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EDITORIAL

The Bainbridge effect: stretching our understanding of cardiac pacemaking for more than a century

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The heart is the engine of blood circulation, so it should not be surprising that its vital role in maintaining life has evolved to be intricately autoregulated. When disconnected from the body's central nervous system, when transplanted into another body, and even when excised and kept alive by suitable perfusion through the coronary vasculature, the heart continues to beat. The spontaneous nature of the heartbeat is driven by rhythmic electrical excitation that is generated within the heart, first shown in *The Journal of Physiology* by Walter Gaskell in 1882 (Gaskell, 1882) to arise from a specialised tissue region at the cardiac inflow from the main systemic veins which, in mammals, is referred to as the sinoatrial node. Key aspects of cardiac output (blood volume pumped per minute) regulation are also maintained in isolated hearts: when venous return is increased (*in situ*, this occurs with every breath or change in posture, physical activity, etc.), there is a compensatory increase both in stroke volume (blood ejected during a single beat) and in heart rate (number of beats per minute).

Discovery of the former response (the 'Frank–Starling law of the heart') is generally credited to Otto Frank (for a translation of his seminal work on frog heart into English, see Sagawa et al. (1990)) and Ernest Starling (who described the relationship between ventricular stroke volume and end-diastolic volume in mammalian hearts in a series of influential papers in *The Journal of Physiology* at the start of the last century; Knowlton & Starling, 1912; Markwalder & Starling, 1914; Patterson & Starling, 1914; Patterson et al., 1914).[1]

The latter response, i.e. the chronotropic effect of mechanical load, was confirmed by Francis Bainbridge in a famous paper published in *The Journal of Physiology* in 1915, in which he showed that right-atrial distension leads to an increase in heart rate (Bainbridge, 1915).[2] In celebration of *The Journal of Physiology*'s 600th volume, we are highlighting the lasting importance of Bainbridge's seminal observations.

In his 1915 paper, Bainbridge increased venous return by rapid intravenous fluid injection into the jugular vein of dogs, which caused an acute increase in heart rate. Bainbridge also measured arterial blood pressure (via a catheter in the carotid artery) and central venous pressure (via a catheter in the iliac vein near its opening into the posterior vena cava). This showed that the positive chronotropic response of the heart was related to a change in venous – and, by implication, right atrial – but not arterial load (increased arterial blood pressure would be expected to trigger the baroreceptor-mediated Bezold–Jarisch 'depressor reflex' and cause a reduction in heart rate; Jarisch & Richter, 1939; von Bezold & Hirt, 1867). Bainbridge found that a doubling of central venous pressure gave rise to a roughly 30% increase in heart rate. Bainbridge's findings were confirmed a few years later by Sassa and Miyazaki, also in *The Journal of Physiology*, who further showed that increased mechanical tension along the atrial wall, caused by distending the auricles and the great veins with an inflatable balloon, was sufficient to induce the observed increase in heart rate (Sassa & Miyazaki, 1920).

The response was subsequently demonstrated to occur also in humans by Ian Roddie and colleagues in a paper published in *The Journal of Physiology* in 1957 in which they showed an acute increase in heart rate in healthy human volunteers when raising venous return by passive elevation of the legs, importantly in the absence of a simultaneous rise in arterial pressure (Roddie et al., 1957). Since that time, an increase in heart rate in response to elevated atrial load has been demonstrated in a multitude of animals across the vertebrate and invertebrate phyla (Quinn & Kohl, 2012), including most recently in zebrafish (MacDonald et al., 2017), demonstrating the evolutionary conservation of this fundamental, auto-regulatory response.

Originally, the positive chronotropic response to stretch seen by Bainbridge was thought to occur solely through an extracardiac, centrally mediated reflex, as it could be abolished by transection of the vagi and cardiac sympathetic nerves and ligation of the suprarenal veins (ruling out a major role for circulating catecholamines from the adrenal medulla; Bainbridge, 1915). However, it has been shown since that an increase in pacemaker rate upon stretch also occurs in the isolated heart (Tiitso, 1937), right atrial tissue (Blinks, 1956), sinoatrial node (Deck, 1954), and even single pacemaker cells (Cooper et al., 2000), indicating that intracardiac mechano-electric coupling mechanisms (such as stretch-activated ion channels; Cooper et al., 2000) are a key contributor (Quinn & Kohl, 2021).

So, where does this fit into our understanding of cardiac pacemaking? It is now well-accepted that the heart's automaticity is driven at the cellular level by mutually entrained oscillators (also referred to as coupled 'clocks'), including trans-membrane ion currents and intracellular calcium cycling. That

[1]The attribution to Frank and Starling, while thoroughly established, is not without question, as earlier work such as a study published by Charles Roy in one of the first issues of *The Journal of Physiology* in 1879 had already shown that for '…each contraction of the ventricle … the quantity of blood thrown out depends on the degree of distension during diastole'; Roy, 1879.

[2]Again, this effect had been demonstrated some 50 years earlier by Stezinsky and von Bezold, who showed that an increase in venous return in rabbits with decentralised hearts resulted in sinus tachycardia; Stezinsky & von Bezold, 1867.

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understanding has been developed, however, largely through investigations of mechanically non-loaded sinoatrial node cells and tissue. In the beating heart, cyclic changes in atrial volume and tissue tension, in large part caused by cyclic changes in ventricular volumes, result in an oscillation of mechanical load. In diastole, the sinoatrial node is stretched, accelerating the onset of the next heartbeat. The Bainbridge effect thus appears to act as an additional oscillator that contributes to pacemaking, tuning automaticity to haemodynamic demand and, potentially, entraining pacemaker cell activity across the electrophysiologically heterogeneous sinoatrial node (MacDonald & Quinn, 2021).

Overall, Brainbridge's demonstration of sinoatrial node mechano-sensitivity has become an essential consideration for understanding the control of cardiac output. Yet even a century after the publication of Bainbridge's transformative paper, the precise subcellular mechanisms responsible for this intrinsic chronotropic effect remain to be elucidated (Izu et al., 2020).

To conclude – the Bainbridge effect is a crucial modulator of heart rate, vital for cardiovascular system autoregulation: when venous return to the heart is increased, it is beneficial that the next contraction cycle is initiated earlier than would otherwise have been the case. In this way, along with a greater ejection on the next beat via the Frank–Starling response, the Bainbridge effect allows the heart to match cardiac output to changes in venous return on a beat-by-beat basis.[3] The Bainbridge effect appears to influence cardiac rhythm over a broad range of mechanical loads: while mechanically unloaded sinoatrial node tissue often shows no or irregular spontaneous activity and moderate stretch restores rhythmicity, excessive stretch can result in arrhythmic responses (Lange et al., 1966). This suggests that a solid understanding of the Bainbridge effect and its underlying mechanisms is important not only for insight into cardiac automaticity and autoregulation, but also holds potential as an under-appreciated therapeutic target for the treatment of sinoatrial node dysfunction. So, 100 years on, the relevance of the Bainbridge effect remains, and continues to stretch our basic understanding of cardiac autoregulation.

[3]During haemodynamic challenges that increase both venous return *and* arterial pressure, elevated heart rate via the Bainbridge effect also opposes potentially detrimental effects of the Bezold–Jarisch reflex by preventing excessive bradycardia or over-distension of the right atrium.

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Additional information

Competing interests

None.

Author contributions

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