40 Years of *Cardiovascular Research*

Editorial

On the first paper in *Cardiovascular Research*: Frequency, force, and beyond

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The force–frequency effect was the subject of the first paper published in the inaugural issue of *Cardiovascular Research* in 1967 (Ref. [1]; see Fig. 1). As a co-author with a longstanding interest in this topic, I was asked by the managing editor, Elizabeth Martinson to comment on this publication and on other research in which I was involved during that period at the Cardiology Branch of the then National Heart Institute in Bethesda. It was an exhilarating time for those involved in the (some might say somewhat excessive) outpouring of laboratory and clinical research papers. That first *Cardiovascular Research* publication arose from the then-prevalent interest in studying the strength-interval relations of cardiac muscle, a term which encompasses such phenomena as postextrasystolic potentiation, poststimulation potentiation and effects of changing the frequency of stimulation. John Blinks, a leader in that field [2], had visited the NIH, and I found his talk concerning studies in isolated cardiac muscle of great interest. It had been difficult to demonstrate the contractile effect of increasing cardiac frequency by electrical pacing on the intact heart because of the accompanying changes in cardiac loading conditions, particularly reduced preload. This study established that increased heart rate has a positive inotropic effect in the whole heart by demonstrating, in a setting of controlled preload coupled with induced single isovolumetric beats of the left ventricle, that peak tension and the rate of tension development increased, with reduced time to peak tension, as well as an upward shift of the calculated force–velocity relation [1]. Submission of the article to *Cardiovascular Research* came about because we had heard of the impending publication of the new London-based journal and were favorably impressed with its high standards for publication; these persist to this day, as we can attest by a recently published article which was finally accepted, but only after much revision [3].

I was also asked to comment on some of my other experiences in research in the years 1966–1968. This period encompassed a panoply of research interests within the group assembled by Eugene Braunwald, then Head of the Cardiology Branch of the National Heart Institute. It was, for example, the era of muscle mechanics. Stimulated by the pioneering work of A. F. Huxley and others on length–tension and force–velocity relations in skeletal muscle, and that of W. F. H. M. Mommaerts in cardiac muscle, Ed Sonnenblick undertook additional experiments on the mechanics of isolated cardiac muscle, particularly force–velocity–length relations. I became fascinated with the possibility of applying some of these principles to the intact heart. Of course, in isolated muscle, the loading conditions are put in place while the muscle is at rest, and in order to study the effects of changing afterload alone in the intact heart it would be necessary to hold other determinants of cardiac function constant. We devised a way to accomplish this by altering the aortic pressure, the major determinant of afterload on the left ventricle, without altering the end diastolic volume and pressure of the left ventricle (the preload), myocardial contractility and heart rate. To this end, together with Jim Covell, then a research trainee, we constructed an ECG-triggered valve system connected to a pressure reservoir which permitted sudden increases or
decreases in aortic pressure during a single diastolic interval, when the aortic valve was closed, so that the ensuing ventricular contraction encountered a different aortic pressure during ejection. This approach permitted description of the inverse relations between afterload and the stroke volume and the velocity of ventricular ejection; also, shifts of the wall force–velocity relation could be induced by changing the inotropic state or contractility using catecholamine infusion [4]. A study followed on the three-dimensional mechanics of left ventricular contraction in experimental heart failure [5]. Based on our demonstration of the pronounced effect of afterload of left ventricular function, in an editorial on cardiogenic shock after acute myocardial infarction [6] I suggested the possibility that the use of aortic balloon counterpulsation, designed to augment diastolic pressure and enhance coronary perfusion, would also be useful to provide systolic unloading of the failing left ventricle to enhance the stroke volume and cardiac output.

In other activity, 1966 saw the clinical application of transseptal left heart catheterization (developed several years earlier when I was in the Clinic of Surgery at the National Heart Institute [7] ) to study a burning question of the time: was there true obstruction to left ventricular ejection in hypertrophic cardiomyopathy, then called idiopathic hypertrophic subaortic stenosis, or was cavity obliteration with catheter trapping responsible for the elevated systolic pressure in the left ventricle? The transseptal approach allowed us to record a high systolic pressure in the inflow tract of the left ventricle just beyond the mitral valve, where angiography showed that trapping did not occur. This finding, together with other evidence, including selective angiography showing the anterior leaflet of the mitral valve abutting the hypertrophied ventricular septum during systole, established clearly that in many (but not all) patients with this disorder there was true obstruction [8]. Our finding justified the use of myomectomy of the hypertrophied septum for relief of the obstruction in patients with proven obstruction. This procedure, developed by Andrew Morrow, Head of the Clinical Surgery, was successful in many patients. A series of reviews by Braunwald, Ross and Sonnenblick entitled “Mechanisms of Contraction of the Normal and Failing Heart” appeared in the New England Journal of Medicine in 1967, summarizing much of the cardiac research by the NIH group in 1960–67 [9]. This work was published as a book of the same title the following year [10].

The initial study of the force–frequency relation published in Cardiovascular Research led to a lifelong interest on my part in this fundamental property of cardiac muscle, now known to be caused by changes in calcium storage and release from the sarcoplasmic reticulum. A later study from my laboratory at the University of California San Diego provided an analysis of poststimulation potentiation in the conscious animal [11]. More recent studies in San Diego found a much larger influence of the heart rate on myocardial contractility during exercise than at rest. In instrumented animals strenuously exercising in a steady state on a treadmill, when heart rate was progressively lowered by atrial pacing after sinoatrial node inhibition, very marked decreases in left ventricular contractility occurred [12]. Also, progressive enhancement of the force–frequency relation was demonstrated in resting animals with graded increases in $\beta$-adrenergic stimulation [13]. These highly important effects can be demonstrated across species, from mouse to man [14]. The regulatory effect is lost in heart failure in animal models as well as in human heart failure [14].

My odyssey of research on the strength-interval relation, which began with that paper in Cardiovascular Research in...
1967, concluded with the 1998 review [14]. However, much remains to be learned about these phenomena, such as whether a calcium/calmodulin-dependent protein kinase may be involved in regulation of the force-frequency effect. We await further developments in this still fascinating field.

References