CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

XXVII. Histological Abnormalities in the Sinus Node, Atrioventricular Node and His Bundle Associated with Coarctation of the Aorta

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SUMMARY A twenty-year-old carpenter died suddenly and unexpectedly nine years after surgical treatment of coarctation of the aorta. Both before and after surgery he had paroxysmal atrial fibrillation, T wave inversions in the ECG and persisting cardiac hypertrophy. At postmortem examination there was focal fibromuscular dysplasia narrowing the sinuses node artery, but other small coronary arteries were normal and there was no focal fibrosis of the ventricular myocardium. Within the sinus node there were several small glomeruli surrounding branches of the sinus node artery. Pericardial fibrosis was present over much of the heart, including margins of the sinus node. The central fibrous body was thickened, particularly on the left, and the His bundle was smaller than normal in cross section. The His bundle appeared displaced toward the right. The atrioventricular (A-V) node was split into an upper and lower half tenuously connected through the central fibrous body which divided it. In its lower half the A-V node was directly continuous with ordinary myocardial cells of the intraventricular septum. Possible developmental relationships between these unusual pathological findings in the conduction system and coarctation of the aorta are discussed. How these findings might relate to the known electrophysiological disturbances and some causes for his sudden death are considered.

SUDDEN DEATH IS NOT UNCOMMON among patients with coarctation of the aorta.1,4 When it happens, the cause is often obvious, e.g., ruptured aorta or subarachnoid hemorrhage, but there are also examples of sudden unexpected death which remain unexplained even after careful autopsy examination. Furthermore, sudden death can and does occur in some patients long after successful surgical treatment of coarctation. Delayed postoperative deaths of this type may be caused by irreversible damage from the hypertension prior to operation, or by associated congenital cardiovascular anomalies, but again there remains a group of deaths with no apparent explanation. This report concerns a seemingly healthy young man who died suddenly and unexpectedly nine years after successful surgical correction of an aortic coarctation. A number of histological abnormalities were present in the sinus node, atrioventricular (A-V) node, and His bundle which not only help explain his own clinical course but may be useful in the general understanding of pathophysiological consequences of coarctation of the aorta.

Case Report

A young carpenter died suddenly and unexpectedly at the age of 20 years, nine years after successful surgical correction of coarctation of the aorta. His presenting complaints originally were palpitations, but he also had a precordial systolic murmur and about 35 mm Hg blood pressure difference between the arms and legs, systolic pressure in the arms averaging about 150 mm Hg. An ECG then showed sinus bradycardia with atrial premature beats (fig. 1). PR interval length varied from short to normal on different examinations but no delta waves were observed among QRS complexes. T wave inversions in most left ventricular leads were present from the first examination and remained stable the rest of his life. Numerous subsequent tracings demonstrated paroxysmal atrial fibrillation (fig. 2). Cardiac catheterization and angiocardiography preoperatively demonstrated severe narrowing of the aorta but no other significant cardiac or vascular anomalies. A maternal aunt died suddenly and unexpectedly at 50 years of age, and several family members had severe coronary disease.

At the time of surgery an aneurysm was present at the aortic end of the ligamentum arteriosum and aortic diameter beyond the coarctation was smaller than proximally. The coarctation and aneurysm were excised and an end-to-end anastomosis was made. He tolerated the surgery well, made a good recovery and returned to an active life. However, bouts of atrial fibrillation continued to recur and were associated with weakness and hypotension, blood pressures as low as 70/40 mm Hg having been recorded. Drinking cold liquids often precipitated the arrhythmia. Various antiarrhythmic programs were attempted without success in completely preventing the paroxysmal atrial fibrillation although quinidine did significantly reduce the frequency and the duration of such bouts. Except during the arrhythmia, his postoperative blood pressures ranged from 120/70 to 150/80 mm Hg.

Prior to his sudden death during mild physical exertion he had been considered in good health and had no complaints other than the palpitations. His death was witnessed as a sudden gasp and then cessation of respirations. During resuscitative efforts he initially had ventricular fibrillation recorded, but when DC countershock terminated the fibrillation, no further electrical activity of the heart could be elicited.
CONDUCTION SYSTEM IN COARCTATION

James, Jackson

Eight 2 mm slices of sinus node were sectioned at 8 micron thickness, with the number of samples from each slice totaling 168 representative slides. All were prepared with either the Goldner trichrome or Verhoeff-van Gieson elastic stain. Proximal to the sinus node its nutrient artery was narrowed by focal fibromuscular dysplasia which was even more prominent in the first portion of the node (fig. 3). A small amount of excessive focal fat and fibrosis was scattered throughout the sinus node. Pericardial fibrosis and adhesions scarred much of both atrial surfaces and involved margins of the sinus node (fig. 4). At multiple points within the sinus there was an unusual periarterial glomoid structure (figs. 5–7). It never measured more than a fraction of a millimeter in maximal dimensions and varied in its density and the number of capillaries it contained. These tiny glomoid masses were consistently near small nerves and some ganglia, and always surrounded a branch of the sinus node artery.

Because of the similarity of this glomoid tissue to chemoreceptors recently studied and found to have their blood supply predominantly from the proximal left coronary system of both human and canine hearts, this region was carefully examined. From the serial sections over 200 representative slides were examined. Several small chemoreceptors of the usual type were found (fig. 8), but they were neither larger nor more numerous nor in any recognizable way different from ones present in normal human subjects.

From the block containing the A-V node and His bundle, nine 2 mm slices were made and 259 selected sections were studied, including serial sections where appropriate to determine histological continuity. Numerous small cysts and other irregularities were present on the right side but not the left side of the membranous interventricular septum, which was intact (fig. 9). The His bundle was smaller than normal in cross sectional diameter (fig. 10). It was somewhat dis-
placed to the right by thickening of the left portion of the central fibrous body (fig. 11). The two bundle branches originated normally but there was scattered focal degeneration in the left bundle branch.

The A-V node was split into an upper and lower half generally divided by the central fibrous body (figs. 12, 13). At multiple points the two halves were tenuously connected. The upper half of this split A-V node was normally continuous with the internodal pathways of the interatrial septum while the lower half was abnormally connected directly to the crest of the interventricular septum and randomly intermingled with ventricular myocardium (fig. 14). Together the two halves comprised a normal size for an adult A-V node. The upper half contained an abnormal amount of focal fat (fig. 15). Approaching the His bundle region, connections between the two halves of the A-V node increased and they then combined to form the His bundle which was encased by collagen of the central fibrous body, no longer having any connection to the crest of the interventricular septum. The A-V node artery was normal.

Discussion

Among the several possibly instructive aspects of this case one must consider the pathogenesis of the atrial fibrillation, the basis for the lifelong inversion of T waves which did not improve despite corrective surgery for the coarctation (nor did the ventricular hypertrophy regress), why the membranous interventricular septum had cysts and irregularities exclusively on its right side, the morphogenesis and clinical significance of the small displaced His bundle and the split A-V node, the possible meaning of apparent chemoreceptor tissue present within the sinus node (where the nutrient artery was thickened by focal fibromuscular dysplasia), and the plausible hypotheses to account for his sudden unexpected death.

Atrial fibrillation need not be associated with any presently recognizable anatomical abnormality, and it is well known from experimental physiology that a variety of autonomic neural perturbations can produce the arrhythmia. The fact that this patient had weakness and unusual hypotension during his paroxysmal atrial fibrillation, and the fact that cold drinks often precipitated the arrhythmia, both speak in favor of a neurogenic or reflex basis. However, the sinus node artery was significantly narrowed and focal pericarditis involved small portions of the nodal surface and even larger areas of free atrial myocardium. While the pericarditis may have contributed by
several mechanisms to the pathogenesis of the atrial fibrillation,10 the arrhythmia had been present preoperatively as well. It is difficult to know how long the focal fibromuscular dysplasia of the sinus node artery had been present, and just what it may have contributed to malfunction of the sinus node. Free motion of a pliable sinus node artery may be a stabilizing factor in the maintenance of normal sinus rhythm.11

One would attribute the T wave inversion at least in part to the left ventricular hypertrophy in our patient, but it is difficult to explain why such hypertrophy persisted. Focal fibrosis of any cause may be responsible for abnormal ventricular repolarization, but the myocardium in the present case was conspicuously free of such fibrosis. One cause for focal myocardial fibrosis can be diffuse narrowings of small coronary arteries. Absence of such narrowings in the ventricular arteries here fits with the normal appearance of the myocardium. The small ventricular arteries being normal also makes it unlikely that the narrowing of the sinus node artery was on the basis of past hypertension or arteritis or some other generalized influence on all small coronary vessels. Asymmetrical sympathetic neural influence on the ventricular myocardium can cause all types of repolarization abnormalities12 and may thus be suspected as the basis of T wave inversions in our case. Such neurogenic influence could furthermore contribute to the pathogenesis of the ventricular hypertrophy and to the paroxysmal atrial fibrillation, but why there should be abnormal autonomic neural control of the heart is uncertain.

There may be a single unifying basis for the abnormally small and displaced His bundle, the split A-V node and the irregular right surface of the membranous interventricular septum. In the postnatal period of the normal development of the human heart there is a molding and shaping process which includes focal degeneration (without significant inflammation, infarction or infection) of the left half of the His bundle and distal A-V node.13, 14 This process is distinctively limited to the left portion of these structures. Its cause is uncertain and its extent on histological examination at any given period during the first few years of postnatal life is variable, but it is ubiquitous in its occurrence. One of the more plausible explanations for its postnatal onset (it is absent during fetal cardiac development) is the new pressure differential across the central fibrous body and region of the A-V node and His bundle: in the fetal heart the pressure on the right and left sides of the central fibrous body of the heart are exactly or nearly equal, whereas soon after birth the pressure on the left side becomes several times greater than that on the right side. This development of pressure

Figure 5. Small masses of glomoid tissue surrounded branches of the sinus node artery. The one boxed in A is shown in more detail in B.

Figure 6. Two smaller glomera are circled in these two sections of sinus node made about 150 microns apart. Black arrow in A indicates a margin of glomus within a tangential section of artery.
FIGURE 7. Details of two glomoid masses are shown here, the one in B being about 30 microns from the one shown in figure 5. A is from a sinus node section 4 mm away.

FIGURE 8. A small normal glomus (arrows in A) near the aorta of this patient is illustrated here. The same glomus is seen at higher magnification in B, along with its adjacent nutrient artery which originated from the main left coronary artery. N is a nerve in A.

FIGURE 9. The slightly thickened membranous interventricular septum is intact in A, but its right surface is irregular; a number of cysts or lacunae are marked with asterisks. The mass of myocardium labeled CS is the crista supraventricularis, TV is tricuspid valve, and LV and RV the left and right ventricle, respectively. The central fibrous body is thickened between the LV and right atrium (RA) in B; arrow marks the left bundle branch originating from the anterior portion of His bundle.
differential depends normally on opening of the pulmonary circulation, closure of the foramen ovale and obliteration of the ductus arteriosus.

Whether aortic constriction or coarctation is a postnatal or a prenatal development, the abnormally greater stress on the left side of the central fibrous body could distinctly influence the morphogenesis of both the His bundle and A-V node as well as the membranous interventricular septum. This stress may have made defective some components of the membranous septum but forced a smoothing completion of the left side or surface. If such physiological stress is responsible for the molding and shaping of the left side of the His bundle and distal A-V node in the postnatal period of normal human hearts, then the presence of any form of left ventricular hypertension (coarctation, aortic stenosis) would be anticipated to accentuate or distort the normal molding process. The end result would be more than usual resorptive degeneration of the left side of this portion of the conduction system, and probable displacement of the structures to the right. That is what was found in the present case.

On the other hand, faulty morphogenesis of the central fibrous body, A-V node and His bundle does also occur in the absence of either hypertension or coarctation. Additional considerations about the faulty A-V node would include possibly abnormal inward migration of the primitive A-V node, which usually becomes located above the central fibrous body, or primary malfunction (abnormal growth) of fibroblasts in the central fibrous body. Division of the A-V node in a lateral direction rather than a vertical one as in the present case has been observed in the heart of a victim of sudden unexpected death who had syncopal spells and heart block, but in that other case the tendon of Todaro was eccentrically placed and contributed to malformation of the central fibrous body. Whatever its pathogenesis, the split A-V node of the present case connected directly to the crest of the interventricular septum, and the potential significance of this anatomical abnormality in the pathogenesis of electrical instability of the heart will be considered later.

Presence of glomoid tissue within the sinus node was surprising. Although this has not been described previously in the human sinus node to our knowledge, there is physiological evidence that chemoreceptor tissue may exist in the region of distribution of the canine sinus node artery. The large number of capillaries in most segments of this glomoid

**FIGURE 10.** Cross sectional size of the His bundle of our patient was smaller than normal. Both his His bundle and that of a normal size control are marked with arrows. Magnification is the same in both photomicrographs.

**FIGURE 11.** The His bundle (arrows) was not only thinner than normal, it was slightly displaced to the right by a thickened central fibrous body (CFB). Section in B is less than 1 mm anterior to the one in A.
intranodal tissue would suggest a chemoreceptor function, as does the histological resemblance to previously described chemoreceptors supplied by a branch of the left coronary artery. Since the latter structures are believed to be responsible for a powerful cardiogenic hypertensive chemoreflex, maximally elicitable by the administration of serotonin (a naturally occurring substance), one must consider the possible contribution of the intranodal glomera in this case to the pathogenesis of hypertension. One of the vexing puzzles about coarctation of the aorta is the fact that the hypertension is not entirely explainable by the mechanical obstruction alone. However, we have no documentation of much hypertension postoperatively in our patient, whereas the nodal glomera were present. Either they did not contribute to hypertension, or it was intermittent and we missed it.

Possible function of the nodal glomera need not be limited to pressure regulation, however, but could include a source of afferent neural signals which had predominantly chronotropic or inotropic efferent effects, without much vasoconstriction. This could help explain the T wave inversion, the ventricular hypertrophy and the paroxysmal atrial fibrillation. However, we have no clue as to how such events would be generated within the glomera or what a possible stimulus might be. One may also ask about a possible relationship between focal fibromuscular dysplasia of the sinus node artery and chemoreceptor tissue in its vicinity, but what it might be is unclear. In other examples of focal fibromuscular dysplasia of the sinus node artery no glomoid tissue was seen. However, due to its small size, it could have been missed.

Finally, we wish to consider possible causes of the sudden unexpected death. It may have been another bout of atrial fibrillation, but one during which stimuli reached the ventricular myocardium during its vulnerable period. Both the abnormal connections of the A-V node and the increased mass of abnormally repolarizing ventricular myocardium would favor this possibility, as would the intermittently rapid A-V conduction (short PR interval). During some of his previous bouts of atrial fibrillation there were QRS complexes of abnormal configuration and at very short cycle lengths. While the ventricular aberration during atrial fibrillation may have been a functional abnormality caused by exceeding the refractory period of a bundle branch, it may also have been due to abnormal routing of conduction through the A-V node, or failure of appropriate conduction through the narrowed and displaced His bundle. It is surprising that no such aberration was recorded during sinus rhythm and that there was no ventricular pre-excitation, although they both may have occurred intermittently at other times and simply been missed. Because of this fragmentation and distortion of the A-V node and His bun-
dle, re-entrant arrhythmias or parasystolic rhythms would be facilitated. The thickened sinus node artery could not only contribute to pathogenesis of the paroxysmal atrial fibrillation, it could also help explain the failure of sinus rhythm to emerge when the ventricular fibrillation was terminated during resuscitative efforts. There is thus a multiplicity of electrophysiological possibilities which have their basis in structural abnormalities, all potentially ending in lethal electrical instability.

Two things which particularly deserve further investigation are the presence or absence of glomoid tissue within the sinus node of other subjects who have or had coarctation of the aorta, and the configuration and histological organization of the A-V node and His bundle of such patients. As a corollary to the latter question, a number of investigators have documented abnormal A-V conduction in patients with coarctation.1, 2, 5, 22 At one time Robert Gross considered the presence of A-V conduction abnormalities as clinically hazardous and a contraindication to surgery for coarctation.23 There is good reason to suspect that abnormal A-V conduction may be a more frequent accompaniment of coarctation than currently thought when one notes the similarity of some histological abnormalities (thick central fibrous body, frayed His bundle) between our case and one reported by Lev and his colleagues.24 Intermittent heart block can easily escape detection, especially if it is of brief duration, and may have been missed in our own patient. In fact, rather little is known about the long-range electrical stability of the heart in any subject before or after surgery for cardiovascular anomalies, despite the growing recognition that sudden death may occur long after successful repair of the hemodynamic abnormality.26, 27

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