potentiation) and a rest contraction by a weaker contraction. This phenomenon is called "depotentiation." Any loss of contractility due to a temporary or permanent slowing of heart rate (increase in cycle length) may thus be called "depotentiation."[25] The restitution mechanism is demonstrated in Figure 2, which is taken from the landmark paper of Kruta and Braveny in 1968.[26] It should also be clear that an early extrasystole potentiates more than does a later one, since an early extrasystole can be seen as the first beat of a higher heart rate than a late extrasystole. This phenomenon has already been described by Hoffman and associates,[27] who also coined the term "postextrasystolic potentiation." All the relevant literature on this subject until 1963 has been superbly covered by Koch-Weser and Blinks.[28]

Thus, the entire mechanism of postextrasystolic potentiation is based on two interrelated principles: (1) the relation between steady-state heart rate and contractility, and (2) the relation between one cycle length and the directly following contraction.

These two principles seem to oppose each other, since at a high heart rate (short RR interval), contractility is high (inverse relationship between RR interval and contractility), whereas at a given heart rate a short(er) cycle is followed by a weak(er) beat (direct relationship between RR interval and contractility).

It takes time (and thus a number of beats) for the contractions to adjust to a higher or lower heart rate. One shorter or one longer interval is just too short to wipe out the preceding contractile state completely, although one interval is enough to reset the contractile state of the myocardium to a new level, as demonstrated by faster or slower restitution.[25,29] One should also realize that a contraction after an extrasystole plus a compensatory pause is affected not only by postextrasystolic potentiation but also by its late appearance on the postextrasystolic restitution curve; or, in other words, a beat after an extrasystole and a compensatory pause is a potentiated rest contraction.

Each change in duration of a cardiac cycle relative to the preceding cardiac cycles has an effect on the contractile state of the myocardium. The degree of that effect is dependent on, among other factors, the available free calcium ions in the extracellular fluid.[30] The role of calcium ions and fluxes in postextrasystolic potentiation has recently been summarized by Wong.[31]

The duration of the effect of an interval change or changes on contractility can be tested only by new depolarizations applied after varying intervals. The new cardiac cycle may wipe out or counterbalance the effect of the previous one. Using random stimulation in isolated rat hearts[32] and intact dogs, and studying human hearts with atrial fibrillation that is accompanied by a random ventricular rhythm,[33] we could demonstrate the continuous effect of potentiation and depotentiation during

(total) irregular rhythms. It was also found that the duration of the effect of a changed cycle length on forthcoming contractions is relatively short in man; this is, of course, of consequence for the effect of RR interval variations on hemodynamic and circulatory parameters[34,35] under all clinical circumstances.

CLINICAL RELEVANCE OF POSTEXTRASYSTOLIC POTENTIATION

The clinical relevance of postextrasystolic potentiation can be divided into visible and invisible aspects. This division is purely pragmatic, since biology in general and physiology in particular are not controlled by our observational skills.

To the visible aspects belongs the use of postextrasystolic potentiation as an intervention for diagnostic reasons or therapeutic purposes. The latter can be ignored because of the high myocardial oxygen cost of paired stimulation.[5,7] The invisible or, rather, hidden aspects are at least as important as the overt aspects, and seem more interesting from a pathophysiologic point of view.

The late (re)discovery of postextrasystolic potentiation in 1956[27] may be the reason that even today its role in the regulation of the contractile behavior of the heart and the circulation in clinical cardiology has either been forgotten or is at least not sufficiently appreciated.[26]

Postextrasystolic Potentiation as a Positive Inotropic Intervention Technique.—The effect of postextrasystolic potentiation on contraction and relaxation of the heart has been analyzed in a host of studies.[36-46] Only in a few instances have the authors mentioned the fact that the (compensatory) pause following extrasystole has an additional effect on the postextrasystolic beat.[47,48]

There is only one strictly proper way to study postextrasystolic potentiation and postextrasystolic relaxation and that is under the circumstances that the postextrasystolic interval is kept equal to the basic interval. We have been able to demonstrate that postextrasystolic end-diastolic volume is equal (within the measuring error) to the end-diastolic volume of the control beat.[49,50] This implies that the Frank-Starling mechanism does not necessarily contribute to the enlarged postextrasystolic stroke volume or the ejection fraction.

Depending on the duration of the postextrasystolic pause, there is more run-off from the aorta, resulting in a more or less reduced aortic pressure, which also may contribute to a larger postextrasystolic stroke volume or ejection fraction. Reduction in afterload can be limited if the postextrasystolic pause is controlled and proper care has been taken that the extrasystole is sufficiently mature to open the aortic valves. After these precautions, postextrasystolic stroke volume and ejection fraction are also enhanced as compared with the control beat; this demonstrates that postextrasystolic potentiation by itself is capable of increasing stroke volume and ejection fraction.[49,50]

In spite of elementary shortcomings in many of the applied stimulation programs, these studies have improved our understanding of the regulation of stroke volume and ejection fraction on a beat-to-beat basis.

Postextrasystolic Potentiation—the Hidden Factor in the Regulation of the Performance of the Heart.—On Apr. 13, 1954, in Atlantic City, a symposium under the auspices of the American Physiological Society on the regulation of the performance of the heart was the prelude to the "new look" on myocardial mechanical behavior. In the opening paper, Katz[51] analyzed several factors regulating the performance of the heart. The following factors were considered: venous return, end-diastolic volume and pressure, atrial blood pressure, cardiac nerves and hormonal and humoral factors, heart rate changes, and systolic residue. The effect of changes in heart rate on the performance of the heart was not yet seen as a direct effect of the RR interval on myocardial contractility but rather one of "setting the minute output to the needs. The changes in heart rate will cause variations in mechanical efficiency and so remove further the influence of the end-diastolic volume upon the energy requirements of the heart." In retrospect, it is clear that at that symposium postextrasystolic potentiation was a hidden factor. In fact, only Rushmer[52] challenged the general consensus that the Frank-Starling mechanism was the paramount factor explaining cardiac performance, and with that stand he really opened the eyes of other American investigators to the muscle factor in mechanical behavior of the heart.

In 1956 Hoffman and associates' paper[27] on postextrasystolic potentiation was published. We may assume that changes in RR interval dominate to a large extent the performance of the heart. In 1960 Braunwald and associates[53] reasoned that it was "unlikely that the duration of the preceding diastole, per se, is the determinant of the characteristics of the subsequent ventricular contraction" and that "Starling's law of the heart operates in patients with mitral stenosis and atrial fibrillation on a beat-to-beat basis."

In 1968 we[32] demonstrated that in the isolated rat heart during random stimulation the characteristics of each ventricular contraction were solely determined by the duration of preceding RR intervals, and this made it plausible that the heart in situ could operate in the same fashion and thus without the Frank-Starling mechanism. Another 10 years was required before M-mode echocardiography enabled us to demonstrate that in the human

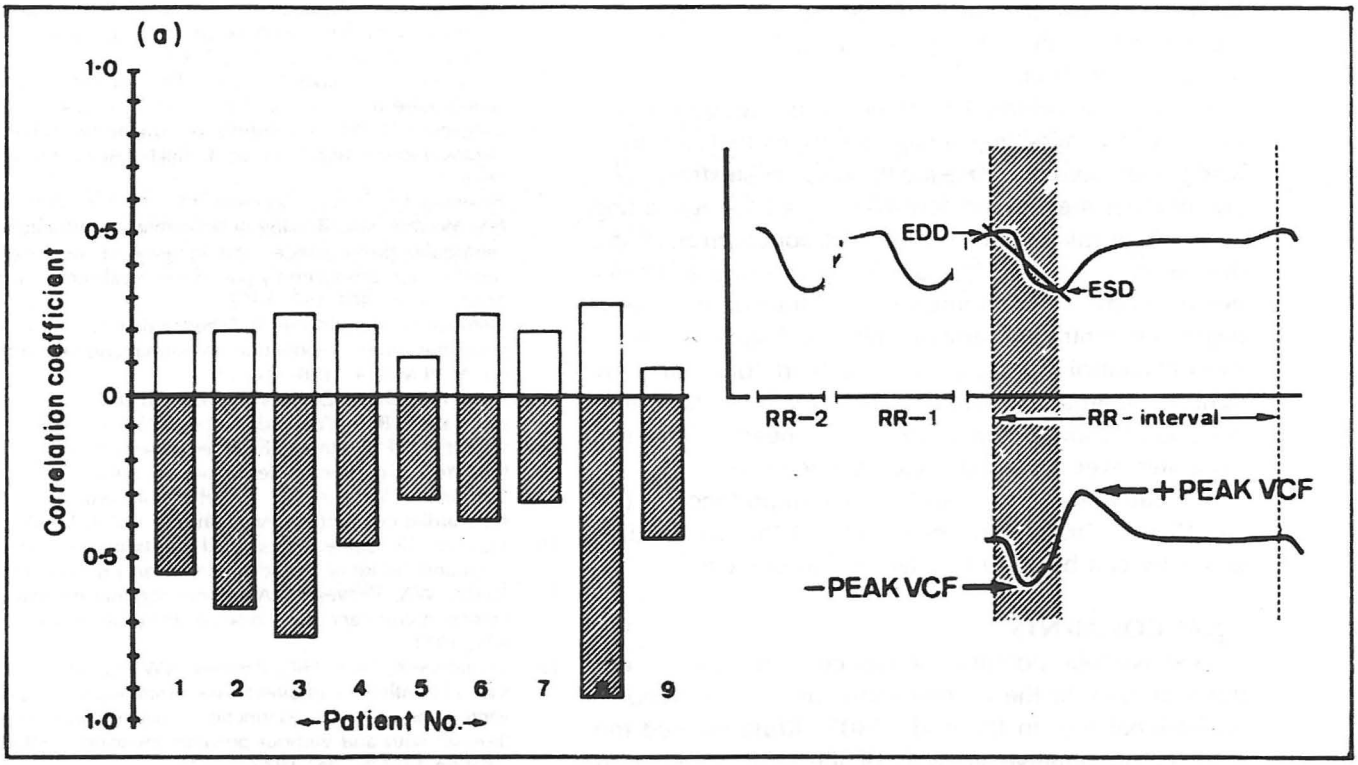

Fig. 3. Relationship between preceding (RR-1, *shaded blocks*) and prepreceding (RR-2, *open blocks*) RR intervals and the maximum rate of decrease in left ventricular internal dimension (-PEAK VCF) obtained from M-mode echocardiography in patients with atrial fibrillation. EDD = end-diastolic dimension; ESD = end-systolic dimension. (From Van Dam and associates.[54] By permission.)

heart during atrial fibrillation there is indeed a direct effect of the RR interval on the characteristics of left ventricular contractions, although because of the aforementioned relatively short duration of influence of postextrasystolic potentiation, the direct effect is demonstrable only during two subsequent cardiac cycles[54] (Fig. 3).

It was also possible to show that relaxation and end-diastolic dimensions are not affected by preceding RR intervals. This is of importance, because it demonstrates that interval-dependent changes in contraction on the one hand and left ventricular diastolic dimension and relaxation on the other hand are not interrelated.[54,55] These findings have recently been confirmed by Blaustein and associates.[56] This implies that in the intact organism as well, beat-to-beat variation of cardiac performance may be regulated by postextrasystolic potentiation and aortic afterload[47] and not necessarily by the Frank-Starling mechanism, as was already anticipated by Rushmer[52] in the mid 1950's.

Since normal human (and all other) hearts never beat strictly regularly, postextrasystolic potentiation must continuously affect cardiac performance, although small variations in the RR interval cause only small variations on a beat-to-beat basis. Nevertheless, postextrasystolic potentiation must be taken into account in the interpretation of the performance of the heart in health and disease, even when its presence is not clearly visible. We make an exception for patients with total heart block and a fixed-rate ventricular pacemaker. Postextrasystolic potentiation cannot operate under those circumstances, and the Frank-Starling mechanism may account for variation in stroke volume and ejection fraction in those patients.

Postextrasystolic Potentiation as a "Catch" in Modern Cardiovascular Diagnostics.—Nuclear imaging of left and right ventricular cavities and derived data for the assessment of ejection fraction and myocardial perfusion make use of averaging the counts of several cardiac cycles.[57,58] Some data-handling programs reject the cycles that are 10% longer or shorter than the average cardiac cycle, but nevertheless the biologic error introduced by these averaging techniques may, to put it mildly, be substantial. For instance, in the case of an extrasystole without a compensatory pause, the extrasystole will probably be rejected, but if postextrasystolic beats are accepted, large errors may result. For that reason, in our nuclear-gated blood pool program, a number of postextrasystolic beats are rejected. This

makes the entire technique unsuitable for patients with more than a certain number of extrasystoles per minute or for patients with atrial fibrillation.

Also, in two-dimensional echocardiography combined with image-"improving" programs that use averaging over several subsequent beats, postextrasystolic potentiation may be responsible in part for remaining poor image quality. It may also introduce errors if the derived data are used for computing volumes and ejection fractions.[59,60] Running video subtraction may, as in digital left ventricular angiography, be highly improved by strict control of the rhythm of the heart, for instance by right or left atrial stimulation. The same holds for roentgen and ultrasound tomography of the heart as long as it integrates over more than one cardiac cycle.

The pathophysiologic and clinical importance of Dr. Earl Wood's brainchild lies in the fact that the cardiac geometry can be reconstructed within one cycle.[61]

FINAL COMMENTS

Postextrasystolic potentiation has come full circle from the beginning to the current status of Dr. Earl Wood's professional life. In the mid 1930's, Kruta opened the field for quantitative analysis of the relation between intervals and strength of contractions.

In the early 1950's, Rushmer[52] led us into the area of dynamic in situ analysis of the mechanical behavior of the heart which resulted in a justified emphasis on muscle-controlled rather than pump-regulated cardiac performance.[62]

In this supplemental issue of the *Mayo Clinic Proceedings*, we commemorate Dr. Earl Wood's contributions to cardiovascular medicine and physiology. The development of new techniques for research and clinical application in the post-war decades has brought our understanding of the performance of the heart to an all-time high level. Yet each heart beat is, and for the time being seems to remain, a challenge to physiologist and clinician alike, and Dr. Wood deserves the credit for having provided us with tools and ideas to meet that challenge now and in the future.

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