Historical Review Article

From Bowditch to beta-blockers: evolution of the understanding of the importance of heart rate and myocardial energetics in cardiomyopathy

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Summary

During the past three decades, every aspect of cardiomyopathy has undergone dramatic change. When examining the literature on the physiological aspects of the failing heart, one immediately recognises that South Africa has made a contribution: Brink, Bester and Lochner evaluated the possible therapeutic aspects of the Bowditch phenomenon and myocardial energetics in cardiomyopathy almost four decades ago, at a time when the condition even had another name, myocardiopathy.

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All aspects of cardiomyopathy – from our knowledge on ultrastructural and physiological alterations, to pharmacological approaches to therapy, surgical treatment modalities and later device-based therapies – have undergone dramatic changes during the last three decades. Even the terminology has changed. If one scrutinises articles from the 1950s to the 1970s one will find that the preferred term then was 'myocardiopathy'.

When analysing the progression of knowledge on the physiology of the failing heart that has made an impact on therapeutic advances over the past 30 years, I am proud to state that South Africa has made a contribution. In 1972, the following article by Brink, Bester and Lochner appeared:[1] A comparison of stimulation frequency and electro-augmentation on myocardial function, extensibility, coronary flow rate, oxygen consumption and glucose metabolism.

Thirty years later, we would see dramatic paradigm shifts regarding the importance of heart rate in cardiomyopathy. Today we understand the importance of heart rate variability and heart rate turbulence as prognostic markers in various cardiovascular disorders and we have conclusive evidence from clinical trials that reducing heart rate in cardiomyopathy confers a survival advantage.

The Bowditch phenomenon

When cardiac myocytes are stimulated at faster rates, they increase their force of contraction.[2] This ability of the vertebrate heart is central to survival and is known as the Bowditch phenomenon.[2,3] It is also known as the 'treppe' or staircase phenomenon.

Henry Pickering Bowditch, famed physiologist (nephew of the well-known Boston physician Henry Ingersoll Bowditch) and later dean of Harvard Medical School,[4] published his classic article in 1871, describing the positive inotropic response of the heart when the heart rate increases. The next 100 years would see many articles examining the response of the myocardium to various stimulation frequencies, effected by electrical devices external to the heart.[2]

It would be many years after Bowditch's article before it became apparent that the failing heart behaves very differently to an increase in heart rate. The failing heart does not exhibit a Bowditch phenomenon – there is no increase in the inotropic response to an increase in heart rate,[5-7] with some failing hearts even exhibiting a reverse Bowditch response. It was during this era that the article by Brink *et al*.[1] raised the issue that it was doubtful whether the phenomenon of increasing heart rate could be used for therapeutic purposes in the failing heart. Today we have ample clinical and laboratory evidence that reducing the heart rate improves the prognosis of patients with heart failure.

In 1967, Brink *et al*.[8] published an article on the work performance of the isolated, perfused, beating heart in Syrian hereditary cardiomyopathic hamsters. In 2007, exactly 40 years later, work on similar Syrian cardiomyopathic hamsters clearly demonstrated that the chronic administration of carvedilol (a beta-blocker) improved cardiac function.[9] This was in striking contrast to the line of thought in 1972, when the Bowditch staircase phenomenon was being explored as a possible therapeutic modality in heart failure. Already in 1972, work by Brink *et al*.[1] had raised the question that this would not be a viable therapeutic option, thus paving the way for a major paradigm shift and the current therapeutic knowledge to use beta-blockers in heart failure patients.

The failing heart as 'an engine out of fuel'

Another important concept realised today in 'modern' cardiology is that the failing heart, as opposed to the normal heart, can be viewed as 'an engine out of fuel'.[10] In 1939, Herrmann and Decherd[11] published an article on the chemical nature of heart failure. However, interest waned over the next few decades, only to be revived in the 2000s with Taegtmeyer[12] elegantly summarising the situation as: 'Metabolism – the lost child of cardiology'.

The human heart displays an enormous energy requirement

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– 6 kg of ATP every day.[10] If this requirement is not met, it will result in the reduction of mechanical energy delivered to the actin–myosin interaction process and a drop in the contractile ability of the myocardium. However, we still do not possess an accurate method for determining the levels of ATP and phosphocreatine near the sarcoplasmic reticulum in the intact, *in vivo* human heart – they are extrapolated from global measurements using ^{18}F-FDG PET imaging.[10]

Already in their 1972 article, Brink, Bester and Lochner[1] had realised the importance of 'myocardial energetics',[10] and glucose uptake and lactate production were analysed when evaluating the Bowditch phenomenon in the isolated, perfused rat heart. Unfortunately, in this case scenario, more than 30 years later we still do not possess the ideal, reliable way to measure myocardial energetics where we need to – in the peri-myofibrillar space, near the sarcoplasmic reticulum and sarcolemmal ion pumps.[10]

Therefore, I conclude that this historical article by Prof AJ Brink *et al*.[1] was one of the bricks that paved the way to the current understanding and use of beta-blockers in patients with heart failure and, furthermore, that it should also be an inspiration to find new and better methods for measuring 'myocardial energetics' – cardiology's lost child, in order to find a whole new therapeutic armamentarium to treat the 'engine out of fuel'.

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Heart of Cape Town Museum

The Heart of Cape Town Museum at Cape Town's Groote Schuur Hospital was launched on 3 December 2007 to commemorate the 40th anniversary of the world's first successful human heart transplant in 1967 by world-famous Prof Christiaan Barnard.

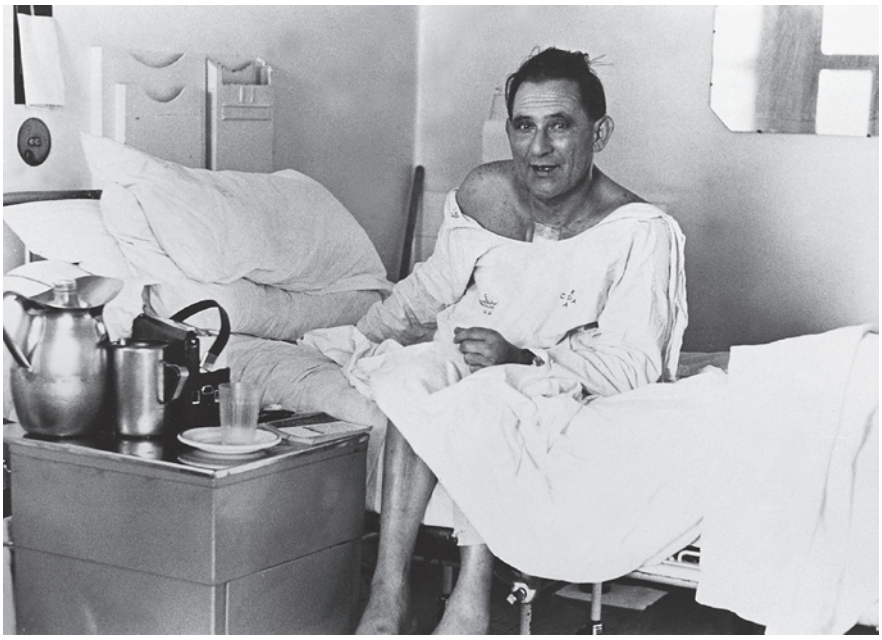
Rating as one of the city's most exciting tourist destinations, the museum operates out of a working hospital and includes the original operating theatres where Barnard transplanted the heart of the donor, 25-year-old Denise Darvall, into the body of the recipient, 53-year-old Louis Washkansky. The museum is a worthy celebration of one of the greatest scientific and emotional moments in medical history.

A guided tour through the museum relates the fascinating chain of events that culminated in the ultimate operation – an emotional and daring surgical procedure which catapulted Barnard to celebrity status and paved the way for sophisticated medical advances in cardiac surgery.

Each room is constructed around an individual element, an indispensable link in the transplant chain, which contributed to the success of the operation. A private investment of R5 million, the invaluable cooperation of the Groote Schuur Hospital administration board and a dedicated team of researchers, writer and graphic designers have created a 'not-to-be-missed' experience.

'No expense has been spared', says museum operator and businessman Hennie Joubert, 'to recreate the drama and wonder of that fateful day when the clinical application of decades of scientific research gave life to a dying man.'

For more information or bookings, e-mail: info@heartofcapetown.co.za



Louis Washkansky, the first heart-transplant recipient in hospital.

Historical Review Article

A Comparison of Stimulation Frequency and Electro-Augmentation on Myocardial Function, Extensibility, Coronary Flow Rate, Oxygen Consumption and Glucose Metabolism

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Abstract. The effects of increased heart rate on the function and metabolism of the isolated perfused rat heart were studied. Single stimuli as well as paired and coupled stimuli were used to increase the heart rate from 80 to 200 beats/min. Heartblock was produced in the rat heart to give a preparation with a heart rate of 80 beats/min. For measurements of mechanical activity a modified Langendorf perfusion system with a myographic force transducer was used. Results indicate that tension development was greater with paired than with single stimuli at frequency rates of 100–160 beats/min. At higher frequency rates there wa.s no difference between single and paired stimuli. However, paired stimuli increased the tension developed per min. (TTM) for all rates studied, whereas they reduced the time to peak height of developed tension for rates up to 160 beats/min. Relationships or length to tension at different rates of stimulation were also determined. Myocardial oxygen consumption and coronary flow rates increased with increasing heart rate, with both single and paired stimuli. Paired stimulation caused significantly greater oxygen consumption at all frequency rates, while the increase in coronary flow rate was similar with paired and single stimuli. The effects of increasing heart rate by single and paired stimuli on the metabolism of [U-^{14}O] glucose were studied. Glucose uptake and lactate production were significantly higher with paired than with single stimuli at a constant heart rate. Paired and single stimuli had a similar effect on the pattern of glucose metabolism with increased heart rate.

The results suggest, in agreement with the suggestion made by other workers, that the potentiating effects of paired stimuli dependent on the interval-strength relationship of the impulses and are probably related to the optimal availability of Ca^{++} at the contractile sites. Furthermore, the increased oxygen consumption, the limited increase in coronary flow rate and the reduced effect of paired stimulation on tension development at higher rates of stimulation make it doubtful whether this procedure can be used for therapeutic purposes in the failing heart.

Key wards: Heart rate, single and paired stimuli, myocardial mechanical activity, oxygen consumption, glucose metabolism.

The relationship of increased contractile force of the myocardium to increased rate [1,3,23,33] and to post extra-systolic potentiation [4,9,11,6] has been widely studied. Also both single and paired stimuli have been used for internal cardiac pacing in clinical medicine [17,22]. In general, it can be stated that post extra-systolic potentiation increases both the force of contraction during systole and the rate of tension development. Several studies have shown that increasing heart rate elevates myocardial oxygen consumption [18, 21, 35]. Paired and coupled pacing also result in an increased myocardial oxygen consumption [22,29,30].

The significance of compliance (compliance meaning distensibility or extensibility) [7,8,10] of the myocardium and the relationship of muscle fibre lengthening, as a consequence or change in compliance to potentiation, is still being investigated. In studies using cat papillary muscle Feigl [8] reported no change in diastotic extensibility accompanying the inotropic effects of altered beat frequency or paired stimulation. A fall in end diastolic pressure was observed in some experiments [27] which could be interpreted as a change in diastalic compliance. Lendrum, Feinberg, Boyd and Katz [19] using an iso-volumic contracting left ventricular preparation in the dog, found that for practical purposes ventricular volume, hence muscle fibre length, remained constant during rate and rhythm changes and therefore could not affect contractile strength.

Other reports have supported the view that altering the period between stimuli (paired stimuli) causes an increase in diastolic compliance as well as increased contractility [2,15,31]. It was suggested that a compliance change during relaxation and diastole is a physiological variable that should be considered as one determinant of cardiac performance [2]. It has also been observed that the degree or augmentation occurring with myocardial contraction is greater the earlier the extra-depolarization is introduced [12,19,32). The mechanism responsible for the pronounced effects of paired electrical stimulation on myocardial contraction remains to be defined, although it has been suggested that the additional activation may promote increased availability of calcium at the contractile sites [14].

The isolated perfused beating rat heart preparation can be studied in a modified Langendorf system adapted for mechanical studies using a differential force transducer [5,6]. With this isovolumic prepara-