CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

XVII. Multifocal Stenoses Due to Fibromuscular Dysplasia of the Sinus Node Artery

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SUMMARY The sinus node artery was focally narrowed by fibromuscular dysplasia in two examples of sudden unexpected death reported here. Although both cases had additional histological abnormalities in the conduction system of the heart, the more striking feature was the focal fibromuscular dysplasia. These findings are discussed in relationship to a large number of similar examples of focal fibromuscular dystrophic narrowing of the sinus node artery observed in other victims of sudden unexpected death, considering some possible mechanisms for lethal electrical instability of the heart and also the possible pathogenesis of such fibromuscular dysplasia.

FOR A LONG TIME it has been known that diminished arterial circulation to the kidney may cause hypertension, but only in recent years has it become widely appreciated that a nonatherosclerotic lesion is often responsible for focal narrowing of the renal artery or even of its intra-renal branches. In most such examples the predominant histological abnormality is a fibromuscular dystrophic process causing such thickening of the arterial wall that its lumen becomes very narrow. For a while after this recognition in renal arteries, it was thought that the lesion was specific there; however, it was soon discovered that the same process occurred in other arteries within the abdomen and in the carotid artery as well. Renal artery stenosis may be responsible for surgically curable hypertension and stenosis of a carotid artery may cause a curable form of focal neurological disease, but there is now little doubt that the same histopathological abnormality may occur within many other arteries in the body, even though the clinical consequences have not been so dramatically clear or readily curable.

In a continuing study of the hearts from victims of sudden unexplained death, we have observed narrowing lesions in certain branches of the coronary arteries which closely resemble that process now called fibromuscular dysplasia. These multifocal narrowings have involved the nutrient arteries supplying those crucial centers normally responsible for electrical stability of the heart, and thereby must be suspect for a role in producing lethal electrical instability and sudden death. The present report will describe multifocal stenoses of the sinus node artery due to fibromuscular dysplasia in two victims of sudden unexpected death.

Case Reports

Case 1

A seven-year-old boy collapsed suddenly while out in the street. When a medical student arrived on the scene, he found the boy gasping for breath about four times a minute. He applied external cardiac massage and performed artificial ventilation, continuing these in the ambulance which took the boy to the hospital. On admission forty minutes after the collapse, the boy was unconscious, no heart beat could be heard and no pulses felt. An electrocardiogram showed slow ventricular fibrillation. Resuscitation was continued while the boy was taken to the operating theater where his chest was opened. No spontaneous contractions of the heart were seen and in spite of manual massage, defibrillation and adrenaline, he failed to recover.

At autopsy there were no significant abnormal findings except in the heart, which weighed 140 grams. There were some obvious patches of pallor in the left ventricular muscle. On microscopic examination there were a few widely scattered small interstitial foci of neutrophils and mononuclear cells lying between apparently normal muscle fibers. Since these findings were not fully adequate to explain the sudden death, special studies of the conduction system of the heart were performed. The vessels responsible for blood supply to the sinus node and to the atroventricular (A-V) junction were grossly normal, as was the appearance of these special regions. Two blocks of tissue containing the sinus node in one and the A-V node with His bundle in the other were excised in toto, cut into slices about 2 mm thick and then sectioned (subserially) at 7 micron intervals.

Three significant abnormalities were found: marked thickening of the sinus node artery caused by focal fibromuscular dysplasia (figs. 1–3), a few widely scattered small foci of inflammatory cells which included one focus at the junction of the sinus node with the right atrium (fig. 4), and the His bundle coursed to the right of the crest of the interventricular septum rather than being in its more usual position to the left of the crest (fig. 5). Such an anatomical variation for the His bundle is seen in about 15% of human hearts and is associated with a very narrow origin of the left bundle branch.

Except within the sinus node itself, and at many points within the node, its nutrient artery had walls of normal thickness and histological organization and its lumen was of normal size (fig. 2A). At multiple other points within the sinus node, however, the same artery exhibited varying degrees of mural thickening and luminal narrowing due to

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fibromuscular dysplasia and a lesser but also variable degree of intimal proliferation. There were very few foci of inflammation (mainly round cells) within or near the sinus node, and no significant areas of degeneration attributable to focal ischemia. Foci of inflammation were even more rarely seen in the A-V node or His bundle, and there was no significant degeneration there.

Case 2

A sixty-four-year-old single man lived with his niece in a terrace house. He worked as a gardener and was thought to be in reasonable health. A stomach ulcer had been diagnosed nine years previously but he was not presently receiving treatment for it. After work one day, during which he made no complaints, he was walking to catch the bus home when he was seen to collapse on the pavement. A policeman driving past in his car at the time stopped to give assistance. The man made an effort to rise but then collapsed and died.

At autopsy examination he was found to have sustained a small abrasion where his head had struck the ground but no deeper injury. Moderately severe chronic bronchitis and emphysema, and a chronic gastric ulcer crater 6 mm in diameter were the only significant extracardiac findings. Except for some small atheromata which minimally narrowed the lumen of the left anterior descending coronary artery, all the main coronary arteries were normal. Scattered small scars were present in the inner half of the left ventricular wall.

Within the sinus node there was multifocal narrowing of the sinus node artery and its branches by fibromuscular dysplasia (figs. 6–10). The narrowing was so extensive in some branches that less than ten percent of the estimated original lumen remained. Relatively recent focal degeneration in the sinus node was compatible with focal deficiency in the nutrient circulation. There was also focal scarring within the midportion of the His bundle (fig. 11) and throughout the ventricular myocardium, most such foci being attributable to multiple narrowings of small coronary branches in those regions.

Discussion

Despite the growing interest in focal fibromuscular dysplasia of arteries, little is known of how and why it happens. Whatever the mechanism may be, there can be little question that the end result is significant narrowing of the lumen of an affected artery and consequently a reduction in blood flow through it. Since the arteries studied in the two present cases notably included those supplying the normal pace-
maker of the heart, we suspect that these narrowings were causally related to the sudden unexpected deaths of both the boy and the man. How they are related or the exact pathophysiology involved is considerably less clear.

If the sinus node fails in its normal pacemaking function, then one would logically anticipate the prompt emergence of an effective A-V junctional pacemaker. However, the A-V junctional region was also abnormal in both subjects, the His bundle being eccentrically placed to the right in the boy and abnormal fibrosis of the His bundle being present in the man. Furthermore, some scattered small foci of inflammation in the myocardium may have further contributed to electrical instability of the heart in the boy. But the more striking abnormality in both cases was multifocal narrowing of the sinus node artery. We have previously observed this same abnormality in victims of sudden death among apparently healthy young athletes, congenitally deaf children, deaf Dalmatian dogs, and in patients who had died suddenly and unexpectedly in the course of primary pulmonary hypertension, Marfan's syndrome, progressive muscular dystrophy, Friedreich's ataxia, scleroderma heart disease and asymmetrical hypertrophy of the heart.

A characteristic example of fibromuscular dysplasia of the sinus node artery from one of these other cases is shown in figure 12.

Given this spectrum of seemingly dissimilar states and diseases, two common features to all of them are the occurrence of sudden unexpected death and marked focal narrowing of the sinus node artery. In many of them there was additional focal narrowing of many other small coronary arteries, including that supplying the A-V node, the potential significance of which was the subject of an earlier report in this series of studies on sudden death. However, here we wish to direct attention to some possible factors in the pathogenesis of fibromuscular dysplasia of the sinus node artery. One such factor may be a heritable fault in the smooth muscle of the tunica media, such as proposed years ago as possibly being responsible for narrowing of multiple small pulmonary arteries. In this consideration, compensatory or reparative events secondary to the primary smooth muscle fault could include either intimal proliferation or disorderly hyperplasia (dysplasia) of the tunica media. The original smooth muscle fault may be metabolic or structural in nature or a combination of these.

Similar consideration may be given to either heritable or acquired faults in collagen or elastin, both of which are normal components of arterial wall. But whereas these become very reasonable suspicions in patients with other evidence of such faults, e.g., as may be expressed in abnormal musculoskeletal development, many of the cases which we have studied did not have extracardiac evidence of faulty collagen or elastin, and the two subjects of the present report in particular did not. Actually, speculation about possible faults in collagen or elastin or smooth muscle may be unnecessarily
discriminatory, since certain mesenchymal cells in the arterial wall may be pluripotent and could differentiate into any one or a mix of all these cell lines. Furthermore, seemingly disorderly hyperplasia of such cells could be the consequence of an attempted repair secondary to mural injury or degeneration, or it could represent some primary form of local neoplasia as recently postulated by Benditt and his colleagues.

Some heritable neuromuscular diseases have been associated with focal fibromuscular dysplasia of the sinus node artery, and one may consequently consider the...
possible effects of local denervation on the integrity of arterial wall. But there are too many instances of similarly abnormal sinus node arteries with no recognizable evidence of any form of neurological disease for this to be the prevalent explanation in all cases.

On the subject of a postulated multifocal arterial denervation of whatever etiology, two points may be applicable to the present cases. First, a similar fibromuscular dysplasia of the sinus node artery has been observed in congenitally deaf children with a long Q-T interval,\textsuperscript{14-19} and these children characteristically have sinus bradycardia which may in part be due to deficient adrenergic neural input to the sinus node. Second, it has recently been demonstrated experimentally that normal adrenergic neural input is essential for the A-V junctional pacemaker to function optimally as an alternate or escape rhythm when the sinus node defaults.\textsuperscript{30} Failure of the normal escape rhythm under such circumstances may be a cause of sudden death. Thus a postulated multifocal abnormality of adrenergic neural input to the heart might not only influence the small coronary arteries, but also serve directly to unstabilize those centers responsible for normal cardiac rhythm. Ultimately, adrenergic neural asymmetry or heterogeneity would have a similar deleterious influence regardless of whether it caused the arterial lesions or the narrowed arteries caused focal neural degeneration.

While heritable or acquired faults of smooth muscle or collagen or elastin, or either acquired or heritable faults of local arterial innervation, may each or all play contributory roles in the pathogenesis of fibromuscular dysplasia of the sinus node artery, one must also consider whether there is something special about this vessel itself which might render it susceptible to mural disease. It is an unusually stressed artery, coursing directly through a comparatively dense collagen sheath which is the normal framework of the sinus node. The sinus node artery arrives at this consistent location after a distance of only a few centimeters from the root of the aorta.\textsuperscript{34, 35} If tethering or similar angulating motion affects the sinus node artery during atrial contraction and relaxation, it may thus be placed under more than usual physical stress. Furthermore, little is known of the spectrum of normal histological organization of the wall of the human sinus node artery, but we are impressed from our own experience that there is wide variability in the components of longitudinal and radial organization of smooth muscle cells in its tunica media, both for the intranodal and extranodal course of the artery.

It may be most useful to recognize from the two present

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{The two different branches of the sinus node artery of Case 2 shown at low magnification in figure 6B are shown here in more detail, at the same magnification for both A and B.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Another narrowed portion of the sinus node artery of Case 2 is shown here from directly adjacent sections, A being stained with Verhoeff-van Gieson elastic stain and B with periodic acid Schiff stain. Both are the same magnification. Note the duplication of the elastic lamina in A and compare to another portion of the same sinus node artery illustrated in figure 10. There was no characteristic distribution or staining intensity of the Schiff-positive material in multiple sections examined from different points in this artery.}
\end{figure}
FIGURE 10. This portion of the sinus node artery of Case 2 is more than 10 mm from the others illustrated. Thickening of its wall and narrowing of the lumen are apparent. A is with Goldner trichrome stain, and B with elastic stain.

FIGURE 11. Focal fibrosis of the His bundle of Case 2 is shown in B to compare to a more normal component of the same His bundle 4 mm away shown in A. Both sections are photographed at the same magnification (reference bar in B).

FIGURE 12. Marked narrowing of the sinus node artery by fibromuscular dysplasia is shown here from one of a number of comparable other cases, as discussed in the text. These are adjacent sections of sinus node, that in A prepared with Goldner trichrome stain and that in B with elastic stain. Magnification (reference bar in A) is the same in A and B.
and similar preceding cases that focal fibromuscular dysplasia of the sinus node artery is a surprisingly frequent finding in victims of sudden death, and to emphasize the need for much more information as to how this association may be causally related. Along with such research it will be valuable to learn how the narrowing process in these sinus node arteries comes to pass, an explanation which it may be hoped will shed important new light on the pathogenesis of arterial disease in general.

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