Cardiac Output: Since When, Who, and How?

By Max E. Valentinuzzi and Ron S. Leder

No doubt at all, arterial blood pressure is absolutely necessary, but if there is no flow or if it is hindered, the whole system faces deep trouble. Thus, you had better have a good pumping action. Ocassionally, people forget this truth.
—Max E. Valentunuzzi

Ancient Rome had a rather complex hydraulic network formed by aqueducts for its water supply and for waste. The system provided a constant stream to central areas, in contrast to modern systems, which deliver water on demand to individual connections. It certainly was a marvel of engineering accomplishment. The date of the first aqueduct is estimated to be 312 BC, and it had nine channels. Whenever possible, these aqueducts followed a steady downhill course. The amount of delivered water has been estimated to have been within the ample range of 322,000–1,010,623 m^3/day, or about 67 L/day per capita. In comparison, today's residents of the United States use approximately 250 L per person per day, that is, roughly four times more [1].

It is philosophically interesting to pose one question: did the Romans have the concepts of pressure and flow? Obviously, in practical terms they did, but as we understand them today, it is doubtful.

Not everybody knows that Palenque, in the Mayan region of southern Mexico, also has one of the best-preserved systems of aqueducts, a unique architectural example. Most of the visible monuments in the plaza date to the period in which the great king Pakal ruled (ca. 700 AD), about 1,000 years after the Romans. The aqueduct is still visible and contains water from the Otulum River [2]. Around 1400 AD, that is, about 400 centuries later, the Incan Empire in Perú, South America, constructed another hydraulic system fed with water that came mostly from nearby rivers and from fresh-water springs on the mountains. Machu Picchu, the most famous of Incan archeological sites, contains a complex aqueduct system. The Incas demonstrated in these works a high degree of engineering skill in the careful gradation of the ducts [3].

The same question and comment come up: did the Mayas and the Incas have the concepts of pressure and flow? Obviously, while perhaps some communication between these two cultures could have occurred, no connection at all with the Romans appears as even thinkable.

Digital Object Identifier 10.1109/MPUL.2013.2279622
Date of publication: 6 November 2013

Blood Flow in Modern Times

Galen (129–ca. 216 AD), the famous Greek physician, failed to recognize the heart's role as a pump. Did he understand what hydraulic pressure or blood pressure were in physical terms? It took 15 centuries for Western science to discover the blood circulation [4]. Why did it take such a long time? This is a good question that some historians have tried to answer [5]. William Harvey (1578–1657) proved the circular motion of blood in the body in 1628, but he did not describe it in terms of pressure and flow [6]. Is that possible? Stephan Hales (1677–1761), slightly over 100 years later, in 1733, actually measured arterial pressure in inches of blood, but he did not refer to volume displacement per unit time, although he reported some volume values (as ventricular volume or total blood volume in horses) and carried out the first experiment on hemorrhaging [7]. Almost another century had passed when, in 1828, Jean Louis Marie Poiseuille (1799–1869) reported in his doctoral dissertation a series of blood pressure values in a few mammals, better expressed this time in millimeters of mercury. He came just a step away from the concept of flow by giving a value of 390 ft/min for blood velocity at the aortic root based on data from an author named Keill (no information could be found about him; the reference in Poiseuille's dissertation is incomplete) [8]. This figure is equivalent to 168 cm/s; the actual average value is in the range of 40–50 cm/s, i.e., roughly one-third of the former or, better, at 45 cm/s, a 1.8-cm diameter aorta would pass (45 × 3.14 × 0.81 × 60)/1,000 = 6.87 L/min, which is a rather typical output flow for a normal young male adult at rest. Why didn't Poiseuille take into account the aorta's cross section in his calculations to obtain

FIGURE 1 Fick, shown here in 1897, developed a method to measure mean cardiac output in the 19th century. (Image courtesy of www.wikipedia.org.)

XVI Sitzungsberichte für das Gesellschaftsjahr 1870.

XIV. Sitzung am 9. Juli 1870.

Inhalt: Fick: Ueber die Messung des Blutquantums in den Herzventrikeln. — Rinecker: Ueber Rötheln und Masern.

1) Das Protokoll der letzten Sitzung wurde verlesen und genehmigt.

2) Neu eingelaufene Bücher werden in Vorlage gebracht.

3) Hr. Dr. phil. Röntgen wird als Mitglied angemeldet.

4) Hr. Fick hält einen Vortrag über die Messung des Blutquantums, das in jeder Systole durch die Herzventrikel ausgeworfen wird, eine Grösse, deren Kenntniss ohne Zweifel von grösster Wichtigkeit ist. Gleichwohl sind darüber die abweichendsten Ansichten aufgestellt. Während Th. Young die in Rede stehende Grösse auf etwa 45ccm anschlägt, cursiren in den neueren Lehrbüchern der Physiologie meist sehr viel höhere Angaben, welche, gestützt auf die Schätzungen von Volkmann und Vierordt, sich bis auf 180ccm belaufen. Bei dieser Sachlage ist es seltsam, dass man noch nicht auf folgenden naheliegenden Weg gekommen ist, auf dem diese wichtige Grösse wenigstens an Thieren direkter Bestimmung zugänglich ist. Man bestimme, wie viel Sauerstoff ein Thier während einer gewissen Zeit aus der Luft aufnimmt und wie viel Kohlensäure es abgibt. Man nehme ferner dem Thiere während der Versuchszeit eine Probe arteriellen und eine Probe venösen Blutes. In beiden ist der Sauerstoffgehalt und der Kohlensäuregehalt zu ermitteln. Die Differenz des Sauerstoffgehaltes ergibt, wie viel Sauerstoff jedes Cubiccentimeter Blut beim Durchgang durch die Lungen aufnimmt, und da man weiss, wie viel Sauerstoff im Ganzen während einer bestimmten Zeit aufgenommen wurde, so kann man berechnen, wie viel Cubiccentimeter Blut während dieser Zeit die Lungen passirten, oder wenn man durch die Anzahl der Herzschläge in dieser Zeit dividirt, wie viel Cubiccentimeter Blut mit jeder Systole des Herzens ausgeworfen wurden. Die entsprechende Rechnung mit den Kohlensäuremengen gibt eine Bestimmung desselben Werthes, welche die erstere controllirt.

Da zur Ausführung dieser Methode 2 Gaspumpen gehören, so ist der Vortragende leider nicht in der Lage, experimentelle Bestimmungen mitzutheilen. Er will daher nur noch nach dem Schema der angegebenen Methode eine Berechnung der Blutstromstärke des Menschen geben, gegründet auf mehr oder weniger willkürliche Data. Nach den von Scheffer in Ludwig's Laboratorium ausgeführten Versuchen enthält 1ccm arterielles Hundeblut 0,146ccm Sauerstoff (gemessen bei 0° Temperatur und 1m Quecksilber Druck), 1ccm venöses Hundeblut enthält 0,0905ccm Sauerstoff. Jedes Cubiccentimeter Blut nimmt also beim Durchgang durch die Lungen 0,0555ccm Sauerstoff auf. Nehme man an, das wäre beim Menschen gerade so. Nehme man ferner an, ein Mensch absorbirte in 24h 833gr Sauerstoff aus der Luft. Sie nehmen bei 0° und 1m Druck 433200ccm Raum ein. Demnach würden in den Lungen des Menschen jede Secunde 5ccm Sauerstoff absorbirt. Um diese Absorption zu bewerkstelligen, müssten aber der obigen Annahme gemäss $\frac{5}{0.0555}$ ccm Blut die Lungen durchströmen, d. h 90ccm. Angenommen endlich, dass 7 Systolen in 6 Secunden erfolgten, würden mit jeder Systole des Ventrikels 77ccm Blut ausgeworfen.

FIGURE 2 Fick's communication to the Würburg's society described his new method (see [9].)

flow? It is difficult to understand, at least looking back now, from the 21st century.

Forty-two more years elapsed until Adolph Fick (Figure 1) described a method in 1870 to measure mean cardiac output. The method was described in a very short communication to the Society of Physics and Medicine in the city of Würzburg, Germany [9], [10]. An English translation was published many years ago by Hoff and Scott [11]. The method was also discussed in an article by Edward Shapiro [12]. Fick was the first to clearly introduce the concept of flow coming out of the cardiac pump (Figure 2). However, he never actually put it into practice because he lacked the means to do so. Human cardiac catheterization (to sample blood gas) was still many years away, even though Claude Bernard, on one hand and Jean Baptiste Auguste Chauveau and Etiènne Jules Marey, on the other hand, (all three in France) performed it for many years almost routinely in animals; Bernard started as early as 1844 [13], [16]. Fick's idea was first tested in dogs by Nestor Gréhant and Charles Eugene Quinquaud in 1886. They reported values of 591–2,614 mL/min for body weights ranging from 7 to 18 kg (Figure 3) [17]. This short communication clearly explains the procedure using CO_2 as physiological marker. Twelve years later, in 1898, Nathan Zuntz and Oskar Hagemann did it in the horse, reporting the results in a very long agricultural yearbook (Figure 4) [18].

The Direct Fick Method

Let us read what Fick said, reproduced from the translation given in [12], although the version given by Hoff and Scott in 1948 [11] is more literal. Those readers with some knowledge of German may compare the following paragraph against the original text shown in Figure 2:

> It is astonishing that no one has arrived at the following obvious method by which [the amount of blood ejected by the ventricle of the heart with each systole] may be determined directly, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time, and how much carbon dioxide it gives off. During the experiment one obtains a sample of arterial and venous blood; in both the oxygen and carbon dioxide content are measured. The difference in oxygen content tells how much oxygen each cubic centimeter of blood takes up in its passage through the lungs. As one knows the total quantity of oxygen absorbed in a given time one can calculate how many cubic centimeters of blood passed through the lungs in this time. Or if one divides by the number of heart beats during this time one can calculate how many cubic centimeters of blood are ejected with each beat of the heart. The corresponding calculation with the quantities of carbon dioxide gives a determination of the same value, which controls the first.

For a long time, Fick's method was a reference (actually, *the* reference), and it is called the direct Fick method. The total flow or cardiac output, $CO = F_t$, exits the left ventricle at high pressure, enters the right heart via the vena cava at very low pressure, is also expelled by the right ventricle at moderately low pressure, and finally, after circulating the body, returns to the right atrium at very low pressure again. If the lungs are considered a node (Figure 5), the continuity principle applied to blood (as the carrier, in mL blood/min) and oxygen (as the transported substance,

RECHERCHES EXPÉRIMENTALES SUR LA MESURE DU VOLUME DE SANG QUI TRAVERSE LES POUMONS EN UN TEMPS DONNÉ, par MM. GRÉHANT ET QUINQUAUD.

Le procédé que nous avons suivi consiste à prendre simultanément dans le cœur droit avec une sonde et dans l'artère carotide d'un chien deux volumes égaux de sang qui sont injectés dans deux récipients vidés d'air par deux pompes à mercure. L'extraction du gaz a été faite à une température de 60° ; nous avons dosé exactement le volume d'acide carbonique qu'ils renfermaient. Toujours comme cela a été souvent démontré le volume d'acide carbonique fourni par le sang veineux a été plus grand que celui qui était contenu dans le sang artériel.

FIGURE 3 The title and first paragraph of the communication presented by Gréhant and Quinquaud in 1886 to the Societé de Biologie. It says: "The procedure we have followed consists of taking with a sound (a probe, a catheter) simultaneously from the right heart and from the carotid artery of a dog two equal volumes of blood that are injected in a container emptied of air by a mercury pump. Extraction of gas was made at a temperature of 60°; we have dosed exactly the carbon dioxide acid there contained. As has always been frequently demonstrated, the volume of carbonic acid given by the venous blood was larger than that contained in arterial blood."

in mL O_2/mL blood) establishes in the steady state condition that

$$F_t[V] + F_{ox} = F_t[A] \quad [\text{mL } O_2/\text{min}], \tag{1}$$

where $[V]$ and $[A]$ stand for the concentration of oxygen in venous and in arterial blood, respectively, while F_{ox} represents the net oxygen uptake in $[\text{mL } O_2/\text{min}]$ via the respiratory system. Solving for F_t results in

$$F_t = F_{ox}/\{[A] - [V]\} \quad [\text{mL blood/min}], \tag{2}$$

which is the famous and well-known Fick's formula. Instead of oxygen, carbon dioxide can be used, as Gréhant and Quinquaud used in 1886. Those familiar with electric circuits will find this similar to the total current converging to and diverging from a node (Kirchhoff's current law) [19]. After all, recall that current is nothing but the amount of electric charge per unit of time (1 amp = 1 coulomb/s), and in (1), we have the amount of oxygen also per unit of time. The numerator in (2) is usually obtained from a metabolimeter (a relatively easy measurement; Gréhant and Quinquaud probably used a water-sealed spirometer in 1886 to collect exhaled CO_2). A normal adult at rest may take up about 250 mL O_2/min. A sample of blood from any artery (the method, thus, requires arterial puncture) and, subsequent determination in the biochemistry lab, gives the arterial concentration of oxygen. The venous concentration of oxygen is not easy. Samples from a peripheral vein are not acceptable because the oxygen consumption varies greatly from tissue to tissue. A representative sample has to be a mixture coming from all tissues. Only the right atrium, or better, the right ventricle, or the best, the pulmonary artery carry venous blood meeting such a requirement. Hence, a probing catheter must be introduced to any of these vascular places to withdraw a few milliliters of blood to be tested in the lab for oxygen content (or carbon dioxide, should this gas be employed as marker). Typical expected normal values are 20 mL O_2/100 mL blood, for the oxygenated blood, and about 15 mL O_2/100 mL blood, for the mixture of venous blood. Thus, the arteriovenous difference is about five. These units are many times referred to by physiologists as so many milliliters of substance percent. When the above figures are replaced in (2), the result is a mean, steady-state value of 5 L/min. The latter is the typical normal figure for a resting adult male. However, the heart was "untouchable," and it took 60 years—from 1870 to 1930—to actually run the measurement in humans.

Pioneers in Physiology

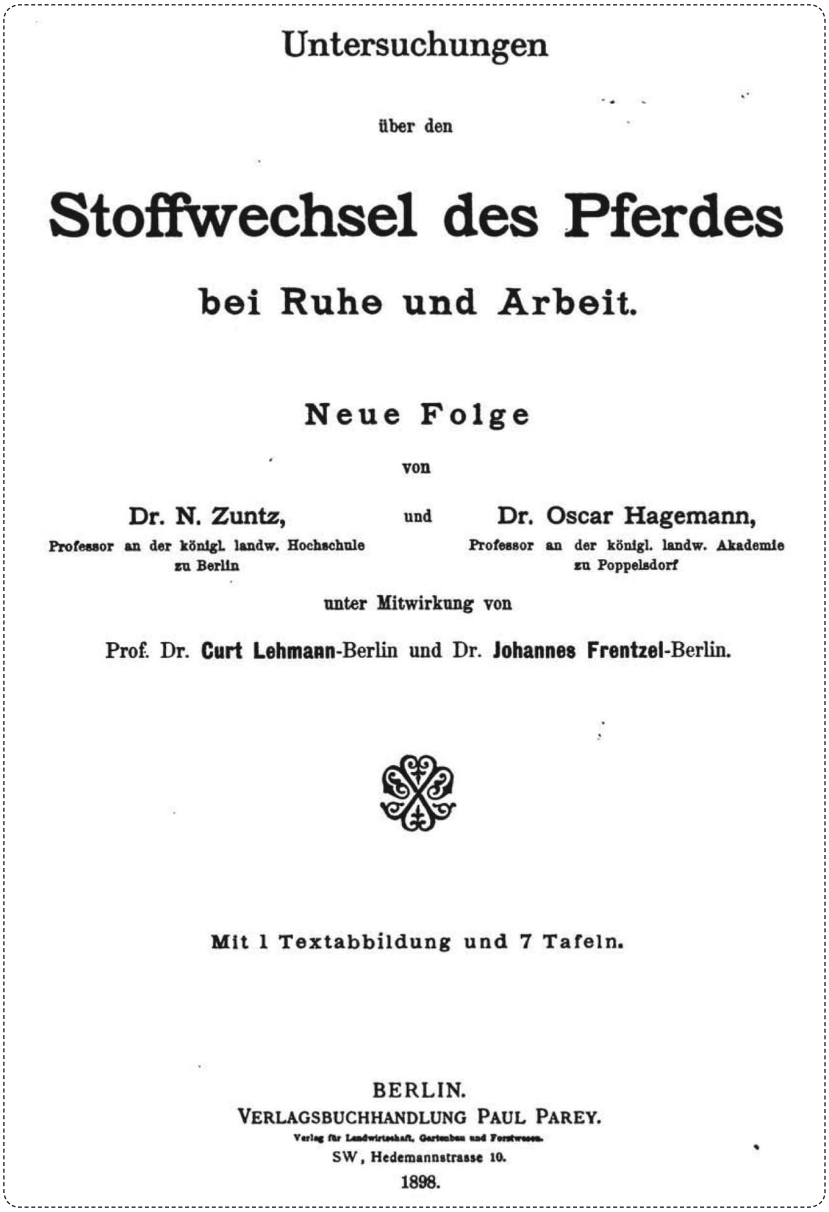
Let us say something about these people's lives, all of whom were important figures in physiology, even though some, perhaps, are less known; one way or another, they were active contributors to the essential concepts of blood flow and cardiac output. The Internet has several sites where more details can be found.

Adolph Fick

Adolph Fick (1829–1901) was born in Cassel, Germany. Very early on, he showed a remarkable talent for mathematics and physics, and when he enrolled at the University of Marburg, he manifestly wanted to acquire credentials in these disciplines. However, influenced by his brother Heinrich (a lawyer), young Adolph matriculated in medicine. Fick turned his attention to physiology, taking a prosectorship with Carl Ludwig in Zurich in 1852, when he was 23, remaining with him for 16 years [20]. Thereafter, Adolph moved to Würzburg as professor of physiology. Throughout his time in Zurich, Fick made several remarkable contributions, also showing interest in philosophy and literature. For example, his is the concept that diffusion is proportional to concentration gradient. Throughout his more than three decades in Würzburg, Fick produced a steady stream of papers [21], [22].

Claude Bernard

Claude Bernard (1813–1878) received his early education in the Jesuit school of his native town, Saint Julien, in France, continuing later in Lyon and becoming an assistant in a druggist's shop. He attempted without success to be a comedy and drama author. At the age of 21, in 1834, he went to Paris and decided to go medical school, coming in contact with the great physiologist François Magendie, whom he succeeded in 1855. Bernard's marriage to Marie Françoise "Fanny" Martin, arranged by a colleague for convenience, was unhappy and brought him many problems. However, physiology and medicine were enriched and significantly advanced by his outstanding contributions. In 1868, Bernard was incorporated into the Academie Française and to the Royal Swedish Academy of Sciences. Louis Napoleon helped him by building a laboratory at the Muséum National d'Histoire Naturelle in 1864. Upon his death, the nation honored him with a public funeral. His tomb is in Paris, at the famous Père Lachaise Cemetery (Figure 6), where many distinguished people rest in peace, for example, the musician Frédéric Chopin. Bernard liked philosophy, and many memorable thoughts can be found in his musings, for example, *Le chercheur devrait prendre des précautions extrêmes pour ne pas trouver ce que l'on cherche* (the researcher should take extreme precaution not to find what he or she is looking for)—good advice indeed. For years, he wrote his ideas and thoughts in a notebook—*le cahier rouge*, or the red notebook, because the cover was red [23].


Untersuchungen

über den

Stoffwechsel des Pferdes

bei Ruhe und Arbeit.

Neue Folge

von

Dr. N. Zuntz, Professor an der königl. landw. Hochschule zu Berlin

und

Dr. Oscar Hagemann, Professor an der königl. landw. Akademie zu Poppelsdorf

unter Mitwirkung von

Prof. Dr. Curt Lehmann-Berlin und Dr. Johannes Frentzel-Berlin.

Mit 1 Textabbildung und 7 Tafeln.

BERLIN.
VERLAGSBUCHHANDLUNG PAUL PAREY.
Verlag für Landwirtschaft, Gartenbau und Forstwesen.
SW, Hedemannstrasse 10.
1898.

FIGURE 4 The Zuntz and Hageman publication, *Investigations on the Exchange of Substances in the Horse Under Resting and Working Conditions*, has contributions from Curt Lehmann and Johannes Frentzel. It was published in Berlin by the editorial house Paul Parey in 1898.

Jean Baptiste Auguste Chauveau

Jean Baptiste Auguste Chauveau (1827–1917) was born in Villeneuve-la-Guyard, France. He was educated at École Nationale Vétérinaire d'Alfort and then École Nationale Vétérinaire de Lyon, where, at the age of 21, he became part of the staff and became the school's director in 1875. Later, in 1886, he was appointed to the position of professor at the Muséum National d'Histoire Naturelle in Paris. With Étienne-Jules Marey (1830–1904), he studied different phases of the cardiac cycle and intracardiac pressures and played a significant role in cardiac catheterization. He was a master experimenter. As with Claude Bernard, the ire of many antivivisectionists became a deeply disturbing headache for him due to his experiments on animals [24].

Etiènne-Jules Marey

Etiènne-Jules Marey was a native of Beaune, France, and died in Paris. In 1849, he enrolled at the Parisian Medical School, qualifying as a medical doctor in 1859. A few years later, in 1864, he set up in a small laboratory to study the circulation of the blood, publishing *Le Mouvement dans les Fonctions de la Vie* in 1868. From 1863 on, Marey perfected his *methode graphique*. By means of polygraphs and similar recording instruments, he analyzed the human and equine gait and the flight of birds and insects. His works were significant in the development of cardiology, physiology, physical instrumentation at large, photography, and cinema. For example, he developed the sphygmograph to measure arterial pulse. In 1890, Marey produced the book *Le Vol des Oiseaux* (*The Flight of Birds*). The Internet abounds with sites full of details about his highly productive scientific life.

Louis François Nestor Gréhant

Louis François Nestor Gréhant (1838–1910) is less known. The information given here was taken from a publication with no clear-cut identification, but it was quite complete and written by Marie-Thérèse Cousin [25]. Gréhant was born in Laon, France, where he started secondary studies, which he finished later in Paris at the Napoleon Lyceum (now Louis le Grand). Thereafter, Gréhant studied physics, ending up in medical school with a doctoral thesis combining both fields (1864). However, he never went into clinical practice. He assisted Claude Bernard from 1865 to 1868, collecting invaluable laboratory experience. In addition, he completed a second dissertation in natural sciences in 1870. In 1893, he was appointed professor of physiology, having produced several outstanding papers in several subjects.

Charles Eugene Quinquaud

Charles Eugene Quinquaud (1841–1894) was a physician born in Lafat, Creuse, a commune in the Creuse department in the Limousin region in central France. He entered medical school in Limoges in 1864 and, in 1868, moved to Paris, where he obtained his doctorate in 1873. He was elected member of the Académie de Médecine in 1892. Quinquaud contributed in many areas of medicine—being a skilled bacteriologist as well as a clinician—and alongside Nestor Gréhant (1838–1910), they became very active in the scientific community. In 1880, 1885, and 1887, Quinquaud won academic prizes for his works. He was editor of the journal *La Médecine Scientifique* [26].

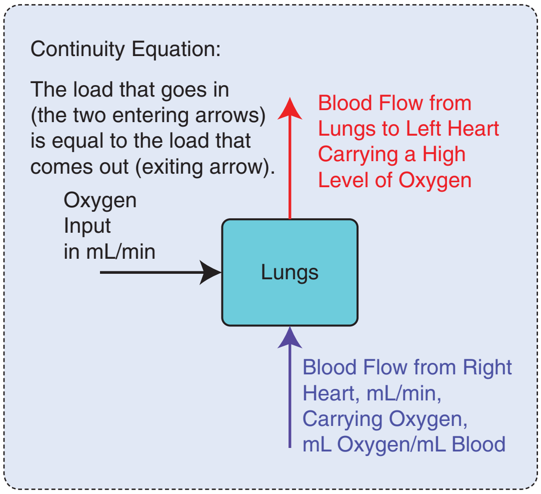


FIGURE 5 In the Fick principle or continuity equation, the lungs are considered a node. The amount of material (oxygen, in this case) that goes into the node in the steady state equals the amount that comes out, always per unit of time. See (2) and the text for unit details.

Nathan Zuntz

Nathan Zuntz (1847–1920) was born in Bonn, Germany. His father was a merchant and a scholar of Hebrew history. Nathan, the eldest of 11 children, was recognized early as possessing a scientific inclination. Yet, his first job was as an apprentice in a Bonn bank. An apt scholar, he was able to read the Bible in Hebrew at an early age. After finishing the gymnasium (an advanced high school in Germany) at 17, Nathan entered medical school at the University of Bonn, where he studied chemistry under Friedrich August Kekulè (1829–1896), physics under Rudolf Julius Emanuel Clausius (1822–1888), and physiology under Eduard Friedrich Wilhelm Pflüger (1829–1910), all three magnificent researchers and highly respected professors. Pflüger supervised Zuntz's doctoral thesis, "Beitrage zur Physiologie des Blutes (Contributions to the Physiology of Blood)," in 1868. In 1870, Zuntz became an assistant to Pflüger while being appointed also as privatdozent in physiology at Bonn. In 1874, he became an extraordinary professor of anatomy at the Medical Faculty of Bonn University, where he remained for six more years. In 1880, Zuntz moved to Berlin to occupy the chair of animal physiology at the Landwirtschaftliche Hochschule, giving up his medical practice. Soon, Prof. Oskar Hagemann, who was already famous for his research on horses, joined the group. It was Zuntz's idea that there should be intermingling of the specialties in the attack on larger research problems (a good bioengineering philosophy). Younger investigators were attracted to this laboratory not only from Germany but from other countries. They found Zuntz to be a man of keen understanding and wisdom and a helpful and kind person. Zuntz's talent in devising methods and constructing apparatuses was superb, with an extraordinary knowledge of the literature of the times. In 1908, he spent the summer at the School of Agriculture of Cornell University in Ithaca, New York. His major investigations were on the subjects of blood and blood gases, blood circulation, mechanics and chemistry of respiration, general metabolism, and nutrition. Over 29 years, he measured his own basal metabolism. The two most complete accounts of Zuntz's career are found in [27] and [28]. However, most of this information was taken from [29], where we found the following striking story:

> Joseph Barcroft (1872–1947), British physiologist, gives an insight into the academic environment in those days in Germany. Barcroft was puzzled for the incomplete studies of the effect of innervation on muscle metabolism that had been done by Zuntz, certainly not well fit to his personality, and Barcroft asked Zuntz why, during a meeting in Teneriffe. To which Zuntz replied: "When I started those experiments, I was assistant to Pflüger in Bonn. He came to my lab one day and finding me at work precisely in that subject he said, 'Well, but you have not asked my permission to do this. Either you stop these experiments or leave my laboratory.' Since I was not in a position to leave the laboratory, I stopped the project."

Oskar Hagemann

Oskar Hagemann (1862–1926) was a well-reputed and active veterinarian (Figure 7) [30] who obtained his degrees (medical veterinary and doctorate) in Berlin (Hochschule and University, respectively). He was a veterinarian for the German Army and was involved in World War I as a veterinarian, even occupying leading responsibilities. (Recall that horses were important components of armies in those days.) Hagemann reached the high positions of rector to the Landwirtschaftlichen Hochschule Bonn-Poppelsdorf (Agricultural High School) and director of the Institut für Anatomie, Physiologie, und Hygiene der Haussäugetier (Institute of Anatomy, Physiology, and Hygiene of Domestic Mammals). For a considerable time, he was a close collaborator of Zuntz, with whom he published several papers.

FIGURE 6 Unfortunately, Claude Bernard's tomb in Paris at Père Lachaise Cemetery, seen here in 1997, is not well kept and is rather hidden. (Photo courtesy of Max E. Valentinuzzi.)

FIGURE 7 Oskar Hagemann in his lab in Bonn, Germany, 1910. The appliances and hardware seen would be compatible with large animal experimentation. (Image courtesy of the National Library of Medicine.)

Cardiac Output in the 20th Century

It is quite amazing, but after the concept was clearly established in 1870, the new century began with scientists having determined the average cardiac output only in canine and equine hearts. Still, 30 more years had to pass before the human heart was reached with a catheter. The many tests and measurements made in animals had not been enough to convince physiologists and physicians that, indeed, the procedure was harmless if properly carried out, and the heart was considered forbidden territory, which is difficult to understand, at least with a 21st-century mind-set. A detailed account of the history of right heart catheterization is found in [31].

In 1929, Werner Theodor Otto Forssmann was the first to introduce a catheter in his own right heart via the brachial vein, so demonstrating the feasibility of the procedure in the human being and paving the way to cardiac output determinations. In 1956, he shared the Nobel Prize with André Frédéric Cournand (1895–1988) and Dickinson Woodruff Richards (1895–1973), although he was severely reprimanded by his superior medical chief for breaking hospital rules at the time. The two latter researchers had started their studies at Bellevue Hospital in New York, resulting in the development of a technique for catheterization of the heart carried out in a series of tests during the 1940s (see the two Nobel lectures by Cournand and Richards from December 1956, which are freely available on the Web with all the scientific references, some of which are also given herein) [32], [33]. Richards' own words say, as quoted from his Nobel lecture:

Originalien.

Aus der II. Deutschen medizinischen Universitätsklinik in Prag. (Vorstand: Prof. Dr. W. Nonnenbruch.)

Zur Bestimmung des zirkulatorischen Minutenvolumens beim Menschen nach dem Fickschen Prinzip.

(Gewinnung des gemischten venösen Blutes mittels Herzsondierung.)

Von Priv.-Doz. Dr. O. Klein.

Zur Bestimmung des Minutenvolumens des Herzens nach dem Fickschen Prinzip beim Menschen, war es bisher notwendig, den Gasgehalt des gemischten, venösen, in die Lunge einfließenden Blutes auf indirektem Wege zu ermitteln. Die Methode von Fick beruht bekanntlich darauf, das Volumen der in einer Minute vom Herzen geförderten Blutmenge aus der Größe des Lungengaswechsels und der Differenz im Gasgehalt zwischen arteriellem und venösem Blute zu berechnen.

Des Näheren geht man dabei so vor, daß die Differenz des Sauerstoffgehaltes des arteriellen und des gemischten venösen Blutes oder die Differenz des Kohlensäuregehaltes zwischen venösem und arteriellem Blut bestimmt wird, die Sauerstoffaufnahme bzw. die Kohlensäureabgabe in den Lungen pro Minute festgestellt und diese Größen miteinander in Beziehung gesetzt werden: [1])

$$\text{Min.-Vol.} = \frac{G\ O_2 \times 100}{O_2\,(a)\,\% - O_2\,(v)\,\%} \quad \text{oder Min.-Vol.} = \frac{G\ CO_2 \times 100}{CO_2\,(v)\,\% - CO_2\,(a)\,\%}.$$

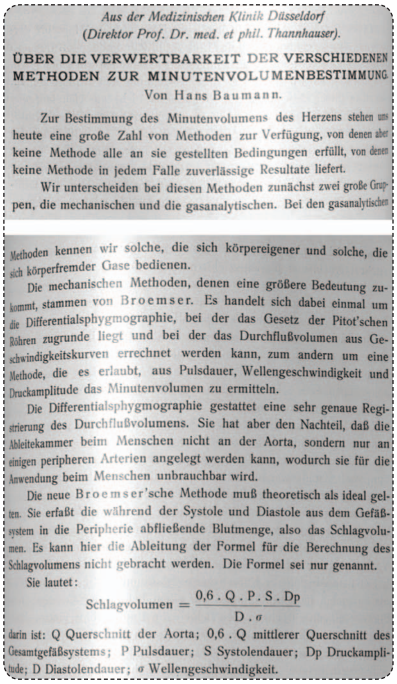
$G\ O_2$ = Sauerstoffverbrauch pro Minute. O_2 (a) = Sauerstoffgehalt des arteriellen Blutes. O_2 (v) = Sauerstoffgehalt des gemischt-venösen Blutes. $G\ CO_2$ = CO_2 Abgabe pro Minute CO_2 (v) = CO_2-Gehalt des venösen Blutes. CO_2 (a) = CO_2-Gehalt des arteriellen Blutes.

FIGURE 8 The first paragraphs of Klein's communication clearly show a simple mathematical expression and its description, either by oxygen or carbon dioxide determinations. The first sentence says: "To determine the heart minute-volume via Fick's Principle in the human being, it was essential to measure the gas content of mixed venous blood entering the lungs" (see [36]).

We were aware of the earlier experiment of Forssmann and had followed closely its isolated uses in Germany, Portugal, South America, and France. It suffices for me to say that late in 1940, Cournand and Ranges took up the catheterization technique, showing in their initial studies that consistent values for blood gases could be obtained from the right atrium, that with this, cardiac output could be reliably and fairly accurately determined by the Fick principle, and furthermore that the catheter could be left in place for considerable periods without harm.

However, in 1930, Otto Klein (1881–1968) measured cardiac output in humans by the direct Fick method, obtaining venous samples with a cardiac catheter (Figure 8) [34]. In 1938, because of his Jewish origin, Dr. Klein had to resign his academic post, and soon after in 1939, he left Germany, going to Argentina. There, Dr. Klein worked at

FIGURE 9 Otto Klein worked for many years at the Durand Hospital, in Buenos Aires. This photo was taken in 1980. Currently, it is one of the city's big health centers. (Image courtesy of www.wikipedia.com.)



Aus der Medizinischen Klinik Düsseldorf
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ÜBER DIE VERWERTBARKEIT DER VERSCHIEDENEN METHODEN ZUR MINUTENVOLUMENBESTIMMUNG.

Von Hans Baumann.

Zur Bestimmung des Minutenvolumens des Herzens stehen uns heute eine große Zahl von Methoden zur Verfügung, von denen aber keine Methode alle an sie gestellten Bedingungen erfüllt, von denen keine Methode in jedem Falle zuverlässige Resultate liefert.

Wir unterscheiden bei diesen Methoden zunächst zwei große Gruppen, die mechanischen und die gasanalytischen. Bei den gasanalytischen Methoden kennen wir solche, die sich körpereigener und solche, die sich körperfremder Gase bedienen.

Die mechanischen Methoden, denen eine größere Bedeutung zukommt, stammen von Broemser. Es handelt sich dabei einmal um die Differentialsphygmographie, bei der das Gesetz der Pitot'schen Röhren zugrunde liegt und bei der das Durchflußvolumen aus Geschwindigkeitskurven errechnet werden kann, zum andern um eine Methode, die es erlaubt, aus Pulsdauer, Wellengeschwindigkeit und Druckamplitude das Minutenvolumen zu ermitteln.

Die Differentialsphygmographie gestattet eine sehr genaue Registrierung des Durchflußvolumens. Sie hat aber den Nachteil, daß die Ableitekammer beim Menschen nicht an der Aorta, sondern nur an einigen peripheren Arterien angelegt werden kann, wodurch sie für die Anwendung beim Menschen unbrauchbar wird.

Die neue Broemser'sche Methode muß theoretisch als ideal gelten. Sie erfaßt die während der Systole und Diastole aus dem Gefäßsystem in die Peripherie abfließende Blutmenge, also das Schlagvolumen. Es kann hier die Ableitung der Formel für die Berechnung des Schlagvolumens nicht gebracht werden. Die Formel sei nur genannt.

Sie lautet:

$$\text{Schlagvolumen} = \frac{0{,}6 \, . \, Q \, . \, P \, . \, S \, . \, Dp}{D \, . \, \sigma}$$

darin ist: Q Querschnitt der Aorta; 0,6 . Q mittlerer Querschnitt des Gesamtgefäßsystems; P Pulsdauer; S Systolendauer; Dp Druckamplitude; D Diastolendauer; σ Wellengeschwindigkeit.

FIGURE 10 Baumann's communication does not refer too much to Fick's idea. It begins by saying: "For the determination of the minute-volume of the heart, there are today a large number of methods, however, no one meets the necessary conditions nor offers satisfactory results." He does not seem to be aware of the previous contributions of Gréhant and Quinquaud and Zuntz and Hageman.

the Durand Hospital [35] in Buenos Aires (Figure 9). He retired in 1951 because of severe health problems. Very little is known about his life afterward other than he traveled to Vienna and did some studies on the composer Brahms. Apparently, he returned to Argentina, where he died in Buenos Aires in 1968, survived by his wife.

H. Baumann, another German physician, for all that we could find out, independently produced a paper on cardiac output in 1930 [36]; it is more or less a brief review displaying many doubts, while offering a comparative numerical table of results (Figure 10). Unfortunately, no biographical details about the author could be located. Did the Nobel Prize Committee know about these previous contributions? It is not fair when recalling Otto Klein's contributions [37]. [An irrelevant coincidence: the Durand Hospital in Buenos Aires is over 100 years old; it serves the neighborhood where coauthor Max E. Valentinuzzi was born and lived for many years, the Almagro Quartier.]

Forssmann was raised under traditional, strict Prussian values: honesty, respect for the law, and surrender of self-interest to the common good. The experiments by the French physiologists convinced him that inserting a catheter into the human heart was as safe for humans as it was for animals. Cautiously, Schneider, his boss, encouraged Forssmann to run experiments on animals to test the safety of the procedure—but for what reason? Forssmann strongly believed in the experiment and without a shred of doubt performed the catheterization on himself [38]. After all, it had been done so many times before in mammals. With the help of a coworker, he punctured his left cubital vein, inserted a well-lubricated ureteral catheter into the vein, and pushed the catheter up. A week later, Forssmann repeated the experiment by himself and experienced a sensation of warmth on the wall of the vein when he moved the catheter. With the catheter in his heart, he walked from the operating room downstairs to the X-ray room, where he proceeded while moving the catheter with the help of a nurse. After his report, a number of papers were published over approximately three years using catheterization for cardiac studies. There was some opposition, and the method was discredited by some people, which led to another ten years passing before Cournand and his coworkers proved that heart catheterization was not merely a clinical curiosity but a safe and sound procedure to study cardiac physiology. Meanwhile, Forssmann catheterized himself nine more times, hoping to get a publishable angiograph of himself, but to no avail. As before, the response of the academic community ranged from laughter and disbelief to admiration, as in [39], which was authored by Forssmann's daughter, who was also a physician. It is a touching narrative full of personal details that tell the inside face of scientific activities.

TABLE 1. TYPICAL CARDIAC HEMODYNAMIC PARAMETERS

Measure	Typical Value	Normal Range
End diastolic volume (EDV)	120 mL	65–240 mL
End systolic volume (ESV)	50 mL	16–143 mL
Stroke volume (SV)	70 mL	55–100 mL
Ejection fraction (E_f)	58%	55–70%
Heart rate (HR)	75	60–100 beats/min
Cardiac output (CO)	5.25	4.0–8.0 L/min

Discussion and Conclusions

The "why not?" questions brought up do not have definite answers beyond mere conjectures. Why did it take 60 years (1870–1930) to reach the human application of Fick's idea, especially when cardiac catheterization had been practiced in animals since 1840? Insufficient technology was obviously a factor, but a lack of basic knowledge was undoubtedly another. A third factor may have been the relative slowness of communications (as compared to what we enjoy today) plus many mere human weaknesses, prejudices, or even sheer envy [40], [41]. We might also add the psychological aspects often influencing human decisions to accept or reject a given concept.

The whole development was unfortunately stained by disbelief, lack of information if not sheer ignorance, prejudices, and even perhaps a competitive spirit; it was significantly delayed, and recognition injustices took place. In the meantime, other techniques were introduced. The measurement of blood flow as a local parameter has its own history, and we do not want to overload this article with excessive words and more references, especially because herein the objective was to give a historical bird's-eye view of the output of the heart as a simple pump, in a somewhat reductionistic approach.

After all, *errare humanum est* while *divinum ignoscere*, and so the world keeps moving. Today, one can walk into a clinic, have a noninvasive Doppler study or other imaging method and, in fewer than 60 min, walk out with hemodynamic data like those displayed in Table 1, which are relevant to evaluate heart performance. We should be glad to live during these times.

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PERSPECTIVES ON GRADUATE LIFE *(continued from page 11)*

This is a really frustrating problem when your effort does not necessarily correlate with your generated data and forward progress on your project. Having said all that, while it is frustrating that you have to work even more when your experiments are not progressing, you really do not have many other options. Sadly, I guess it is just part of the training process and something with which every graduate student has to deal. Therefore, in terms of maintaining a work–life balance in the lab, it seems that you must hope for some luck so that your experiments work with at least some frequency to maintain both progress on your project and in your personal life.

I am not sure how to solve the work–life balance problem. Maybe just start the conversation about it earlier? Set expectations for number of hours worked? Attempt to assess what you want your life to be like in five, ten, or 20 years? I guess there is no clear answer. It varies from individual to individual, but I hope to figure it out for myself someday.

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