Carl J. Wiggers and the pulmonary circulation: a young man in search of excellence

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Reeves, John T. Wiggers and the pulmonary circulation: a young man in search of excellence. Am. J. Physiol. 274 (Lung Cell. Mol. Physiol. 18): L467–L474, 1998.—Oddly, Carl Wiggers (1883–1962), who is remembered for his work on the systemic circulation, may be considered the “American father of the pulmonary circulation.” In nearly 20 papers published in the American Journal of Physiology between 1909 and 1925, he reported the first reliable pressure contours in the pulmonary artery, inquired into the relationship between respiration and pulmonary arterial pressure, examined right atrial and right ventricular function, and demonstrated how right and left heart dynamics relate to heart sounds. He also stimulated direct visualization of the lung microcirculation. Method and concept are inextricably linked in the progress of science. His contributions to the pulmonary circulation were based on his high-fidelity pressure and sound recording instruments, which he ultimately applied in the left heart. Wiggers’ search for excellence in method brought him well-deserved fame in the systemic circulation, but the search began in the lung.

That the “American father of pulmonary circulatory physiology” was Carl J. Wiggers, M.D., is rather surprising because he is primarily remembered for his work on the systemic circulation. Yet he pioneered reliable pressure contours in the pulmonary artery, inquired into the relationship between respiration and pulmonary arterial pressure, examined right atrial and right ventricular function, and demonstrated how right and left heart dynamics relate to heart sounds. In the first quarter of the 20th century, he was an astonishingly productive researcher (18, 23–41, 43–46). In fact, beginning in 1908, at age 25, he published, by 1925, some 20 full-length articles that had to do with the pulmonary circulation and/or the right heart, and most of the articles were in the American Journal of Physiology. Two papers have been selected for emphasis here. His 1914 paper on the pulmonary pressure contour illustrates his intense, persistent drive for excellence of method (28). The second paper, which was done by a young colleague in the physiology department (13), was probably stimulated, and certainly encouraged, by Wiggers. The work involved direct visualization of the lung microcirculation, and it reopened a whole field of endeavor that had lain dormant for centuries.

It was no accident that Wiggers was asked to write on “The regulation of the pulmonary circulation” for the American Physiological Society’s first issue of Physiological Reviews (39). Although Bowditch, the first president of the American Physiological Society, and
Garland (2) had published in the British Journal of Physiology (1879) an excellent article on respiration-related pressure changes in the lung circulation, the promissory note of a follow-up paper was never fulfilled. In the American Journal of Physiology before 1908, the single article by Wood (47) on the pulmonary circulation repeated and confirmed (with perhaps less than convincing data) a portion of the classic studies of the British authors Bradford and Dean (3). Wood seems not to have returned to the subject. By contrast, the persistence of Wiggers’ investigations into the lung circulation and the quality, importance, and number of his publications appear to qualify him as the American “father of pulmonary circulatory physiology.”

One wonders why Wiggers chose pulmonary circulatory physiology and why he persisted in it for so many years. His entry into physiology may have been more chance than choice. As a University of Michigan medical student, he intended to take his laboratory elective in pharmacology, but a clerical error in the registrar’s office assigned him to physiology instead. As Wiggers (42) commented, the error “perhaps determined my future career.” Then, in 1903, while still a student, he had the opportunity to receive a small stipend as an assistant in the student physiology laboratory, a job that allowed him time for reading and research. As the son of German immigrants, he could speak and read German, and now he was stimulated to learn French to follow the European physiological literature. By 1905, he had published in the American Journal of Physiology his first paper, the results of his student research on the cerebral circulation (23). In 1906, the Board of Regents at Michigan found it necessary to separate the teaching of medical from dental physiology. Even though Wiggers had just obtained his medical degree, he was offered an instructorship in physiology to teach the dental students. His acceptance was influenced to “a considerable extent” by the small but fixed salary which allowed him “to contemplate marriage” (42) (Fig. 1). With the responsibilities of family life, a secure income in academic physiology, and increasing involvement in its adventures, the die was cast, and physiology became his life-long career.

That he chose to work on the pulmonary circulation may also have come about largely by chance, dictated initially by economics (42). As an instructor at Michigan, he made $1,000/yr, with a mandatory, unpaid 3-mo-long summer vacation. He arranged to work during the summers of 1908–1910 at Parke Davis and Company in Detroit, thereby increasing his meager annual income by $300. At Parke Davis, he began investigating hemorrhagic shock because, as a student, he had seen a patient die from postoperative internal hemorrhage. Having found that epinephrine constricted cerebral vessels (23), he examined the possibility that it might constrict arteries in other organs including those of the lung, thereby reducing blood loss. He devised a simple, instantaneous, accurate method for measuring blood loss (24), and using mercury manometers, he measured pulmonary arterial and left atrial pressures (25) (Fig. 2). Although he found epinephrine was useless in retarding major hemorrhage, including that from the lung, he noted that the systemic pressure was better maintained during hyperpnea than during depressed ventilation. He also noted that during hypotension, stroke volumes increased after closure of the chest. He (42) considered that “additional blood was returned to the heart during inspiration and was expelled during the succeeding expiration.” These studies of hemorrhagic shock piqued his interest in the relationship between respiration and circulation, particularly that of the lung, and emphasized to him the need to better understand pulmonary arterial pressure changes during breathing. Realizing that the available methods were not reliable for systolic and diastolic pressures, he arranged to spend several months in 1912 in Munich with Otto Frank, who had devised new types of vascular pressure recorders. And it was his move to Cornell Medical College in 1911 that made possible that visit to Munich. Graham Lusk, his new chief, was from Munich and gave him the crucial recommendation to Frank. Also, Lusk gave, probably from his own pocket, $500 for the purchase of new apparatus that Wiggers could use after his return.

On his arrival in Munich, because of Frank’s busy schedule, Wiggers was fortuitously left on his own for 4 wk (42). These were spent in mastering Frank’s difficult publications and his mathematical formulations for the design of high-fidelity pressure recorders and in
sketching the instruments in the laboratory (42). He found Frank a “brilliant analyst, a skillful systematist, a talented mathematician, and a creative thinker.” But Frank was also dogmatic and closed to the point of secrecy. Wiggers (42) records that “Einthoven once said to me, ‘You are probably the only outsider who has seen his experimental laboratories.’” Once, on finding Wiggers examining an apparatus, Frank shouted “put that down, how dare you examine an instrument that has not been described?” Furthermore, Frank refused Wiggers’ request to take examples of the instruments back to the United States. Looking back, Wiggers (42) states:

Such a restrictive attitude in sharing newly developed apparatus was contrary to my scientific upbringing and threatened to frustrate my future use of them. Therefore I connived with the laboratory mechanic who could use some extra money to make copies for me. In a sense, therefore, I smuggled the equipment I needed out of the laboratory... In the fall of 1912 I returned to Cornell Medical College with a bagful of new optical recorders, anxious to apply them experimentally. The incentives for pushing ahead vigorously were many. A virgin field lay before me; opportunity was knocking on the door and I would have been a dullard, indeed, not to open it and look for adventures that lay beyond.

Frank had worked on myocardial function in the frog, Starling was hard at work on the left ventricle of dogs, and it may be that the “virgin field” Wiggers had in mind was the relatively unexplored pulmonary circulation. If Wiggers ever wondered about the ethics involved in “smuggling” the instruments out of Frank’s laboratory, these thoughts do not appear in his autobiography. Perhaps he felt he was following Lusk’s directive. Perhaps he felt justified that the particular instruments he brought back could not be used in the mammalian lung circulation and that several generations of new design were required for his application. Furthermore, he was ever careful to give Frank credit for the concepts involved.

Whether or not Frank ever knew of the “smuggling,” he had no hard feelings.

With the passage of years, I revisited O. Frank twice at his Institute and again met him at the International Congress of Physiology. On such occasions he often took the opportunity of joining me and seemed to enjoy our reunion. I thus came to recognize certain sterling qualities that had hitherto remained hidden beneath an austere exterior. O. Frank really wanted to be a genial fellow, but recognized he lacked the capacity for ingratiating himself. Frank welcomed me warmly when I revisited his institute in 1923 and again in 1926, giving me the freedom of his newly equipped laboratories. He even congratulated me on my accomplishments and apologized for his lethargy in writing (42).

Precision in Pulmonary Arterial Pressure Recording

“Precise records of the pressure changes in the pulmonary vessels have, to the writer’s knowledge, not been published.” This first sentence of Wiggers’ 1914 paper (28) on the contour of the pulmonary arterial pressure curve was correct. In the few prior studies of the pulmonary circulation, other investigators had mostly used a mercury manometer, where the top of a mercury column was indicated on a revolving smoked drum. In their now classic article on the pulmonary circulation, Bradford and Dean (3) had used a mercury manometer to measure the pulmonary arterial presor response to hypoxia. Wiggers had used such manometers in his first study of the pulmonary circulation (Fig. 2). Only over-damped pressures could be recorded. Furthermore, normal pulmonary arterial pressures, being only 10–20 mmHg, are so low that the sensitivity was small. Pulmonary venous and left atrial pressures were lower still, such that interpretation of changes was nearly impossible.

Wiggers, from his 1909 study of pulmonary hemorrhage in dogs (25), had become interested in the cause of the respiratory variation in pulmonary arterial pressure. However, he must have been dissatisfied with the pressure recordings from a standard mercury manometer because in 1910 he turned to a valved mercury manometer that would facilitate identifying the maximal and minimal pressures with each heart beat (26). After he had inserted the valved manometer into a branch of a dog’s pulmonary artery at thoracotomy, he closed the chest to make the measurements. The results were, he felt, good enough to say in an abstract (26) that while the pulmonary arterial pressure fell with inspiration, the pulmonary arterial pulse pressure increased. However, he realized the “inability of maximal and minimal valved manometers to record actual pulse pressures” (27). Before publishing the results in full, he sought to confirm his findings using another instrument, the Hürthle manometer, which employed a recording spring attached to a membrane manometer. But in a pilot study that comprised the first part of his 1912 paper, when he used both instruments in the same experiments, the pressures from the “membrane manometer failed to agree with those of the valved manometers” (27).
He wondered about the adequacy of the Hürthle manometer, and in the main body of the 1912 report, he described how he redesigned it to obtain maximal and minimal pressures during the respiratory cycle (27). The redesign resulted in an extremely complicated instrument with a chamber, membrane, coiled spring, and valve to measure systolic pressure and an analogous assembly to measure diastolic pressure; both chambers were joined to a third. However, using the instrument together with intrathoracic and intra-abdominal pressures, he confirmed that the pulmonary arterial pressure (relative to the atmosphere) fell with inspiration and rose with expiration (27). But, in contrast to the 1910 abstract, he found that the pulse pressure decreased. In addition to the conflicting findings, he had problems with the instrument itself; it required repeated adjustment of the degree of damping, and he feared the tracings might not meet the standards set by Frank (9). Indeed, examination of the pressure contours (Fig. 3) suggests they are much improved compared with those of the mercury manometer. However, both systolic and diastolic pressures appear to be underdamped, and motion artifacts are present.

Wiggers himself was not satisfied. He redesigned and simplified the whole manometer (28) (Fig. 4) based on the equations laid out by Otto Frank and utilizing the concepts he had learned in Munich. He designed a wide (3.5-mm) glass cannula that would connect the pulmonary artery to a single chamber. The chamber had a side arm capped by a thin (0.4-mm) elastic membrane on which a small mirror was strategically placed to reflect a light beam to the recording paper. Because the liquid-filled system was rigid, pulsations in the pulmonary artery would immediately and accurately be transmitted to deform the elastic membrane, thus causing the mirror to redirect the light beam on the paper. The membrane and mirror had a small mass and, therefore, little inertia. Use of a light beam magnified the motion of the mirror, resulting in a weightless lever arm. A second mirror rigidly attached to the chamber reflected a part of the same light beam to the paper to give an indication of apparatus motion during respiration and to provide a baseline. A stopcock at the top of the chamber allowed removal of bubbles, which would otherwise degrade the response of the instrument.

At issue was how fast this instrument could follow instantaneous changes in pressure. The more rapidly the membrane oscillated after a single shock, the better it could follow the pressure changes in the pulmonary artery. To help measure the interval between oscillations, Wiggers, with characteristic thoroughness, not only knew the paper speed in the recorder but also compared the oscillations in his instrument with those...
in a tuning fork of known frequency (28) (Fig. 5). The frequency response in his instrument was 158 cycles/s, nearly six times the minimum value suggested by Frank for adequate vascular recording. Clearly, the instrument was adequate to measure the pulmonary pressure contour, and the cannula was small enough that once implanted into a pulmonary artery of the dog, the chest wall could be reclosed.

For the first time, a reliable contour of pulmonary arterial pressure could be seen, as well as changes in that contour with respiration, lung inflation, increased venous filling, or hypoxia (28) as illustrated in Fig. 6. The instrument also allowed the first recording of high-fidelity pressures from the right ventricle (30), confirming that the 1861 right ventricular pressure contour obtained (with an air-filled tambour) in the horse (5) was remarkably good. Furthermore, Wiggers’ instrument allowed the first precise, simultaneous recordings of right atrial, ventricular, and pulmonary arterial pressures (38) (Fig. 7). It was 10 years before Hamilton and colleagues modified Wiggers’ transducer design (14) to record pulmonary arterial pressures via 18-gauge needles through the chest wall of unanesthetized dogs (15). Johnson et al. (17) used the modification by Hamilton et al. (14) to demonstrate the important roles of respiration-induced intrathoracic pressure changes on the pulmonary and systemic pressures and of pulmonary venous pressure changes on the pulmonary arterial pressure. It was nearly another decade before Bloomfield (1) and Cournand and colleagues (6, 7) used modifications of the Wiggers-Hamilton transducer as adapted to an intracardiac catheter to measure right heart pressures in unanesthetized man, for which Cournand along with Dickinson W. Richards and
Werner Forssmann received the Nobel Prize in 1956. For some four decades after Wiggers’ 1914 report, membrane transducers were still widely used during clinical cardiac catheterization, and they were gradually replaced by high-frequency responding electrical transducers that wrote on cathode ray tubes. Evolution of Wiggers’ 1914 pressure transducer had required almost 5 years of self-criticism and dogged work. The advances were largely methodological and were based on the theoretical and practical efforts of Otto Frank in the frog’s circulation, but without Wiggers’ work, the foundations of pulmonary hemodynamics would likely have been delayed some decades.

Direct Observation of the Transilluminated Lung

In 1661, M. Malpighi used an early compound microscope to directly observe the pulmonary capillary circulation. In 1733, the scientific, active, and perhaps too zealous parish clergyman Stephen Hales estimated the transit time through the capillaries. Direct microscopy was not attempted again until the early 1920s when Hall transilluminated the lungs of cats and rabbits. Hall’s report indicated that capillaries had a continuous but complex and occasionally reversed flow, no observable pulsation, and no vasomotion. Although the abstract and the paper indicate Hall as the single author, Wiggers appeared to be very much involved. During conduct of the research, the Nobel Prize-winning Dane August Krogh visited Wiggers’ laboratory sometime after delivering the Hanna lecture on the motor activity of capillaries. Wiggers reports:

His visit was most opportune as Harry Hall and I had been observing the minute vessels of the transilluminated lung and had been unable to observe active capillary vasomotion. Professor Krogh kindly watched one of our preparations and agreed with our observations, remarking, “Of course, one would not expect such changes in the pulmonary capillaries, because they are apparently devoid of Rouget cells.”

Hall was a colleague with Wiggers in the Department of Physiology at Cornell Medical College from 1919 to 1923, after which he took another position in Boston. His work was not published until 1925; there is no other record of his interest in the pulmonary circulation; his name does not appear again in Index Medicus, and he never joined the American Physiological Society. Thus, while Hall conducted the experiments in the early 1920s, one must consider that Wiggers was the impetus for the work. Today, the leading laboratory directly viewing the lung microcirculation is that of Dr. Wiltz Wagner at Indiana University. I asked Dr. Wagner to comment on Hall’s paper and his current view of the field:

Hall and Wiggers deserve great credit for starting in this country and in Germany the avalanche of effort over the past 70 years to observe directly the pulmonary microcirculation. The problems that Hall and Wiggers faced are the central ones facing observers of any microcirculation, i.e., the tissue must be held motionless and the micro, and macro, physiology must be normal. However, technical advances over the last 25 years have overcome some of the difficulties encountered by earlier workers. The recent work has provided a description of how the distribution of capillary transit times varies with pulmonary flow. Also, investigators have found that transit times are shorter in the more dependent lung, that at low alveolar volumes the lung is perfused like a sheet, but at high volumes the capillaries are recruited segment by segment, and that surprisingly small arterioles and venules constrict with alveolar hypoxia. Unlike the systemic circulation, the pool of leukocytes are sequestered exclusively in the pulmonary capillaries, where the trapping mechanism is by mechanical plugging rather than by adhesion molecules, and where diapedesis occurs from the capillaries rather than from the venules.

However, many questions remain to be answered. It is not clear whether the “unrecruited” capillaries are perfused by plasma, in which case the metabolic function of the capillaries could run all the time, or how those microcirculatory vessels without a complete muscular coat constrict with hypoxia. Although it has been accepted since Wearn’s 1934 paper that blood flow switches among capillary segments, we do not know whether the switching is an active process or a passive characteristic of the complex pulmonary capillary bed. And of course we are left with the unknown function of pulmonary arterial innervation. One wonders what effect those nerves might have on capillary recruitment and the distribution of transit times. Early this century Hall and Wiggers started the research avalanche and it is still gathering momentum.

Back Pressure and the Contour of Pulmonary Arterial Pressure

Wiggers interpreted his pulmonary arterial pressure recordings in closed-chest dogs as showing some downstream “back pressure” during inspiration, possibly from the left heart. The origin of that back pressure has subsequently been the subject of intense investigation and controversy, with increased flow, compression by alveolar pressure, and/or an increase (relative to pleural pressure) in the left heart pressure being the leading contenders. Thus, in a very real sense, the two reports, i.e., high-fidelity pulmonary arterial pressure recordings and direct microscopy of the lung microcirculation, have continued to stimulate investigators. As an example of continuing interest arising from Wiggers early studies are comments (at my request) from Dr. Solbert Permutt, who has for more than 40 years examined the relationship between lung inflation and vascular function:

Stimulated by your letter of November 4th, (1997) I looked over a notebook that I have kept since 1956 or 57 on papers of the pulmonary circulation and some of my views on these papers as I read them. On pages 30–32 are my notes on Carl J. Wiggers. At this time I was very interested in spontaneous inspiration which could impede the output of the left ventricle and I certainly was impressed with the idea that Wiggers was developing of a “back pressure” effect. I am still very much impressed with the idea of a back pressure effect from lung inflation. This was just the concept we had developed in the early 60’s to account for a parallel shift in the pressure.
flow curve where the alveolar pressure was higher than the left atrial pressure. This we attributed to a waterfall effect; and we explicitly stated that the alveolar pressure acted as a back pressure. At that time, we had not considered what Wiggers was bringing up in 1921; i.e., that spontaneous inspiration could raise the pressure in the pulmonary artery (relative to pleural pressure) by virtue of the rise in left atrial pressure acting as a back pressure. Our appreciation of this paper of Wiggers did not occur, however, until a year or two before our 1979 paper on the effects of respiration on left ventricular function (Circ. Res. 45: 719–728). His understanding (in the early years of this century) of the significance of the directional change in the pulmonary artery pressure relative to pleural pressure puts him well ahead of his time. I am also sending a copy of my recent view of the history of the mechanics of the pulmonary circulation (19).

Oddly, after his 1921 review, Wiggers seems to have lost interest in the respiratory effects on the lung circulation, even though the issue had initiated his quest to develop adequate pressure recording instruments and it had excited considerable interest from other scientists. For example, Maurice Visscher’s thoughtful, prescient 1924 review (20) of respiratory effects on the lung circulation extensively quoted Wiggers’ work. He indicated that Wiggers’ precise recordings had faithfully demonstrated the pressure changes for the first one to three beats after inspiration but that he had failed to note the rather large subsequent pressure changes. But by 1924, Wiggers was making the transition to the systemic circulation; he never returned to his initial question of respiratory effects on the pulmonary arterial pressure, and he never referenced Visscher’s paper.

Conclusion

Why, one asks, has Wiggers not been more widely recognized as the “American father of pulmonary circulatory physiology”? Partly, it may be that Wiggers himself was modest about his early contributions, and, in addition, as he recognized, he was more concerned with method than about concept during those years. In 1962, on looking back, he wrote (42):

My personal studies had not contributed significantly to an understanding of the regulation of the pulmonary circulation, but it did give me a background for assessing the current work in 1920. As I looked over the previous physiological reviews on the subject, I was impressed with the general tendency to accept the author’s conclusions rather than to weigh them against the methods by which they were obtained. I was reminded of the statement of Flourens “Tout dans le recherche experimentelle depend sur le methode, car c’est le methode qui donne les resultats” [sic].

It was Wiggers’ attention to methodological detail in the lung circulation that began his long career. Once he had developed his high-frequency apparatus for recording pulmonary arterial pressure, he went on to apply it to the right heart chambers. It was then a logical step to use the same principles to develop a high-frequency apparatus for recording heart sounds. Combining the two and adding the apex impulse recorder and the recently developed electrocardiogram, he could then simultaneously record the phonic, mechanical, and electrical events of the heart. By 1923, he (41) had integrated these components into a single scheme that, with subsequent modification, has been a standard curriculum for generations of biomedical students. He began more and more to investigate the systemic circulation, utilizing these powerful tools he had developed for the lung and applying them to persons with heart disease. Furthermore, his industry, competence, innovation, and ability to encourage young people brought to his laboratory for training some of the brightest young minds in the country. He taught his students and research fellows the careful attention to methodological detail that he himself retained throughout his career. Method and concept are inextricably linked in the progress of science. Wiggers’ search for excellence in method brought him well-deserved fame for his work on the systemic circulation, but the search for excellence began in the lung. More than anyone else, he was the “American father of pulmonary circulatory physiology.”

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