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Hugo Kronecker and the Dependence of Heart Function on Blood Supply

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Hugo Kronecker (1839–1914) (Fig. 1) was born in Liegnitz, a Silesian town that, at the time, belonged to the Prussian kingdom. He became interested in mathematics and natural sciences very early on. He studied medicine in Berlin, Heidelberg, and Pisa, and received the M.D. degree in Berlin. Even while a student in Heidelberg he had contact with Hermann Helmholtz (1821–1894) and Wilhelm Wundt (1832–1920). Beginning in 1868, he worked in the Leipzig Physiological Institute with Carl Ludwig (1816–1895). He received the habilitation (permission to lecture) in 1872 with a thesis on fatigue and recovery of skeletal muscle.[1] Since he was fluent in French, English, and Italian, he took care of the many foreign young scientists who visited or worked in the Leipzig Physiological Institute and created an international atmosphere. In 1878, he moved to Berlin to become department director in the Physiological Institute of du Bois-Reymond (1818–1896). In 1885, he was appointed chairman of Physiology at the University of Bern, Switzerland. There he built a new Institute of Physiology which he named "Hallerianum" in memory of the eighteenth century physiologist Albrecht von Haller (1708–1777) who was born in Bern and had worked there for some time.

Kronecker was instrumental in the planning of the first International Physiological Congress, which took place in 1889 in Basel, Switzerland. He was also involved in the founding of the international research station on top of the Monte Rosa mountain and carried out many studies on high-altitude physiology. Although he covered many topics in different research areas, his main interest was focused on cardiac physiology.

In the study in which he showed the dependence of heart function on blood supply, he originally extended the experiments conducted by Henry P. Bowditch (1840–1911) in the Leipzig Physiological Institute.[2] In the course of these studies he did experiments on the isolated perfused turtle heart. The preparation he used was similar to that created by Elias Cyon some years earlier[3] for the isolated frog heart.[4] The perfusate entered the ventricle via one of the caval veins from a Mariotte flask and was ejected into the aorta, where the pressure could be recorded by a manometer. Kronecker used a double-barreled, two-way cannula that allowed rapid and complete washing of the ventricle.

This isolated turtle heart was perfused with bloody rabbit serum that had been shaken (*Pf S* in top recording of Fig. 2). The height of the contraction amplitudes showed that the ventricle functioned well (I, top recording in Fig. 2). When the same heart was perfused with sodium chloride (*Pf K*, top recording in Fig. 2) for 90 s, the contraction amplitudes became smaller in an irregular manner until the heart came to a complete standstill (III, top recording in Fig. 2). The heart could easily be resuscitated when blood was added to the saline perfusion medium, that is, when red blood cells and the normal ionic constituents were provided (bottom recording in Fig. 2). Heart function could be completely abolished four times by saline perfusion and completely restored by addition of the bloody perfusion medium. Kronecker concluded that heart function is critically dependent on the supply of oxygen-containing blood in the perfusate.[5]

The results of Kronecker were confirmed by Merunowics,[6] who conducted experiments on frog hearts. Bloody saline (one part of freshly defibrinated rabbit blood plus four parts of 0.6% NaCl) induced a positive chronotropic effect and rhythmic contractions of the apex of the frog heart. Continuous perfusion with pure saline (0.6% NaCl) led to cardiac arrest after different periods of time. In this situation, neither electrical nor mechanical stimuli could elicit contractions; however, when bloody saline was used, rhythmic contractions reappeared.[6]

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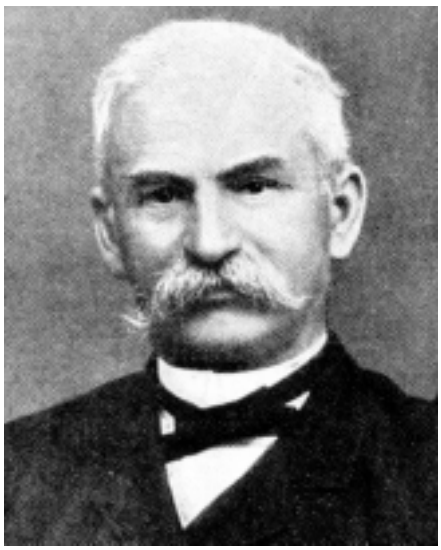

FIG. 1 Hugo Kronecker (1839–1914). Reproduced from Ref. No. 1 with permission of the publisher.

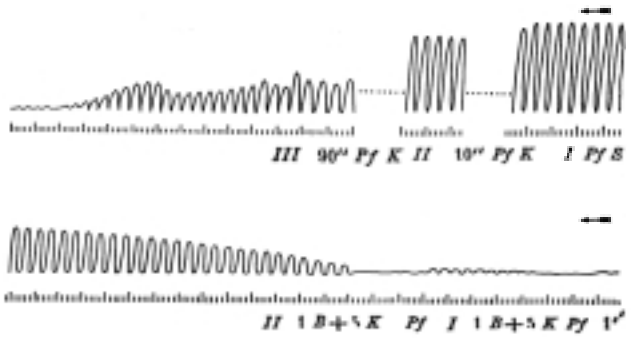

FIG. 2 Recordings (from right to left, respectively) from an isolated turtle heart. The heart was filled with blood-containing serum (top recording, right, *Pf S*). When this was replaced with sodium chloride (*Pf K*), the contractions became lower until beating stopped (top recording, left). When a 1:5 blood-sodium chloride mixture (1 *B* + 5 *K Pf*) was infused, heart function was restored (bottom recording). Combined original Figures 25 and 26 from Ref. No. 5.

Isolated perfused frog and turtle heart preparations were necessary to discover the dependence of heart function on blood.[2–4] The hearts of these animals do not have coronary arteries, so that deficiency in oxygen and in the normal ion constituents could be induced by exchanging blood with saline solution. In the intact animal, oxygen deficiency could only be brought about by coronary artery ligation, which was done in the dog and in the rabbit.[7] This intervention, however, was complicated by arrhythmias and cardiac death so that no conclusion as to the effect of blood supply could be made. In fact, Julius Cohnheim (1839–1884), who was pathologist at Leipzig, inferred from these in vivo studies that a toxic substance must have been generated during ischemia that induced arrhythmia and cardiac arrest.[7]

Kronecker's approach to affecting heart function by rapidly exchanging the perfusion fluid was a new experimental design in studies on the isolated heart. By replacing bloody perfusion medium with saline it was, however, not possible to discriminate between the effects of the deficiency in oxygen supply and in extracellular calcium ions on cardiac contraction. Both deficiencies may have contributed to the slowdown and ultimately arrest of contractions (Fig. 2). It was about 20 years later that Sidney Ringer (1835–1910) used this approach in studies in which he perfused the isolated frog heart with solutions deficient in calcium ions. The time course of the reduction in contraction amplitude and the occurrence of cardiac arrest that he observed[8] was quite similar to that obtained by Kronecker (Fig. 2).

In the isolated mammalian heart, the effect of blood supply to the coronary arteries was first shown by Langendorff (1853–1908). In his preparation, the coronary arteries were perfused retrogradely; the left ventricle was nonworking and was beating empty. He demonstrated that cessation of coronary blood flow leads to loss of contraction and that restoration of blood flow results in the resumption of contraction.[9, 10] Metabolic studies on the isolated perfused working rat heart preparation[11] were done about 90 years after Hugo Kronecker's experiments. From this sequence of historical events, the credit must be given to Kronecker for being the first who examined the effect of blood and its constituents on heart function and thus for initiating studies on cardiac metabolism.

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