Carl Ludwig's (1847) and Pavel Petrovich Einbrodt's (1860) physiological research and its implications for modern cardiovascular science: translator's notes relating to the English translation of two seminal papers

Jochen Schaefer[a], Brigitte Lohff[b], Janke-Jörn Dittmer[a]

[a] International Institute for Theoretical Cardiology (IIfTC), Kiel
[b] Institute for the History, Ethics and Philosophy of Medicine, Medical School Hannover, Germany.

ABSTRACT
Respiratory interactions with the heart have remained a challenging physiological phenomenon since their discovery more than two hundred and fifty years ago. In the course of translating the seminal publications of Carl Ludwig and his disciple Pavel Petrovich Einbrodt into English, we became aware of some under-appreciated aspects of their work that contain useful insights into the history of the phenomenon now called respiratory arrhythmia. Ludwig observed arrhythmic effects of respiratory movements in experiments on dogs and horses and published his findings in 1847. He subsequently undertook further work on this problem, together with Einbrodt.

Already in 1847 Ludwig had mentioned an exciting observation on the possible role of mechanical factors of the respiratory movements on the action of the heart in a dog in whom he had artificially induced bouts of coughing. Einbrodt decided to systematically develop methods to increase or decrease the pressure of the air the animal had to breathe. He observed that this procedure led to a greater or lesser degree of compression or decompression of all the organs in the thoracic cavity without apparently causing harmful consequences during the time of its application.

How the mechanical influence of breathing affects cardiac activity during respiratory arrhythmia has been the subject of scientific discussions and controversies over a period of more than 150 years and is still unresolved. Recent publications suggest that cardiac mechano-electrical coupling plays an important role in the emergence of cardio-respiratory interdependence.

Keywords: Respiratory arrhythmia – Heart rate variability - Cardiac mechano-electrical coupling – Philosophy and history of science

1. Introduction

What can modern cardiovascular science learn from publications on cardiovascular and cardiopulmonary physiology dating back more than 150 years? This question pertains to the paper of Carl Ludwig: "Contributions to the knowledge of the influence of the respiratory movements on the circulation of blood in the aortic system" (1847) and to the paper of Pavel Petrovich Einbrodt[1]: "On the influence of the respiratory movement on heartbeat and blood pressure" (1860).

Ludwig and his co-worker Einbrodt provided a wealth of observations through their animal experiments that relate to the direct mechanical influence of respiration on the heart. These findings, however, were quickly pushed into the background, as a model of a nervous regulation of cardiac activity mediated by respiration – *via* the vagal and sympathetic nervous system – seemed more convincing, and explained these phenomena at the organism (rather than organ) level. This interpretation thus provided the prerequisite for the concept of respiratory arrhythmia – a variation in heart rate during the respiratory cycle. Experiments were performed to verify or disprove a direct influence of mechanical factors on cardiac activity (Titso and Tootson, 1935; Hammouda, 1937). The notion of direct cardiac "*Mechano-Elektrische Rückkoppelung*" ('Mechano-Electric Feedback'),

[1] We decided to take for our translation the German spelling of the name of *Einbrodt* and not its Russian representation *Ějnbrodt*.

however, only began to truly gain momentum after R. Kaufmann and U. Theophile (1967) showed the influence and impact of direct mechanical stimuli on cardiac tissue. The concept of mechano-electric feedback has since benefitted from extensive experimental confirmation that there is indeed intrinsic mechano-electric transduction in cardiac tissue (Kohl and Ravens, 2003, Lab, 2006).

In the following, we wish to elaborate on biographical data of Ludwig and Einbrodt and explain the main aspects of their publications pertaining to the phenomenon of respiratory arrhythmia. In addition, we will contemplate some epistemological particularities and pursue the question of why their findings were "forgotten" during the development of cardiovascular science. For a better understanding of the German-English texts, we shall put some technical remarks at the end of these translators' notes.

2. Biographical sketch of Carl Friedrich Wilhelm Ludwig (1816 – 1895)

Carl Ludwig was born in Witzenhausen/Germany (Schröer, 1967, Kahle, 1987, Beneke, 2005). From 1834 until 1839 he studied medicine at the Universities of Marburg, Bamberg, and Erlangen. He obtained his MD degree in 1840 with a thesis on the effectiveness of cod-liver oil. Ludwig started his scientific career in the Department of Chemistry with Wilhelm Bunsen and one year later became a prosector with Ludwig Fick in the Department of Anatomy. In 1842 he published his PhD thesis on the blood vessels of the kidney. In his paper he described for the first time the physiological function of the glomeruli. During this period Ludwig became engaged in studying the physiology of the circulation and its measurement. Three years later he was appointed Associate Professor of Comparative Anatomy at the University of Marburg/Lahn.

Ludwig cultivated a close friendship with Hermann von Helmholtz, Emil Du Bois-Reymond, and Ernst Brücke, the then young generation of German physiologists. In 1847 Ludwig constructed and described in detail the kymographion (Chaderevian, 1993), a device that could record the blood-pressure curve as a function of time [(Ludwig, 1847) pp. 243-244, 257-267, figures 1 to 5, plate I]. Two years later he was appointed Professor of Anatomy and Physiology at the University of Zürich/Switzerland. In 1855 he moved to Vienna as Professor of Physiology and Zoology at the Surgical-Medical Military Academy (*Josephinum*). At age 36, Ludwig wrote an influential compendium of physiology based on a mechanistic view of the organism in which he stated: *"Scientific physiology has the task to ascertain the performances of the animal organism and to deduce those same with necessity from their elementary condition."* [(Ludwig, 1852) p. 1]. Ludwig dedicated his handbook of physiology to his friends Ernst Brücke, Emil Du-Bois-Reymond, and Hermann von Helmholtz, the so called physical society (Lohff, 1996). In 1865, he was offered the Chair for Physiology at the new Institute of Physiology in Leipzig, which he accepted and held until his death in 1895.

In Leipzig, Ludwig gained enormous influence on the development of physiology in Europe and the United States of America (Lenoir, 1988). Within the next 25 years, more than 200 students from Germany and abroad studied and worked at the Ludwig laboratory, including: Ivan Petrovich Pavlov, Heinrich Irenäus Quincke, Julius Bernstein, Ernst Mach, Hjalmar Öhrvall, and William H. Welch. Otto Frank (1865-1944) devoted himself at the Ludwig Institute to studying the pressure-volume relationship of the heart and was able to describe mathematical deductions through systematic measurements (Sagawa et al., 1990, Lohff, 1999). Together with Elias Cyon, Ludwig studied heart function using the isolated perfused heart (1868) and together with his disciple Henry Pickering Bowditch (1840-1911) he discovered the *all or none-law* of the heart (1871) and the *staircase-phenomenon* (for review, see (Schaefer et al., 1992)). In cooperation with Luigi Luciani (1840-1904) he investigated the phenomenon of the non-tetanisability of heart muscle (1872). Ludwig carried out numerous additional studies on the anatomy and physiology of the cardiovascular system, for example, on the genesis of the first sound of the heart, cardiac innervation, nervous regulation of blood-pressure, the filtration theory of urine function, gland secretion and secretory nerves, and the absorption and metabolism of fat, protein, and sugar. Ludwig also constructed the first mercury vacuum blood gas pump (1859)[2], and in 1868 an improved version of this device (Schröer, 1967, Gerabek, 1991, Beneke, 2005). Furthermore, the Ludwig school in Vienna and Leipzig served as a model for scientific teamwork in the 20th century.

3. Biographical sketch of Pavel Petrovich Einbrodt (1833-1865)

He was born in Moscow, November 5, 1833 (or possibly 1835) (Fischer, 2012). After having attended secondary school, Pavel Petrovich studied medicine at the Medical Faculty of the University of Moscow (1851-1857). The University of Moscow was founded in 1765, but had been meagrely endowed until the mid-19th century. From the middle of the century onwards, however, a policy shift occurred that allowed the Medical Faculty in Moscow and the Medical-Surgical Academy in Petersburg to become leading centres of medicine in Russia (Pfrepper, 2009). Einbrodt received a doctoral degree with a thesis entitled: *De pericarditide acuta* (‘*Acute pericarditis*’). In 1857 he became Assistant of the Prosector at the Institute of Anatomy.

In the 19th century it was attractive for many young prospective scientists from the United States of America and other European States to come to France or Germany for their further training. Einbrodt, endowed with a stipend from the Russian ministerial government, went to Berlin and to Vienna, which were home to the most modern research institutes in physiology at that time.

At the Institute for Physiology at the Friedrich-Wilhelm-University in Berlin, Emil Heinrich Du Bois Reymond (1818-1896) acquainted Einbrodt with the most recent research results in experimental neurophysiology. At the *Josephinum* in Vienna he carried out research with Ludwig on the influence of the respiratory movements on the heartbeat and blood pressure. In the 1860s Einbrodt was promoted to an Extraordinary Professorship position for Physiology at the University of Moscow.Only one year after his appointment as Full Professor for Physiology in 1864, Einbrodt died on July 6, 1865 in Montreux and was buried in the cemetery of Vvedenskie Gory, Moscow.

4. Carl Ludwig: Contributions to the knowledge of the influence of respiratory movements on the circulation of blood in the aortic system

In his publication of 1847, Ludwig worked with the new recording device that he had developed (later called the *kymograph*), to establish whether it was suitable for reliably registering simultaneous physiological parameters such as blood pressure and respiration. His apparatus offered, for the first time, the possibility to demonstrate the mechanical influence of respiration on the activity of the heart and, thus, to measure and assess the relations between blood pressure and pulse on the one hand and respiration on the other hand. The results which he published were obtained in hundreds of measurements on the horse and dog. In the course of his experiments, Ludwig made and described several additional discoveries, which – as described below – have hitherto not been attributed to Ludwig’s paper of 1847, but were ascribed to later “re-discoverers”.

4.1. Description of important results and discoveries

Carl Ludwig used the kymograph to pursue a research topic in warm-blooded animals. He could show that blood pressure increased with expiration and decreased with inspiration (Chadarevian, 1993, Beneke, 2005).

Ludwig correlated the (simultaneous) measurements of pulse pressure and respiratory movements and thereby laid the foundations for quantitatively analysing the phenomenon of respiratory arrhythmia. Ludwig tried to explain the observed phenomena without the detailed knowledge of basic physiological mechanisms such as:

- baroreceptors, which were discovered by Heinrich Hering (Hering, 1923);
- chemoreceptors, which were discovered by Jean-François Heymans and his son Corneille Jean François Heymans at the end of the 1920s (Heymans, 1938) (Corneille Heymans received the

[2] The invention of the vacuum mercury gas pump provided the basis for all consecutive devices for measuring the O_2 and CO_2 content of blood and tissues. Thus, this methodology became also the backbone for further developments in cardiovascular science until the 1960s (Astrup and Severinghaus, 1986, Severinghaus, 1993).

Nobel-prize for Physiology or Medicine *"for his discovery of the role of the sinus and aortic mechanism for the regulation of respiration"* in 1938);
- pulmonary mechanoreceptors (or the Hering-Breuer-reflex) (Hering, 1868, Breuer, 1868);
- central nervous respiratory or circulatory centres, or the electrical phenomena which govern the activity of the heart (Eyster and Meek, 1921).

Thus, Ludwig attempted to analyse basic mechanical factors in order to understand the interdependencies between breathing or coughing and heartbeat. Since then, many casuistic and systematic studies have shown that coughing can be helpful in improving the bradycardia and hypotension that may occur after intracoronary injections of contrast medium and can even enable a patient to maintain consciousness during episodes of ventricular fibrillation (Criley et al., 1976) and asystole (Wei et al., 1980).

Ludwig further speculated on a relationship between body size and heart rate (Schmidt-Nielsen, 1999). Maybe it was an "advantage" not to be confounded by the abundance of later knowledge and data acquisition that might, by its complex nature, obscure very basic mechanisms. It seems as if he extracted the role of mechanical influences of breathing on the activity of the heart solely by analysing the recorded curves.

4.2. Summary of Ludwig's discoveries

- Textual descriptions and first experimental application of the kymograph [(Ludwig, 1847) pp. 257-267; fig.1-5].
- Exact measurement of pressure in the pleural space [(Ludwig, 1847) pp. 243, 257-267].
- Respiratory arrhythmia in its various manifestations in the horse and in the dog [(Ludwig, 1847), Plate XII; fig.15)].
- Experiments for mechanically assessing pressure in the thoracic cavity [(Ludwig, 1847) pp. 250 ff.].
- The effect of sectioning the vagus nerve on pulse rate and its regularity [(Ludwig, 1847) p. 253].
- The effect of coughing on the heartbeat [(Ludwig, 1847) p. 255, Plate XIII; fig.19].
- The relationship between body-size and heart rate [(Ludwig, 1847) pp. 256-257].
- Exact time measurement up to 1/100 of a second, allowing for a measurement error of pendulum amplitude [(Ludwig, 1847) p. 264].

5. Pavel Petrovich Einbrodt: On the influence of the respiratory movements on the heartbeat and blood pressure

At the session of the Viennese Academy of Sciences on April 12, 1860, Carl Ludwig, at this time Professor for Anatomy and Physiology at the Surgical-Medical Military Academy at Vienna, presented the comprehensive manuscript of his Russian-born guest scientist Pavel Petrovich Einbrodt, as only members of the Academy were allowed to speak. The 60-page manuscript had appeared already in the same year in the minutes of the proceedings of the Viennese Academy of Sciences under the title: *Über den Einfluss der Athembewegunqen auf Herzschlag und Blutdruck.* Einbrodt not only resumed the work carried out by his mentor Ludwig in 1847 and critically discussed the methodological approaches used at the time, but also expanded the experimental scope by presenting a device to alter the respiratory pressure within the lungs and the bronchial tree during an experiment, enabling the researcher to control the mechanical pressure of the lungs exerted on the heart (Einbrodt used this methodology on dogs).

5.1. Respiratory Arrhythmia

Einbrodt discussed how he had to deal with the fact that his experiments were contradicting the prevailing hypotheses on the influence of breathing on heart rhythm:

"This shall become our duty all the more as the facts obtained from the experiments mentioned above contradict current assumptions on the influence of normal breathing, which I do not have to repeat here. – It is, thus, our obligation to examine these assumptions once more, and if they should be confirmed, to pursue the reason for the observed contradiction." [(Einbrodt, 1860) pp. 406 ff.].

Einbrodt continued with the following considerations:
"(a) During the inspiration, the number of heart beats will be increased, which is becoming particularly evident at the end of the inspiratory movement. The acceleration of the heart beats during inspiration is a nearly regular phenomenon and not uncommonly so pronounced that it can be verified well without finer equipment by the mere laying of the hand on the chest in the cardiac region." [(Einbrodt, 1860) p. 408].

"On the other hand, the facts on the influence of breathing that we have presented [here] partly contradict the hitherto generally accepted assumptions, since we have found that the increase in blood pressure only takes place at the onset of expiration and is yielding in its further course to a decrease. In contrast to this [our findings] it is taught that blood pressure rises during the total duration of the expiration, moreover that the number of heart beats decreases during the expiration; however, increasing during the course of the inspiration, whilst it is assumed, that the expiration is accelerating the heartbeat, whereas the inspiration is slowing it down. Furthermore, that in the course of inspiration there is an augmentation of the blood pressure, whereas one has until now believed, that the inspiration is reducing the average value of the blood pressure." [(Einbrodt, 1860) p. 410].

Thus, it is evident that the phenomenon of respiratory arrhythmia has indeed been systematically investigated as early as in 1860 (Aikele, 1998).

5.2. Description of important results and discoveries
Einbrodt discussed at length the evidence of a direct mechanical influence of respiratory movements on the activity of the heart, which led him to new insights on the relation between respiratory pressure and pulse:

"*Positive respiratory pressure [+RP] changes the beat sequence of the heart ... in a twofold manner, by at one time producing a direct stimulation of the heart and secondly inducing an excitation of the vagus nerve.* [(Einbrodt, 1860) p. 373].
If one considers a little bit closer [this] behaviour in the number of heart beats with persisting +RP, then it will be readily evident that [this is not] a simple influence. And by analysing the circumstances closer, one becomes convinced that the +RP is effective in two directions: 1) by inducing a direct stimulation of the heart and 2) by the excitation of the Vagus. If one assumes these two effects of the +RP as really existent, then one can easily deduce the diverse behaviour in the number of heart beats with persisting +RP from their mutual interaction, considering the facts that have become known by the simultaneous stimulation of the heart and the N. vagus with induction currents. Let us contemplate the reasons a little bit closer that seem to support our assumption. [(Einbrodt, 1860) p. 374.].
The quoted observations seem to justify our assumption of a direct stimulation of the heart, and I only want to emphasise that the pressure of the lung on the outer surface of the heart should probably be regarded more as a favouring element, whilst the true cause of the stimulation is taking place on the inner surface of the heart and can be deduced from the blood flowing in under pressure. […]. *Now the heart is being compressed from the inside and the outside through blood and lung. It, thus, has to introduce a vigorous action (movement); likewise the live heart will beat more quickly, when it is squeezed between the fingers*." [(Einbrodt, 1860) p. 375].

5.3. Summary of Einbrodt's discoveries
The following can be ascribed to Einbrodt as first experimental observations. They are presented here, with the caveat that additional historical research is needed to verify and complete the list:

- First description of a cardiac catheterisation of the right atrium by a flexible tube: *"The first mentioned effect, that is the elevated tension under which the organs in the chest cavity located at the outer surface of the lungs will be placed in consequence of a +RP is accessible to direct measurement. To do this, I chose for easily obvious reasons the right atrium, into which I introduced an elastic catheter via the vena jugularis externa"* [(Einbrodt 1860) pp. 369, 373].
- First description of using a balloon (vesicle) to change the pressure in the right atrium: *"If one introduces, namely, as I have done in an experiment with a dog, a catheter into the right*

atrium via the vena jugularis externa at the end of which is lashed a fine vesicle (the urinary bladder of a rabbit) and attempts to inflate the bladder in the right atrium through the hollow catheter, one will observe the very same phenomena as with the +RP. Also, here the arterial blood pressure will experience an increasing reduction with a growing inflation." [(Einbrodt, 1860) p. 370]. (Roughly 100 years later, Otto Gauer (1909-1979) used the technique of placing a balloon in the right atrium for his studies on the circulatory basis of fluid volume control (Gauer and Henry, 1963)).

- Increase in brain pressure in response to the bradycardia following stimulation of the vagus nerve [(Einbrodt, 1860) pp. 377-379, 383, 414 ff]. This phenomenon was taken up again and discussed 50 years later (Rickl, 1927).
- Description of the effect of opium on the respiratory brain centre [(Einbrodt, 1860) pp. 364, 383-384, 407].
- Generating a negative respiratory pressure by applying a graduated vacuum [(Einbrodt 1860, pp. 363, 368, 398-400].
- Direct stimulation of the heart in concert with negative respiratory pressure [Einbrodt, 1860) pp. 373 ff., 402-403, 412].
- Einbrodt mentions the execution of a classical *Valsalva* manoeuvre on himself [(Einbrodt, 1860) p. 384], without being aware that the *Valsalva* manoeuvre had been previously described (Valsava, 1704).[3]

6. Methodological, epistemological, and history of science aspects in the analysis of both publications (1847 and 1860)

Of potential interest for the medical historian, as well as scientists of today, are the reflections of Ludwig and Einbrodt on the meaningfulness and validity of their own experimentally obtained data. Furthermore, their epistemological thoughts on their results have not lost their significance after more than 150 years. The visionary nature of their reflections becomes evident in light of new experimental data on mechanical transduction in the heart that were presented at the recent Mechano-Electric Coupling (2013) conference in Oxford, showing that classifying these into an integrated and holistic concept at the organism level remains challenging [(Ravens, 2013) p.61]. Thus, we are confronted with the question of why Ludwig and Einbrodt have been "forgotten".

6.1. Strategy and pattern of scientific argumentation in Carl Ludwig's paper

Ludwig always respected the work of his pupils and took care to point out to the reader the students' share of participation in experiments and studies. For example, he justified in the spirit of good scientific practice why he could use the data obtained by his pupil Gerau, supplementing them by his own new data that had been attained by more precise measurements with "better devices". In other words, Ludwig's insistence on exact measurements was for him an indispensable prerequisite before he allowed himself to infer scientific conclusions from inaccurate data: "*All hypotheses that easily flow out of the presently available data material are of such doubtful value and confute each other even at a superficial reflection, that one justifiably will exempt me from rebutting or confirming them"* [(Ludwig, 1847) p. 256]. Ludwig's statements concerning the conclusions and generalisability of experimentally obtained results characterise his style of research: *"As to answering the question to what extent the phenomena described in this paper can be applied to humans, we allow ourselves the remark that the difference is found in the appearance of the dog and of the horse"* [(Ludwig, 1847) p. 256]. The question of transferability of data attained in an animal model to humans allowed him to offer as explanation a possible association: The pulse curve of a dog might be compared to that of a child, and a horse to that of a grown-up.

Ludwig freely and openly exposed the results of his research for interpretation and discussion. This type of scientific dialectic characterised the generation of investigators during that era. It is one of the

[3] See also our translators' note in Chapter 5.1. As to the missing mention of the *Valsalva* manoeuvre, one might add as a possible assumption that Antonio Maria Valsalva (1666-1723) primarily was referred to in connection with his main opus *De aure humana* (1704) which was mostly perceived as an anatomical investigation of hearing.

central reasons for the success of the Leipzig School in the advancement of European and American physiology under Carl Ludwig.

6.1.1. Questions on the missing reference to earlier research results

Descriptions of the influence of respiration on the arterial pulse are usually ascribed to Stephen Hales' experiments of 1733.[4] We can only speculate why Ludwig did not comment on the first observations of the peculiarities of and the influences on the pulse by the phenomenon of respiratory arrhythmia published by Steven Hales (1677-1761). A possible answer might be that Hales in both his volumes of *Vegetable Staticks* (1724/25) and *Haemostaticks* (1733) compiled an abundance of observations without discussing the rules or "laws" governing the observed phenomena. The collection of observations alone had been a minor goal for the generation of young physiologists gathering around Ludwig in the mid-19th century. Ludwig wanted to establish a measuring, science-oriented, experimental physiology. Perhaps Ludwig did not know of these older observations, as experimental physiology emerged only during his lifetime. Perhaps Ludwig might not have regarded publications from the early 18th century as helpful for his new concept of experimental physiology. Textbooks from which the physiologists of this period could draw their knowledge and stimulation for new investigative research were Johannes Müller's: *Handbuch der Physiologie* (1833-1840) and Albrecht von Haller's: *Elementa physiologiae corporis humani* (1757–1766). Referring to older literature had been cultivated in the lexica in the mid-19th century, but it had not been of central importance. Ludwig had been fascinated by a physiology based on measurements. Hales had collected a wealth of observations on the activity of the heart, but had not evaluated them and brought them into an overriding context of physiological functions.

6.1.2. "Missed inventions"

Another interesting question is why Ludwig apparently did not recognise that he had created a rather simple technique for avoiding or abolishing a pneumothorax (air trapped next to the lungs within the thoracic cavity). The diagnosis of this phenomenon was well known since the middle of the 14th century. The French physician Marc Gaspard Itard described the phenomenon in detail in 1803 (Laennec, 1819). Physicians since Hippocrates knew the risk to patients suffering from a pneumothorax. Iatrogenic pneumothoraxes were given to people with tuberculosis in an effort to collapse a lobe, or entire lung, around a cavitating lesion. This was known as "resting the lung" (Sim and Keogh, 1993). The introduction of a chest tube into the thoracic cavity, which Ludwig used to measure the intrapleural pressure, bore this risk, but could also easily be turned into a therapeutic tool by applying suction to it, thus creating a reduced pressure and abolishing the pneumothorax. Instead, Ludwig tried a "treatment" for pneumothorax by exerting an external compression on the chest walls [(Ludwig, 1847) pp. 258-261]. It took several more decades before Gotthard Bülau (1835-1900), an internist in Hamburg, published his method of using a vacuum to remove the air from the thoracic cavity in order to treat a pneumothorax (Bülau, 1891).

6.2 Strategy and pattern of scientific argumentation in Pavel Petrovich Einbrodt's paper

Only 13 years after the publication of Ludwig's paper, Einbrodt presented a systematic examination of respiratory arrhythmia. Einbrodt attributed the need for further study to the complexity of the phenomenon and the challenges associated with conducting experiments in a living organism. Here is how Einbrodt and Ludwig formulated it in their paper:

"Under the influence of breathing, the beat sequence of the heart and the pressure of the blood undergo a change that has experienced until now neither a correct interpretation nor a sufficient explanation.[....] Two determining reasons seemed to make it advisable to resume anew the topic that I have already treated earlier. Foremost was the desire for an explanation of the phenomena, in which I had not succeeded 12 years ago, on the basis of the present state of knowledge of science; next to that I had, however, convinced myself by some preliminary experiments, that [...] in comparing the pulse and respiratory curves a mistake had crept in. [....] The phenomena which undergo modification as a result of the respiratory movements, and which initially come into question with regard to the

[4] A detailed analysis of his original works of "Statical Essays" (1726/27; 1733), however, show, that this observation apparently was made during an experiment in a dog already in 1706/7 and has been referred to by Hales himself in Statical Essays containing Vegetable Staticks [(Hales, 1726) pp. III, 255-258].

influence of breathing, elude more precise analysis, because they are all composed of different and at the same time always changing elements, the occurrence of which can therefore never be observed individually; the sequence of heartbeats, for example, is well known to be derived from many basic elements, being affected by the excitability of the heart (its muscles, nerves, and motoric centres), the degree of excitation of the prolonged medulla and of the vagus nerve, the animal's blood volume, which can vary over such a broad range, the temperature of the blood flowing into the heart, and so forth. Likewise the tension of the blood is a varying one, depending on the mass of blood that is at the disposal of the heart, and on the resistances in the capillaries, and on the amount of the developed cardiac forces that will be enacted for the benefit of the blood, etc. The respiratory movements themselves will exert a variable influence on the aforementioned circumstances, and, namely, on the blood distribution and the influx of blood to the heart, even in one and the same animal according to the depth and duration of its individual acts, and with different animals even with the same depth and duration of the latter one, depending on the particular constitutional conditions" [(Einbrodt, 1860) pp. 361-362].

Einbrodt also made a contribution to the presentation of experimental results in physiology by alluding to the superiority of graphical recordings versus the mere palpatory examination of the pulse [(Einbrodt, 1860) p. 383]. Thereby he stressed the importance of physiological methodology that was still in its infancy. He considered the registration of inner organic processes by means of the "objective" graphical record as essential for furthering scientific progress [(Schaefer et al., 2011) pp. 44-48; 84]. Einbrodt therefore developed a method and an apparatus by which he could induce positive, as well as negative, respiratory pressures against which the animal had to breathe. He was also able to vary and manipulate the extension and inflation or deflation of the lungs within the thoracic cavity, and thus influence the mechanical factors (pressure) that act on the heart and the great vessels.

Einbrodt's work on respiratory arrhythmia raised further questions, posed by Einbrodt himself: *"Therefore, we now have to try to investigate more closely the conditions of the observed data in order to resolve this contradiction and to substantiate the reasons for the similarities and the differences between the usual breathing and the artificially produced high respiratory pressure"* [(Einbrodt, 1860) pp. 410 ff.]. Einbrodt clearly stated that an experimentally obtained result does not have the same biological relevance as observations made in an organism or in a cardiovascular system performing under natural conditions. It is clear that he judged the value of his own experimental observations by contrasting them openly and frankly with the divergent results of other scientists at the time [(Einbrodt, 1860) pp. 383-384]. Leading scientific discourses in this manner is a distinguishing trait of nearly all experimental physiologists of this era. The resolution of the discrepancy between the interpretation of experimental findings of 1847 versus those of 1860 thus became a central concern of his entire paper. In this era it was also not unusual to perform self-observations [(Einbrodt, 1860) p. 413] within physiological experimentations, whereby it is interesting to note that Einbrodt could not observe a respiratory arrhythmia in himself during his self-experiment.

7. Historical reflection on loss of knowledge

It is an interesting historical question as to why in the years following Einbrodt's paper of 1860 the knowledge of a direct mechanical influence of the respiratory movements on the activity of the heart as well as the phenomenon of respiratory arrhythmia seemed at first to be disregarded or disputed and subsequently lost or forgotten.

In the years following Einbrodt's paper, knowledge dealing with direct mechanical stimulation of the heart apparently was becoming less important, possibly as a consequence of new insights that emphasised the role and impact of the vagus nerve and the sympathetic nervous system on cardiovascular function. In this context, the role that physiology textbooks have played is an important topic that has to be investigated more closely. For instance: did Ernst Wilhelm von Brücke, Carl Ludwig's friend and former Viennese colleague, allude to a possible mechanical effect of the respiratory activity on cardiac actions, without mentioning Einbrodt's paper of 1860 (Brücke, 1885)? In 1864, Carl Ludwig and his co-workers became concerned with the impact of nerves on blood pressure. Together with Elias Cyon (Ludwig and Cyon, 1866), they showed in 1865 that the splanchnic nerve has a central role in the regulation of the cardiovascular system. Breuer and Hering reported in 1868 that a persistent distension of the lungs of anaesthetised animals decreased the frequency of the inspiratory effort or caused transient apnoea (Hering, 1868, Breuer, 1868). Evidently, the state of stretch of the lungs at each moment is signalled to the respiratory centres. This sequence of events is called the Hering-Breuer-reflex. Bilateral transsection of the vagus nerve eliminates the Hering-Breuer-reflex (Schmidt and Thews, 1989). Demonstrating the reflex nature of respiration meant a departure from previous physiological understanding and changed the way scientists viewed the relationship and role of the lungs within the nervous system and the cardiovascular system. Additional aspects in studying the complex role of breathing frequency on the pattern of respiratory sinus arrhythmia and blood pressure attracted the interest of physiologists in the following years (Sharpey-Schafer, 1965) and more recently (Wei et al. 1980, Waxman et al., 1989 Wei et al. 1980).

The concept of mechanical *versus* nervous effects on cardiac activity, however, has continued to fascinate physiologists during the 20th century (Tiitso and Tootson, 1935, Hammouda, 1937). Newer publications[5] show that in transplanted hearts a non-autonomic mechanism of heart rate fluctuation with ventilation (Bernardi et al., 1990) or during execution of the Valsalva manoeuvre (Ambrosi et al., 1995) exists. Quite recently this complex of controversial themes has seen a new approach, bridging the gap between the theory of system dynamics, its application in modelling and characterising the dynamics of oscillators, (Voss, 2009, Sin et al., 2010) and testing its applicability in humans. *"The results obtained from physiological data reproduce the known physiological facts of the neuronal refractory phase as well as those of the respiratory sinus arrhythmia. In comparison with the coupling functions of numerical models they suggest that the underlying mechanism is associated with the immediate mechanical effect of the regular dynamics of respiration on the cardiac cells, for instance the sinus node cells. This relationship concurs with the explanation of the respiratory sinus arrhythmia by the phenomenon of mechano-electrical-feedback*" [(Kralemann, 2010) p.62, Kralemann et al., 2013)].

8. Technical remarks concerning the translation of Ludwig's and Einbrodt's texts and figures

Ludwig's and Einbrodt's contributions are examples of the cumbersome way in which scientific papers in the first half of the nineteenth century had been printed. It shows how illustrations were used and put together and how the practice of citation and print had developed before the advent of photography and digital print. This becomes particularly evident in the meticulous way in which Ludwig constructed the many highly detailed tables in which he compiled the hundreds of entries that he had recorded in his experiments. The same holds true for Einbrodt's tables in his publication of 1860. Unfortunately, the quality of the scans that were at our disposal did not allow us to use an optical character recognition system for transferring the data of the tables into a more readable and translatable grid. We therefore had to use the original German grids and enter the English translation into them.

Texts

In our translation, we have tried to preserve the style and the manner in which scientific publications used to be written in Germany one hundred and fifty years ago. In order to facilitate the direct comparison between the German original and the English translation, we placed the respective passages on opposite pages. In this endeavour it was not possible to succeed line by line because of the differences in the vocabulary and sentence structure of the two languages.

Footnotes are numbered consecutively in the translation of the text and not per page as in the German original. Our notes or explanations within the text are added in parentheses and italicized. Page numbers in the translation correspond to those in the German original. The tables themselves were supplemented or replaced with translations of German terms, abbreviations, and legends that correspond to the respective passages in the text.

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[5] Regarding this complex topic, we can only refer to individual publications which, of course, represent merely a small part of the literature.

The reader therefore requires some patience as the resulting English style remains "quite German". Some sentences and text passages proved difficult to understand in the German original and were almost untranslatable. We, therefore, had to split some sentences in order to make them intelligible.

There are some additional peculiarities: The nomenclature and writing used for anatomic structures and their orthography is different from today's: *e.g.* for *art. cruralis* or *Cruralis* we would now prefer to use femoral artery. Some confusion may also arise from the variant use of the terms for speed, velocity, or rate, vesicle, *etc*.

Plates and figures
At this time illustrations were summarised in "*Tafeln*" ('plates') and composed as groups of graphs and curves, which were designated as figures. The use of these different terms is confusing to the reader of today. In the German text and its English translation we have, therefore, put the plates at the end of the text. Since legends were at Ludwig's and Einbrodt's time apparently not yet in use for explaining and identifying the figures within the plates, we used the pertinent text passages as legends.

The plates X-XIV, showing the illustrations and curves which Carl Ludwig referred to in his article, were incorporated within an appendix at the end of the total volume together with other plates and charts from other articles in the volume. This appears to have been quite usual at his times and makes it difficult for readers of today.

The plate I (woodcarving) in Einbrodt's paper shows the illustration of the apparatus which Einbrodt had devised and used and the figures which Einbrodt is referring to. There seem to be, however, discrepancies in the numbering of some figures in the copies that were at our disposal.

9. German-English Translation of Carl Ludwig: *Beiträge zur Kenntnis des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme* [Contributions to the knowledge of the influence of the respiratory movements on the circulation of blood in the aortic system] http://dx.doi.org/10.1016/j.pbiomolbio.2014.08.001

10. German-English Translation of Pavel Petrovich Einbrodt: *Über den Einfluss der Athembewegung auf Herzschlag und Blutdruck* [On the influence of the respiratory movement on heartbeat and blood pressure] http://dx.doi.org/10.1016/j.pbiomolbio.2014.08.001

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