Starling’s “Law of the Heart”: Rise and Fall of the Descending Limb

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The descending limb of Starling’s relationship between right atrial pressure and cardiac output was the cornerstone of his “law of the heart”; it was widely accepted in physiology. However, the original meaning of the law faded away over the years: the descending limb proved to be an experimental artefact.

This paper is a continuation of “Starling’s Law of the Heart” a historical misinterpretation,” which was published about two years ago (2). There it was argued that Starling formulated his law first and foremost as a confirmation of the viscoelastic theory of muscle contraction. That theory proposed that “through excitation muscle acquires new elastic properties and a fixed amount of potential energy which can, depending on the load, become work or heat.”

Starling based his view in particular on the occurrence of a descending limb in the relationship between right atrial pressure and cardiac output (9) as shown in Fig. 1C. This historical note discusses evidence that the descending limb of the Starling curve is not an inherent property of intact ventricular myocardium. The experimental foundation of Starling’s law has some other origin.

Not one single word in the original formulation of the “Law of the Heart” reveals that it is based on the relationship between right atrial pressure and cardiac output in the canine heart-lung preparation (Fig. 1C). The Linacre lecture on the heart, presented at Cambridge in 1915 (13), reads, “The law of the heart, contracting against an occluded aorta, Frank’s data were transformed by Patterson et al. (8) to predict the behaviour of the dog heart (Fig. 1B).

A similar descending limb was described by Frank (3) for the frog heart, contracting against an occluded aorta. Frank’s data were transformed by Patterson et al. (8) to predict the behaviour of the dog heart (Fig. 1B).

The experimental data of Patterson and Starling (9) from the canine heart-lung preparation presented in the same issue of the Journal of Physiology and shown in Fig. 1C convinced Starling that a descending limb occurred also in the canine heart. Assuming that it had its origin in common with the corresponding limbs found for skeletal muscle and frog ventricle, he concluded that the universal nature of the viscoelastic model of muscle contraction was confirmed beyond any reasonable doubt. With time, not only his conclusion (2) but also his assumption were proven wrong.

Filament overlap

In the 1950s it became clear that in skeletal muscle, the descending limb of the force-length relationship can be explained by the decrease in overlap between thick and thin filaments. This finding contributed significantly to the establishment of a new theory on muscle contraction now generally referred to as “the cross-bridge theory.”

Because in myocardium of frogs and mammals the respective lengths of thick and thin filaments are comparable to those in skeletal muscle, a similar descending limb of the force-length relationship may be expected for the heart. However, it is not possible to stretch living frog or rat myocardium beyond sarcomere lengths of 2.4–2.6 μm without irreversible structural damage; passive force is already very high at 2.3 μm.

Therefore a decrease in filament overlap cannot be held responsible for the descending limb of Frank’s or Starling’s curve (Fig. 1, H and F). The assumption that the descending limbs in heart and skeletal muscle followed from the same mechanism, the starting point for Starling’s interpretation of his experiments, therefore does not hold. Descending limbs can have different origins.

Yet another argument indicates that Starling’s assumption was invalid. Over the last 20 years the pressure-volume relationship of dog left ventricle has been studied in considerable detail (11). It was found that pressure and volume of the canine ventricle are at the end of systole related through the Emax line (Fig. 2A). This line predicts for any pressure what the volume will be at the end of systole. Therefore, when arterial pressure is kept constant, as Starling tried to achieve by his elegant (Starling) resistor, and filling of the ventricle is varied, the changes of end-diastolic volume and stroke volume (end-diastolic volume minus...
end-systolic volume) are virtually the same (Fig. 2B). Thus, irrespective of the precise shape of the E_max line, the relationship between filling of the ventricle and its output cannot, according to the pressure volume properties of the ventricle, show a descending limb.

### Spurious descending limbs

Starling’s experiments were more systematically repeated during the 1950s by Sarnoff and Mitchell (12). These investigators related indices of left and right ventricular filling to left and right ventricular stroke work and called these relationships “function curves.” Because pressure and heart rate were kept about constant in Starling’s experiments, cardiac output in Fig. 1C is proportional to stroke work. Therefore the Starling curve, as far as the occurrence of a descending limb is concerned, can be directly compared with Sarnoff’s right and left ventricular function curves.

Only the results of Starling (Fig. 1C) show a descending limb. The disappearance of this part of the cardiac function curve and the fact that the viscoelastic theory of muscle contraction, falsified by Fenn in the early 1920s, was no longer alive in the mind of investigators in the 1950s obscured the true meaning of Starling’s law and inspired new interpretations.

Why the descending limb, found in 1914 by Patterson and Starling (9), did not reoccur later was discussed by Berglund et al. (1). They report that, in some of their own experiments, the atrial pressure tracing shows tricuspidal regurgitation when the pericardium is removed. Furthermore, the right ventricular function curves (open pericardium) which they present do not show any tendency to curve down.

For frog hearts, Winniwarter (14) presented much more convincing evidence that valvular regurgitation can cause a descending limb at high atrial pressures when the pericardium is removed. However, texture and architecture of the frog heart are so different from that of the dog that reliable extrapolation of these findings to Starling’s results (Fig. 1C) requires further experimental confirmation. Winniwarter’s (14) results are no doubt relevant for the preparation used by Frank (Fig. 1B), but Frank (3) was well aware of the danger of valvular regurgitation and we cannot but assume that he avoided this experimental pitfall.

The conclusion therefore is that the mechanism causing a descending limb is different for each of the three experimental cases shown in Fig. 1. In skeletal muscle there is a descending limb because of the diminishing overlap of thick and thin filaments with increasing muscle length. Frank (3) may have filled the ventricle so much that heterogeneity of the length of the myocytes may have dominated the picture and, therefore, an increasing fraction of decrease in cardiac output and could be responsible for the descending limb of the Starling curve.

However, in the experimental example shown by Berglund et al. (1) the atrial pressure tracing indeed changes, but no fall in cardiac output occurs when the pericardium is removed. Furthermore, the right ventricular function curves (open pericardium) which they present do not show any tendency to curve down.

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overstretched myocytes did not survive the experiment. In Starling's case the best explanation available until today is that valvular regurgitation caused the descending limb in his relationship, although the experimental proof is rather weak.

The descending limb and heart failure

Starling suggested that when a heart was filled so much that it arrived at the descending limb, it in fact failed. The failing heart was in his view a normal heart which was overfilled and could no longer cope with the amount of blood from the veins. This concept on the mechanism of cardiac failure acquired clinical interest between 1940 and 1960. The considerable time lag between Starling's original work and the recognition of his findings by clinicians reflects the vast distance in thinking between clinicians and physiologists, as discussed by Pickering (10). In his attractive expose this author relates, as an example of the clinician's ignorance of circulatory principles, that "being an intern in 1930 to one of the best physicians . . . I was asked to transfuse a patient . . . whose jugular veins were intensely distended . . . the patient developed acute pulmonary edema and died."

The potential importance of the descending limb for a better understanding of the failing human heart was recognized in particular by Howarth et al. and McMichael and Sharpey-Schafer (5-7). During the early days of their enthusiasm, the key argument was that, when digitalis was given to a patient in failure, venous pressure dropped while at the same time cardiac output rose (7).

The provocative interpretation was that the action of digitalis was on the veins and that by diminishing venous return, output of the failing heart would rise, travelling the descending limb of the Starling's curve upward (Fig. 3A). However, two years later it was agreed that the functional state and thus the position of the Starling curve of a heart could change (3), and therefore one should consider the changes in cardiac function as a family of curves (Fig. 3B).

Finally McMichael (6) adopted the view that the descending limb does not occur in normal well-compensated hearts but that it occurred in hypodynamic states only (Fig. 3C). It is doubtful whether this view was based on any well-documented observation.

Hindsight

Looking back in time and distinguishing fact from fiction in Starling's experimental work is an easy job compared with developing for the first time a heart-lung preparation and skillfully performing experiments with it, trying to understand yet unknown principles of cardiac function. When pointing out from today's comfortable position some experimental and conceptual shortcomings of the past, one cannot but feel uneasy. The fact is, however, that, in its various forms, Starling's law of the heart had a large impact on research efforts for many years. Consequently, one wonders how concepts and research would have developed if three of the nine experiments of Fig. 1C that show a descending limb had been removed from the graph because of experimental shortcomings and had been replaced by three others not showing that phenomenon.

Nowadays, to indicate the ascending portion of the length-tension relationship (or pressure-volume relationship) one usually speaks about the Frank-Starling mechanism instead of "Starling's Law of the Heart"; research is still going on to unravel the underlying molecular mechanisms. Starling's name is hardly used anymore to indicate the relationship between ventricular filling and output. Graphs of that nature are most often called "ventricular function curves." The descending limb of intact myocardium has disappeared from the scene altogether, leaving behind visible traces of turbulence in the history of cardiovascular research.

References