Patent Foramen Ovale and Paradoxical Embolization: A Historical Perspective

HEIDI LIPPmann, R.N. AND TERENCE RAFFERTY, M.D.

Department of Anesthesiology, Yale University School of Medicine, and The Yale-New Haven Hospital, New Haven, CT

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The use of transesophageal echocardiography for intraoperative management of critically ill patients allows for routine evaluation of foramen ovale patency. The high prevalence of preoperatively unrecognized flow-patency of this structure has led investigators to emphasize the potential for paradoxical embolization in any patient undergoing anesthesia. This perspective led us to research earliest documentation of paradoxical embolization through a patent foramen ovale as a historical issue with present day relevance. This report examines the 1877 text of Julius Cohnheim in which he described a fatal case of paradoxical embolization to the middle meningeal artery. The 1880 manuscript of Moritz Litten documenting paradoxical embolization to the lower extremity is also presented. Both translations, to our knowledge, represent the first such representations of both the original 1877 edition of Cohnheim's work and Litten's journal article.

The advent of transesophageal echocardiography has facilitated intraoperative evaluation of the foramen ovale [1-5]. The high prevalence of preoperatively unrecognized flow-patency of this structure has led investigators to emphasize the potential for paradoxical embolization in any patient undergoing anesthesia [4]. This perspective led us to research earliest reports of paradoxical embolization through a patent foramen ovale.

The authorship of the first report of this entity has been attributed to Julius Cohnheim (1839-1884), a protegé of Virchow and Traube, and erstwhile Professor of Pathology and Pathologic Anatomy at the Universities of Leipzig and Breslau (Appendix) [6]. This attribution is based on a report of a fatal case, the details of which appear in his 1877 text, "Lectures on General Pathology" [7]. The following translation, derived from Volume I of this series ("The Pathology of the Circulation") (Fig. 1), represents the specific wording of the report:

"I just recently had a case of a deadly tötliche embolus in the A. Foss. Sylvii¹, in a 35-year old woman. Her heart valves, ascending aorta and all arteries were intact. However, in the lower extremity a long drawn-out thrombus was found. And what I found next I never thought of, to put these two together, until I had a close look at the heart. I found a very large foramen ovale through which I could pass three fingers with ease. Now I could no longer ignore the fact that a torn-off piece of thrombus arising from the V. cruralis²,

Address reprint requests to Heidi Lippmann, R.N., Dept. of Anesthesiology, The Yale-New Haven Hospital, New Haven CT 06510.

¹Middle meningeal artery (artery of the fossa cerebri lateralis Sylvii)[8].
²Femoral vein (vein of the crural or femoral ring)[9].

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while traveling through the heart, (passed) out of the right atrium into the left atrium and to the A. Foss. Sylvii.”

In the preface to the second edition (1882) of this text, Cohnheim notes that certain sections of the text had been revised and expanded. This led us to compare directly the relevant sections of the two editions. In this second edition, the report of paradoxical embolization makes reference to an additional case, as follows: “Litten reports a similar situation in which a thrombus located in the right atrium passed through a patent foramen ovale and was the cause of multiple emboli throughout the arteries of the body.” The specific citation quoted, *Virch. A. LXXX*, p. 381, represents a two-article series involving disparate topics, namely, hepatic carcinoma and
systemic embolization. In the second of these articles, Moritz Litten (1845–1907) (Appendix), an assistant to Virchow in Breslau, presented a description of the clinical and postmortem findings of a case of paradoxical embolization to the lower extremity (Fig. 2)[11]. The patient's clinical course is described at great length. The following account of the pre-morbid events represents an outline of relevant details: a 43-year old woman presented with gangrene of the lower extremity. On examination, the right femoral pulse was not palpable and the artery "felt like a hard tube." Thrombosed veins were noted. The skin between the right knee and the foot was gray-green in color, with areas of sloughing. The heel had a large ulceration and "the toes were mummified." There was no sensory perception or motor response to electrical stimulation in the calf. Past history included recurrent episodes of dyspnea, hemoptysis and pleuritic pain. The patient's hospital course was marked by worsen-

FIG. 2. Reproduction of the title page and binding of Litten's companion articles in Virchow's Archives. The second in the series, "Concerning embolic muscle changes and the resorption of dead muscle fibers," incorporates clinical and autopsy findings.
ing of her pulmonary status, sepsis and, ultimately, death. The pertinent autopsy findings included evidence of recurrent pulmonary emboli and the following:

“Portions of the right femoral artery and vein were filled with organized thrombus. The venous thrombus could only be traced to the knee. . . . on the left, the arteries [were] clear. In contrast, the veins from Poupart’s ligament downwards contained a 6 to 7 cm long totally occlusive thrombus. Multiple old embolic scars were found in the pancreas and kidneys. The autopsy findings, namely, the embolic nature of the arterial thrombus in the right femoral artery, the existence of other [emboli], and evidence of old embolic processes in the systemic circulation were unequivocal. The origin of the embolic material is unknown. The pulmonary veins, the valves of the left heart, the trabeculae carneae the same, just like the left atrium, the aorta and its branches—everything was intact. . . . A closer inspection of the organs, performed by Professor Virchow, at my request, solved the riddle in a very unexpected way. They found a patent foramen ovale. At the same time they found a collection of thrombus in the right atrium. This [thrombus] was the source of the lung emboli. This material was also responsible for all the emboli in the systemic circulation. The foramen ovale provided a means by which this process could occur!”

It should be noted that, at the time of these publications, principles for elucidating the nature of occlusive thrombotic material at postmortem were well established. In addition, Cohnheim was aware that mechanisms by which paradoxical embolization might occur were not limited to passage of the embolus through a foramen ovale. This is shown by the following quotation pertaining to arterio-venous fistulae excerpted from his writings: “Arteries and veins can communicate directly. Such a bypass of the capillary system would favor (paradoxical) embolization” [6,9]. Litten, in turn, makes frequent reference to Cohnheim’s data, and, indeed, both authors had been collaborators in Breslau [12]. Accordingly, it seems irrefutable that the findings from both cases indeed represented the authors’ proposed mechanism.

In our translations, we have attempted to faithfully reproduce the precise wording of the original texts; the, at times, stilted prose reflects the writing style of the authors. Indeed, Meynell, in his historical review of the Sydenham Societies, now defunct organizations which were active in collating and translating classic medical works at the turn of the century, makes the point that the solicited editors had particular difficulties in translating German texts due to “the metaphysical qualities of contemporary German scientific prose” [13]. In addition, McKee, in the preface to his 1889 translation of the second edition of “Lectures on General Pathology,” notes that “Cohnheim himself was no lover of rhetoric; his style of lecturing was simple, often conversational; and he wrote as he spoke” [14]. In our translations, we have attempted to faithfully reproduce the precise wording of the original texts. Accordingly, the somewhat stilted prose reflects the writing style of the authors.

Our translations, to our knowledge, represent the first such representations of both Litten’s journal article and the original 1877 edition of Cohnheim’s work. Alexander McKee, Curator of Museums, Royal College of Surgeons in Ireland, had previously translated the contents of the second edition of Cohnheim’s text (vide supra). The report of Litten, being extant and, indeed, quoted in this second edition, has led one historian to mistakenly attribute the initial documentation of paradoxical
embolization to Litten [15]. However, our findings clearly indicate that this was not so. Further, at the conclusion of his article, Litten specifically states that the findings in his report support Cohnheim’s earlier observation regarding the passage of embolic material through a patent foramen ovale, and cites the first edition text as his reference source.

In conclusion, we have reproduced the earliest documented reports of paradoxical embolization through a patent foramen ovale as a historical vignette with present-day relevance.

APPENDIX

Julius Cohnheim (Fig. 3) was born in Demmin, Prussia in 1839. He received his medical degree in 1860. Following completion of his doctoral thesis, performed at the Pathological Institute of the Charité Hospital under the guidance of Virchow, he was granted a formal academic appointment at this renowned intellectual center. Here, he was also heavily influenced by Traube, the noted internist, to whom he dedicated his textbook. His work was temporarily interrupted by service as a surgeon in the Danish War of 1864 [15]. At age 29, Cohnheim was appointed as Professor of Pathology at Kiel University. He was subsequently granted a prestigious Chair at Breslau. It was here that Litten became one of his students [14]. Cohnheim’s ultimate ambition was the Professorship in Vienna. This Chair did become vacant. However, his recurrent incapacitating illnesses, due to gout, precluded him from being considered for the position [14,16]. His final appointment was at Leipzig, where he died on August 15, 1884.

Cohnheim was a prolific researcher. His early investigations included delineation of the structure of skeletal muscle and its nerve endings, the disposition of the sensory nerve endings in the cornea, the pathological features of choroidal tuberculous and systemic trichinosis. He also conclusively established that white blood cells are capable of diapedesis, a controversial finding at the time. At Kiel, he demon-

3This disorder was the cause of his early demise, the diagnosis being confirmed at autopsy by demonstration of urate deposits in the renal parenchyma [15].
strated that the effects of arterial obstruction depend on the presence or absence of an adequate collateral circulation beyond the obstruction. While at Breslau, he developed his embryonic theory concerning the genesis of tumors. His final publications included demonstration that coronary arteries are, in fact, end-arteries.

Moritz Litten (Fig. 4) was born in Berlin on August 10, 1845. He became a physician in 1868, having studied in Heidelberg, Marburg and Berlin. Following the Franco-Prussian War, he undertook a two-year tour of major medical centers of learning which included sojourns in Vienna, Prague, Paris, London, and Edinburgh [17]. From 1872 to 1876, he served as an assistant to Cohnheim at Allerheiligen Hospital in Breslau, while concurrently furthering his expertise in internal medicine [18]. In 1876, he was appointed as the Senior Attending Physician at von Frerichs’ clinic in the Charité Hospital in Berlin where he established himself as a respected independent investigator [17]. In 1884, he became a full Professor, and was subsequently made Chief of the City Hospital [18]. During his lifetime, he published major treatises on pulmonary infarction, the sequelae of mesenteric artery occlusion, amyloidosis, sepsis, endocarditis, hepatic carcinoma, miliary tuberculosis and basophilic function, most of which are found in Virchow’s Archives. He died in Berlin on June 1, 1907.

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