The work by Giulio Ceradini in explaining the mechanism of semilunar cardiac valve function

Diana Troiani and Ermanno Manni
Institute of Human Physiology, School of Medicine, Catholic University, Rome, Italy

Submitted 21 June 2010; accepted in final form 8 March 2011

Troiani D, Manni E. The work by Giulio Ceradini in explaining the mechanism of semilunar cardiac valve function. Adv Physiol Educ 35: 110–113, 2011; doi:10.1152/advan.00071.2010.—Using an excised pig heart preparation with tubes, a manometer, and a visualizing apparatus, Giulio Ceradini, an Italian physiologist working in the years of 1871–1872 in Carl Ludwig’s famous laboratory in Leipzig, Germany, illustrated the mechanism of closure of the semilunar valves. He was the first to conceive that the closure of the heart valves depends not on a static back pressure nor upon eddies but is primarily the consequence of the decelerated systolic efflux. This pioneer research of Ceradini was first published in German in 1872 (4). The purpose of the present report is to revisit Ceradini’s pioneering experiments and his interpretation of heart valve closure, which remains as true as it was in 1872.

pulmonary artery; flow profile; axial tread; centrigugal eddies

GIULIO CERADINI (Fig. 1) was born on March 17, 1844, in Milan, Italy. In 1862, he entered the School of Medicine of the University of Pavia and graduated in Medicine and Surgery on August 1868 at the University of Palermo, where, after the death of his father, he followed his twin brother Cesare, who was professor of Construction Theory at the School of Engineering in that university. He married in the fall of 1868 to a distinguished Milanese lady, Carlotta Bozzolo, and he then returned to Milan and worked in the Ospedale Maggiore. His early medical experiences and considerations were published in a research report (7) on the causes of death in the course of immersion. In 1869, he moved to Heidelberg, Germany, where he was mentored by Hermann von Helmholtz (1821–1894). During this period, he published his first important paper (11), where he introduced the Greek terms “mejokardie” and “auxokardie” to indicate the minimum heart volume at the end of systole and the maximal heart volume at the end of diastole; both these terms, now forgotten, were used in many physiology textbooks for more than a century (22).

Following the advice of von Helmholtz, he moved, in 1871, from Heidelberg to Leipzig, where he spent 2 yr working with Carl Frederick Wilhelm Ludwig (1816–1895), the first physiologist to introduce graphic analysis in 1847 (36). In Ludwig’s famous laboratory, other distinguished Italian physiologists, such as Luigi Luciani (1840–1919) and Angelo Mosso (1846–1910), were trained. Mosso remembered Ceradini as “a most powerful genius” in his commemoration of Ludwig (24, 36). In addition, Hugo Kronecker (37) met Ceradini in Leipzig and wrote a moving commemoration (18). Ludwig wrote, in a letter to Ceradini, “I will have much to learn from your future...” In Ludwig’s laboratory, Ceradini carried out his most famous investigation on the function of the semilunar valves and blood circulation (4, 9). The experimental device conceived by Ceradini was used by many other European researchers, such as Leonard Landois, a pioneer in the study of blood transfusion and the phenomena of agglutination (20). Ceradini refused the position of Assistant Professor in Leipzig offered by Johann Nepomuk Czermak (1828–1873) and returned to Italy. He was with Moritz Schiff (1823–1896) in Florence, Italy, where he became a friend of Luigi Luciani, who wrote an impressive commemoration of Ceradini (21). Luciani claimed that “Ceradini’s name will undoubtedly be linked to the history of physiology” (21). In October 1873, Ceradini was appointed Full Professor of Physiology at the Medical School of Genoa in Genoa, Italy. Ceradini’s efforts to organize a proper laboratory in Genoa were frustrated, and he directed his interest to the history of circulation. His attitude as a historical critic emerges from a monograph on the history of the precursors of Harvey’s discovery of blood circulation (10, 13). Ceradini attributed to Andrea Cesalpino and Realdo Colombo priority over Michael Serveto for the discovery of the principles of circulation. A hot controversy broke out with the German theologist H. Tollin and the physiologist W. Preyer, who sustained opposite views and considered Realdo Colombo a plagiarizer (8). As reported by Thomas Henry Huxley concerning Realdo Colombo in the lecture “William Harvey and the Circulation of the Blood” (16) delivered in the Free Trade Hall (London, UK) on November 1878, “…indeed the only man who did anything which was of real importance was Realdus Columbus.”

The eclectic genius of Ceradini also emerges from his studies on the physics related to the railway traffic. He conceived automatic devices (block systems) for avoiding railway crashes (6) and received a prize at the First International Exhibition on Electricity held in Paris, France, in 1881. He resigned from his university position in 1882, and, in the last years of his life, he had another controversy with a monk of Mantua, Italy, who attempted to usurp him of the priority in the discovery of two globes built by the famous 16th century geographer and cartographer Mercatore, which were neglected in a room of the library of Mantua. Ceradini wrote a critical review of almost 300 pages on the Globi Mercatoriani (5); according to experts, the book is considered a most distinguished history of geography.

Letters and acknowledgements document Giulio Ceradini’s generous, open-minded, and independent spirit. Ceradini died in Milan on July, 1894, at 50 yr of age, of what we hypothesize now as a cancer of the intestine. A collection of Ceradini’s papers was gathered and published in 1906 (12).
Ceradini’s most important study was the illustration of the basic mechanism of semilunar valve function (4, 9, 12), which, at the time, was very little understood; it remains, in the 21st century, a matter of research and debate for the achievement of ideal valve prostheses (30).

Ceradini conceived a simple technique for observing the behavior of the semilunar valves during the cardiac cycle (Fig. 2). First, he excised the heart from a pig and then introduced a visualizing apparatus (Rüdinger’s speculum cordis) into the pulmonary artery of the heart. The right ventricle was connected by tubes to a pump, so that different pressures could be induced and systole and diastole simulated. A manometer was connected by tubes and Rüdinger’s apparatus to the pulmonary artery to monitor pressure values (9). The same procedure was also applied to the left ventricle to visualize the aortic valve closure. The pulmonary artery flow profile was similar to that of the aortic valve, but the velocity magnitude was lower.

Such a preparation was so successful that it was described in textbooks and systematically and routinely carried out into the 1960s in Italian medical schools to demonstrate cardiac valve function. Ceradini, in particular, was able to illustrate heart valve hemodynamics and blood flow characteristics through the valves. He distinguished in the blood flow through the semilunar valves a central or axial stream and a peripheral stream, which he described as follows (translated from Ref. 9):

“The former exhibits the maximal speed and the lower pressure, elicits centrifugal eddies that reflect centripetally. They have a relevant role in keeping, during the systolic efflux, the valves in a semi opening position with vibration of the edges. When the blood flow decelerates, the central stream declines progressively and the peripheral centripetal eddies have an important role in provoking closure of the valve inducing a swallow nest approach of its borders.”

To appreciate the different velocities of the axial and peripheral flow components, Ceradini perfused the cardiac chambers with a solution of opaque (yellow) powder of *Lycopodium clavatum* spores and analyzed the role of blood currents during the systolic efflux; he described this as follows (translated from Ref. 9):

“During the systolic efflux the axial flow component provokes the semi-opening of the valves while the centripetal eddies in the Valsalva sinuses do not permit a total opening of...
the semilunar valves because they tend to produce a closure position. When the efflux decelerates the centripetal eddies continue and provoke the closure of the valves. Essentially, this mechanism can be recognized valid also for the atioventricular valves."

Ceradini first showed that the role of the semilunar valves was not only to decrease the diastolic reflux but to stop it completely. His observations clearly indicated that the closure of the valves was not the effect of the beginning of diastole but of the end of systole. Ceradini demonstrated that, at this moment, no regurgitation was possible as the valves, having already reached prediastolic closure, remain in this position, providing elastic tension. As stated by Ceradini (translated from Ref. 9):

“The form/disposition (geometry), small volume, compliance, flexibility, specific weight, similar to the surrounding blood, assure to the mechanism of closure the mostly efficient use of the action of vortices, not taken into account by hydraulic. Indeed, heart valves reach in their function the ideal of perfection.”

He then concluded:

“Valve equilibrium, incompatible in artificial (mechanical) pumps, provides the greatest contribution to the marvelous perfection of heart valves.”

Just by means of simple experiments with excised pig hearts and tubing arrangements, Ceradini could illustrate fluid dynamic processes involved in valve closure. Ceradini was the first to verify and describe that, first, the elastic equilibrium position of the semilunar valves is not of closure but of semiopening. Such a concept of the valve intrinsic potential to open was confirmed by Thubrikar et al. (32) almost 100 yr later. Second, during systolic efflux, the arterial root (bulb) and three Valsalva sinuses dilate and the semilunar valves assume and maintain the position of being semiopen while their free borders vibrate. A deep sound occurs [the first sound (S1)]. Rene Theophile Hyacinthe Laënnec (1781–1826), the inventor of the stethoscope, had distinguished the two heart sounds, attributing, erroneously, S1 to ventricular systole and the second sound (S2) to atrial systole (29). The principal high-frequency elements of S1 are related to the movement and acceleration of blood in early systole, as reported by Ceradini, and are influenced by left ventricular contractility (dP/dt) and the ejection of blood into the root of the aorta. Third, it is toward the end of systole, end of the ejection period, and blood flow deceleration that the semilunar valves quickly close (this was called the systolic dead point). A short lasting acute tone, S2, occurs when the cups of the semilunar valves strike one another and set the columns of blood in the great vessels into vibration. Heart sounds originate as vibrations of the cardiac valves and travel as transverse vibrations with low velocity over the walls of the ventricles and great vessels (23). Fourth, the formation of centripetal eddy currents between the leaflets and their respective sinuses contribute to the leaflet’s smooth closure of semilunar valves. The importance of vortexes in the sinuses of Valsalva had been advanced by Leonardo da Vinci (28). Finally, during the following diastole, the closed semilunar valves stretch toward the ventricular cone; in this way, they form with the borders a tetragon with the apex toward the cardiac apex.

Ceradini’s conception of valve closure was termed “the breaking of a jet at an ostium” by Henderson and Johnson (14): “That is essentially the same conception as that of Ceradini.” Their experiments were published in 1912, and, recalling Ceradini’s research “[It appears to us that few writers have grasped exactly the idea which Ceradini meant to convey] (14), they substantially recognized his idea, as reported in their paper (14): “It is the lateral inrush into the wake of the breaking jet beyond the ostium which is normally the cause of the closure of the heart valves.” Since then, the mechanisms of valve closure have been explained based on Henderson and Johnson’s concepts. Bellhouse and Talbot (1, 2, 31), in the 1960s, provided model studies and supporting analytic work on the role played by the vortex flow in the sinuses of Valsalva during the closure of the aortic valve. Parmley and Talbot (25), in the Handbook of Physiology in 1976, concluded that the pressure difference caused by flow deceleration actuates the valve and the vertical inflow-outflow within the sinuses permit forward-moving ventricular fluid to fill the increasing volume behind the cups rather than the reverse flow from the aorta behind the valves. This concept was expanded by Sacks and Yoganathan in their 2007 review (30) on heart valve hemodynamics, flow characteristics, and the biomechanics of valve tissues, where they, however, claimed that “we do not as yet fully understand all the biomechanical aspects of valve development and function…” (30).

Essentially, Ceradini’s description of valve function has been validated by 20th century investigators (15, 26, 27, 32, 33). In the last 40 yr, computational and geometric models of valve function have represented exciting approaches, yet a fully dynamic simulation has not been reached due to the complexity of valve anatomy, its geometry, motion, deformation, and flow, and their interactions (3, 19, 30, 34). Finally, although our present understanding of valve function has definitely increased, to date, an ideal nonthrombogenic, non-calcific prosthetic device able to maintain normal valve mechanical properties and hemodynamic flow has yet not been conceived (17). Several researchers are now exploring tissue engineering strategies toward the development of a heart valve equivalent (35).

Conclusions

After Henderson and Johnson, no one to our knowledge has cited Giulio Ceradini’s research and his pioneering intuition on the elegant and complex function of cardiac valve hemodynamics. His insight into heart valve closure was confirmed in the 20th century (14, 27, 30, 32) and remains as valid today as it was in 1872. Giulio Ceradini was a man of science, a keen controversialist, and a man of literature; his writings are distinguished by clarity, force, and charm.

ACKNOWLEDGMENTS

The authors express special thanks to the Ceradini family for providing the original writings of Giulio Ceradini. This article is dedicated to the memory of Laura Ceradini (1950–2008), grandniece of Giulio, on the second anniversary of her death.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
REFERENCES