# Introduction

The purpose of the present book is to bring together current ideas of the interval–force relationship, as propounded by some of the main contributors to current research on the subject, and to review the evolution of our knowledge of the subject since the publication of Bowditch's original paper in 1871.

Unlike the other important intrinsic controlling system of heart muscle – the length–tension relation – the force–interval relationship has been relatively neglected. Professor Jochen Schaefer (who first fired our own interest in the subject) and his collaborators consider the historic reasons for this neglect in the first chapter of the book, which includes their translation of Bowditch's paper. Their discussion is of considerable interest from a general point of view, since it illustrates how the fate of scientific contributions may depend on factors other than their intrinsic value. Later sections of the book address the basic cellular mechanisms which underlie interval–force processes, the ways in which these processes manifest themselves in the mechanical behaviour of cardiac muscle, and their relevance to the function of the intact heart. To our knowledge, systematic reviews of these topics have not been brought together before. Our other justification is the recent upsurge of interest in interval–force events.

A number of ambiguities in terminology need comment. The first concerns the main topic itself, which is variously referred to as the force–frequency, force–interval, interval–strength, or interval–force relationship. We have not attempted uniformity in this book, though we prefer the latter term because it identifies the independent and dependent variables appropriately (compare length–tension), and embraces events related to single as well as repetitive stimuli. Two other ambiguities which

arise are related first to the use of the term 'force', and secondly to the precise meaning of the term 'staircase' or 'Treppe'.

**Dimensions of 'force'**

Force is measured in dimensions of mass times acceleration (e.g. 1 kg m $s^{-2}$ = 1 newton). When force is expressed per unit of cross-sectional area of muscle (N $m^2$), it is termed a stress. The term *tension* is widely used, usually in a non-specific way to indicate either force or stress. Pressure is also force per unit area, but this time exerted within the cavity of the ventricle rather than across the cross-sections of the muscle. The rate of rise of force, stress or pressure obviously divides these variables by time. In our opinion, the inconsistency with which these terms are used in force–interval descriptions only affects the quantitative magnitude of the variable being used. When they are used comparatively as a function of interval or frequency, the same relationships will emerge. Again, therefore, we have not attempted to impose uniformity. The situation which differs fundamentally from these circumstances is that of cardiac ejection. The confusion that arises from including ejection variables has plagued the study of interval–force relationships in the intact heart. Thus in considering the effects of interval or frequency, we must exclude effects on variables such as stroke volume if we wish to confine ourselves to the intrinsic mechanisms within muscle that Bowditch described. In this book such exclusion has generally been followed, but since the clinical relevance of interval–force processes is a legitimate interest, their possible influence on ejection variables in the intact heart is discussed at the end of the book.

**'Staircase' or 'Treppe'**

There are three ways in which these terms are used, schematically represented in Fig. 1:

1. Following a prolonged period of rest, stimulation of the muscle causes a progressive increase of force to a plateau (Fig. 1(*a*)).
2. Following a period of low frequency stimulation, stimulation of the muscle at a higher frequency results (after an initial decrease in force) in a similar pattern of increase to that shown in 1(*a*) (Fig. 1(*b*)).
3. During steady-state stimulation, the final plateau of force may progressively rise with increasing steady-state frequency (Fig. 1(*c*)).

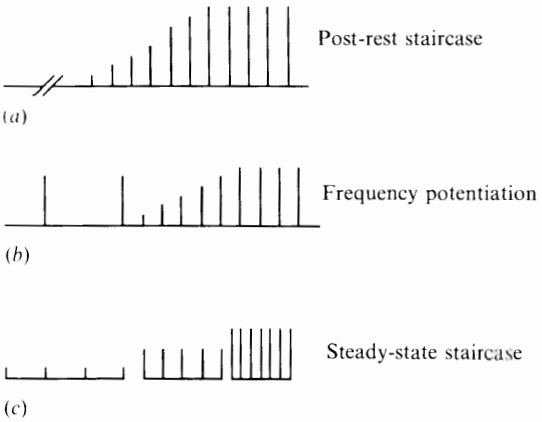


Fig. 1. Schematic representation of 'staircase' or 'Treppe'.

The first two examples involve the same underlying mechanism and, in our opinion, could simply be termed 'Treppe'. However, the reader should be prepared to meet other terminologies. Of particular note is that of Koch-Weser and Blinks (1963), who described a 'positive inotropic effect of activation (PIEA)'. The reason for coining this term was to separate it from the initial drop in force (Fig. 1(*b*)) which they termed the 'negative inotropic effect of activation (NIEA)'. The latter term has lost its *raison d'être* because this is now recognized to be incomplete mechanical restitution (see chapter by Jóhannsson). For this reason, PIEA has also dropped out of fashion, although it remains a reasonable term. One could argue that the term 'frequency potentiation' is the most appropriate. This mechanism is also responsible for the strong beat that follows a return to the low frequency. The third application of the term 'staircase' (Fig. 1(*c*)) has a different meaning because the final steady state force depends on the balance between the effects of incomplete mechanical restitution and frequency potentiation. Thus, as long as the latter dominates, force does increase more or less stepwise, but if incomplete mechanical restitution dominates there may be a decrease in force, as occurs in rat ventricular muscle. This has led to the very misleading terms 'negative staircase' our 'negative Treppe'. Our preferred terminology for this effect is 'steady state interval–force relationship'.

Bowditch described nearly all these phenomena and also post-extrasystolic potentiation, an important interval–force relationship that has escaped terminological ambiguity more than the others. However, we should point out that there is no necessity for the premature beat which

imparts potentiation to the ones which follow to be an extrasystole in the clinical sense of that word, i.e. a beat originating from an abnormal site in the heart. Thus the phenomenon might more accurately be called 'post-premature-beat potentiation'.

**The sub-cellular sites involved in force–interval phenomena**

In Fig. 2 we present a remarkable record of steady state interval–force responses in a single cell. This confirms the assumption that we have all made that force–interval phenomena do reside in the myocytes themselves. However, the frog is not typical of the species usually studied because it has little internal store of activator. This is a subject to be discussed in considerable detail in this book, and a subject of considerable controversy as to its subcellular site.

The experiment illustrated in Fig. 2 is of some interest in showing that the steady-state interval–force phenomenon need not depend on any of the postulated internal mechanisms of calcium handling that dominate the thinking of our co-authors and ourselves. Thus we should emphasise that our book is really confined to the consideration of properties of mammalian myocardium. Even with this limitation, the material available for discussion is excessive, and the selection for presentation to a certain

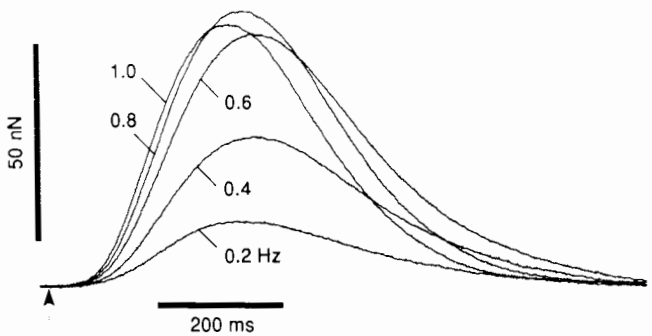


Fig. 2. The isometric contraction of a single frog ventricular heart cell was measured using an ultrasensitive force probe. The cell was field-stimulated, initially at a rate of 0.2 Hz. The stimulus rate was then increased in a cumulative, stepwise fashion to 1.0 Hz. The tenth twitch obtained at each new stimulus rate is shown. The increase in stimulus rate resulted in an increased initial rate of rise and a decreased time to peak of contraction. At the highest stimulus rates, the rate of relaxation also increased. The arrow indicates the onset of the stimulus pulse. (From Tung, L. (1987). By copyright permission of the Biophysical Society.)

extent arbitrary. We therefore apologise to the many scientists whose excellent approaches to this subject are not covered, while expressing our great thanks to our contributors for the effort they have put into their contributions. One name in particular is missing – that of Kiichi Sagawa. We have in our files a typically cheerful and optimistic letter from him about the chapter he intended to contribute with Dan Burkhoff. In the event, his death intervened. His contributions to cardiac mechanics need little chronicling, and many chapters of this book attest his more recent work on interval–force processes. In common with many of the contributors to this book, we shall miss his friendship and enthusiasm deeply.

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## References

Koch-Weser, J. & Blinks, J. R. (1963). The influence of the interval between beats on myocardial contractility. *Pharmacological Reviews*, **15**, 601–52.

Tung, L. (1987). Force–frequency relation in single frog ventricular heart cells. *Biophysical Journal*, **51**, 111a.