Histopathology of the Conduction System in Sudden Death from Coronary Heart Disease

By J. T. Lie, M.D.

SUMMARY
Sudden cardiac death (SCD) has been attributed to the development of lethal dysrhythmias in coronary heart disease victims, and several recent autopsy surveys showed that 10 to 50% of SCD patients had unsuspected acute myocardial infarction (AMI). The present study concerned histopathologic findings of the conduction system in 49 SCD (within six hours of the onset of acute symptoms) patients; 39 with established AMI (group A) and ten without (group B). Both groups showed high incidence of cardiomegaly, significant coronary artery disease affecting one or more vessels, and acute myocardial ischemia detectable by specific histological criteria. Stenosis of nutrient vessels of the conduction system was present in about 50% of the atrioventricular (A-V) node arteries and about 25% of the sinoatrial (SA) node arteries in both groups of SCD patients. Nonspecific "degenerative" changes (fibrosis, fatty infiltration, or both) of the conduction tissue, which might or might not represent results of old ischemic injury, also occurred with similar frequencies. Acute changes (infection, hemorrhage) of the A-V node and bundle branches were found only in two group A patients, both had massive septal infarction. Thus, the conduction tissue appeared more resistant to ischemic injury and was overtly damaged only on rare occasions in fatal AMI. The scarcity of acute lesions in the conduction system itself suggested that lethal dysrhythmia in SCD was probably due to electrical instability of the acutely ischemic contractile myocardium rather than a direct injury to the specialized tissue of the heart.

Additional Indexing Words:
Cardiac dysrhythmia  Coronary artery disease  Myocardial ischemia
Myocardial infarction  Autopsy study  Atrioventricular node infarction

The most disturbing finding of any inquiry into the natural history of coronary heart disease is the alarmingly high incidence of sudden cardiac death (SCD); epidemiological studies, both here and abroad, have repeatedly shown that, in about 40 to 70% of all deaths due to coronary heart disease, the victims died outside of a hospital or were dead on arrival. For a cohort of patients with myocardial infarction, there are as many deaths within the first 24 hours as during the next five years. Recent pathologic studies have not only reaffirmed the prevalence of severe coronary atherosclerosis in SCD, but also revealed that 10 to 50% of the victims had unsuspected acute myocardial infarction (AMI), and an even higher proportion had inapparent early myocardial ischemia. Although electrophysiologic evidence supports the notion that ventricular fibrillation or cardiac asystole is the most important mechanism of pre-hospital and hospital SCD, whether the lethal cardiac arrhythmia is associated with acute or specific lesions of the conduction system has not been documented. Because of this unsettled question, a study was carried out to determine the histopathology of the conduction system in 49 SCD, some with and some without unsuspected AMI.

Patients and Methods
The 49 SCD were selected from a larger group of 120 patients previously reported, composed of all 39 patients with histologically demonstrable acute myocardial infaracts (group A) and ten of the remaining 81 patients without acute infaracts (group B). The patients, 35 men (mean age: 57 years) and 14 women (mean age: 62 years), died suddenly within six hours of the onset of acute symptoms. All but four deaths were witnessed. Sixty-eight percent (33/49) of the patients died at home, 12% (6/49) at work, 8% (4/49) at various sporting events either as participants or spectators, and 12% (6/49) in the ambulance or a hospital emergency room. Physical activity immediately preceding the terminal event was described as strenuous in only 14% (7/49) and moderate, mild, or none (resting) in the remainder. Resuscitations including defibrillation were attempted in the attended patients, but not all electrocardiographic monitoring records preceding the terminal event were available.

In every instance, a complete autopsy examination had

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excluded noncoronary causes of death. The gross and microscopic examination of the coronary arteries and the heart were conducted as described in detail previously.\textsuperscript{5, 12, 13} The methods of studying the conduction system were similar to those described by Lev.\textsuperscript{14, 15} About three to five sinoatrial (SA) and six to nine atrioventricular (A-V) conduction tissue blocks were prepared for histologic examination. Special care was directed to the correct sequence of tissue blocks during processing so that the topography of the conduction tissue could be reconstructed. From these tissue blocks, every fourth and the adjacent 5–7μm sections were stained by hematoxylin-eosin (H&E), elastic van Gieson (ELVG) or Movat’s pentachrome, and the nonenzymatic hematoxylin basic fuchsin-picric acid or HBFP stains.\textsuperscript{16} All intervening sections were kept available for examination when needed. An average of 200 to 350 sections of the conduction system were examined per patient. Cardiomegaly was defined as heart weight exceeding the maximum of a normal range related to the body weight,\textsuperscript{17} and in most instances, this meant heart weight exceeding 350 g. Significant coronary artery disease was defined as 75% or greater luminal narrowing due to atherosclerotic plaques, estimated from the vessel’s cross-sectional appearance. Myocardial infarcts were dated histologically in the H&E stained sections, classified as acute (up to four weeks) and old (over four weeks), according to the criteria described by Mallory et al.\textsuperscript{18} Infarcts involving the inner one-third to one-half of the ventricular wall thickness were regarded as subendocardial, and those extending to 75% or full thickness as transmural.

### Results

**Major Cardiac Findings**

The 49 SCD hearts in this study, irrespective of whether AMI was present (group A) or absent (group B), shared many common anatomical characteristics (table 1). All hearts had a right preponderant coronary artery distribution and showed a comparable high incidence of cardiomegaly (69% and 70%) and significant coronary artery disease affecting one or more vessels (87% and 90%). Recent coronary thrombosis was uncommon (18% and 20%). Early myocardial ischemia (less than six hours), identified in the conventional H&E stained histologic sections by myofibrillar degeneration\textsuperscript{19} and by positive HBFP staining reaction (figs. 1 and 2), was present in the majority of cases (85% and 80%), mainly around established infarcts and in the subendocardium. Only occasional hearts showed positive HBFP staining of the conduction fibers. Healed or old infarcts (fibrous scars) were present in about half of the patients (46% and 40%).

The histological age of acute infarcts in group A patients ranged from less than 12 hours to 28 days; two-thirds (26/39) were more than 12 hours old. Subendocardial infarcts outnumbered transmural infarcts by the ratio of 2:1 (table 2). About one-half (19/39) of the infarcts were anteroseptal; one-third (13/39) were posteroseptal, and the remainder (7/39) were anteroseptal.

**Table 1**

<table>
<thead>
<tr>
<th>Group*</th>
<th>Number of patients</th>
<th>Cardiomegaly (&gt;350 g)</th>
<th>Significant coronary artery disease†</th>
<th>Recent coronary thrombosis‡</th>
<th>Healed myocardial infarcts</th>
<th>Acute myocardial ischemia§</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>39</td>
<td>27 (69%)</td>
<td>34 (87%)</td>
<td>7 (18%)</td>
<td>18 (46%)</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>7 (70%)</td>
<td>91 (90%)</td>
<td>2 (20%)</td>
<td>4 (40%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>34 (69%)</td>
<td>43 (88%)</td>
<td>9 (18%)</td>
<td>22 (45%)</td>
<td>41 (84%)</td>
</tr>
</tbody>
</table>

* A: with recent myocardial infarct; B: without recent myocardial infarct.
† Determined by histologic aging to be less than 24 hours old.
‡ Number with 75% or greater luminal narrowing of one or more major epicardial coronary arteries.
§ Determined by positive HBFP staining and myofibrillar degeneration.

**Conduction System**

Table 3 summarizes the histopathologic findings of the conduction system. Intimal thickening with significant luminal narrowing occurred commonly in the nutrient vessels of the conduction system, affecting the SA node artery in about 25% of cases and the A-V nodal artery in about 50% of cases. Although there was no recent thrombosis of the conduction system nutrient vessels, A-V node necrosis was seen in two group A patients, both had thrombosis of the right

### Table 2

<table>
<thead>
<tr>
<th>Histologic age of infarct*</th>
<th>Number of cases†</th>
<th>Type of infarct‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 – 12 hours</td>
<td>13 (0):</td>
<td>4 TM</td>
</tr>
<tr>
<td>13 – 24 hours</td>
<td>12 (2):</td>
<td>5 TM</td>
</tr>
<tr>
<td>25 – 48 hours</td>
<td>3 (0):</td>
<td>0 TM</td>
</tr>
<tr>
<td>3 – 7 days</td>
<td>7 (3):</td>
<td>2 TM</td>
</tr>
<tr>
<td>8 – 14 days</td>
<td>3 (1):</td>
<td>2 TM</td>
</tr>
<tr>
<td>15 – 28 days</td>
<td>1 (1):</td>
<td>0 TM</td>
</tr>
<tr>
<td>Total</td>
<td>39 (7):</td>
<td>13 TM</td>
</tr>
</tbody>
</table>

* Determined by the criteria of Mallory et al.\textsuperscript{18}
† Numbers in parentheses indicate cases with coronary thrombosis.
‡ TM = transmural infarct; SE = subendocardial infarct.
an example of inapparent early myocardial ischemia in SCD. Left panel) Histologically normal myocardium in the conventional stained section (Hematoxylin-eosin stain, X 100). Right panel) Consecutive serial section of the same myocardium, showing positive HBFP staining (seen here as black staining) indicative of early myocardial ischemia (Hematoxylin-basic fuchsin-picric acid stain, X 100).

Figure 1

Myofibrillar degeneration, indicative of acute ischemic injury, in the heart of a patient with sudden coronary death. Note the eosinophilic and irregularly spaced transverse "contraction bands" and the more lightly stained granular cytoplasm (Hematoxylin-eosin stain, X 256).

Figure 2

Table 3

Histopathology of the Conduction System in Sudden Death from Coronary Heart Disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of patients*</th>
<th>Conduction system</th>
<th>Disease of specialized fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SA node artery</td>
<td>A-V node artery</td>
<td>Type of disease†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N:</td>
</tr>
<tr>
<td>A: With infarcts</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antero-septal</td>
<td>19 (3)</td>
<td>5</td>
<td>9‡</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Postero-septal</td>
<td>13 (2)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antero-septo-poster</td>
<td>7 (2)</td>
<td>2</td>
<td>4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Without infarcts</td>
<td>10 (2)</td>
<td>3</td>
<td>6</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49 (9)</td>
<td>13</td>
<td>24</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate cases with coronary thrombosis.
†N: normal; F: fibrosis, fatty replacement and vascularization; A: acute infarction and/or hemorrhage.
‡Including one case in which an embolus was present in the A-V node artery.
Abbreviations: SA = sinoatrial; A-V = atrophicventricular.
CONDUCTION SYSTEM IN SUDDEN DEATH

Moderate to marked degrees of fibrosis, myocytolysis, fatty replacement and vascularization of the specialized fibers of the conduction system (fig. 6) were not uncommon. These nonspecific “degenerative” changes were just as prevalent in SCD patients with AMI (group A) as in those without (group B), and affecting, in decreasing order of frequency, proximal segments of the bundle branches, the A-V bundle, the A-V node and the SA node (table 3). In general, fibrosis and fibrofatty replacement of the conduction tissue were more common in patients after the fifth decade of life.

Discussion

A comparison of this study and our previous anatomic studies of coronary victims12,13 showed that there were no specific histopathologic lesions of the

Figure 3
Left bundle branch (LBB) in a SCD. Top panel) Hemorrhage in the left bundle branch (between arrows). S = infarcted ventricular septum (Hematoxylin-eosin stain, × 60). Bottom panel) Higher magnification of the boxed area showing hemorrhage and myocytolysis of the necrotic LBB fibers (Hematoxylin-eosin stain, × 160).

Figure 4
Acute lesions in a SCD patient with massive antero-septo-posterior MI. Top panel) Infarcted A-V node (AVN) and marked intimal thickening of the A-V node artery (A); CFB = central fibrous body; V = a venous channel (Hematoxylin-eosin stain, × 25). Bottom panel) Higher magnification of the boxed area showing necrotic conduction fibers, marked polymorphonuclear infiltrate, and organized thrombus in the vein (V) with an eccentric residual lumen (Hematoxylin-eosin stain, × 60).

Figure 5
Right bundle branch in the same SCD shown in figure 4. Left panel) Necrosis of the right bundle branch (between arrows) in the midst of infarcted ventricular septum. T = tricuspid valve (Hematoxylin-eosin stain, × 40). Right panel) Higher magnification of the boxed area showing necrotic RBB fibers and inflammatory infiltrate (Hematoxylin-eosin stain, × 100).
Figure 6

Nonspecific degenerative changes of the conduction tissue in SCD. Top left panel) Fibrosis and fatty infiltration of the A-V node. CFB = central fibrous body. Top right panel) Septate fibrosis of the His bundle (HB) with myocyte lysis. Bottom left panel) Almost completely sclerotic His bundle (HB) with fibrosis of the proximal segment of the left bundle branch (LBB) and complete fibrous interruption of the right bundle branch (RBB). Bottom right panel) Fibrosis of the His bundle (HB), right bundle branch (RBB) and left bundle branch (LBB). Hematoxylin-eosin stain, all × 40.
CONDUCTION SYSTEM IN SUDDEN DEATH

conduction system peculiar to SCD, and a seemingly intact conduction system did not preclude the development of lethal cardiac arrhythmias. Irrespective of whether death occurred suddenly or while under hospital care for myocardial infarction, acute ischemic necrosis of the conduction tissue was an exceptional finding. Only two of our 49 SCD patients had acute injury to the conduction tissue, affecting the A-V node and the peripheral bundle branches (figs. 3-5). In both instances, the patients had massive AMI involving the ventricular septum. Nonspecific "degenerative" changes (fibrosis, fatty infiltration, or both) of the conduction system, which might or might not represent previous ischemic injury, were just as common in patients who died suddenly as in those who did not (table 3), and just as common in patients who died in sinus rhythm as in those who had various types of conduction disturbances. These changes occurred more commonly in SCD and AMI patients after the fifth decade of life, and thus might well be only manifestation of aging. Indeed, studies by Levin and Davies have clearly demonstrated that with aging there was progressive increase of collagen and fatty replacement of the conduction tissue in patients who had died of noncardiovascular diseases.

The lack of a specific finding of acute lesions in the conduction system of the vast majority of SCD was compatible with the proposed mechanism of the terminal event, namely ventricular fibrillation or cardiac asystole, but in no way excluded the possibility of bradyarrhythmias occurring shortly before death. Although there is, to our knowledge, no published anatomical study of the cardiac conduction system in SCD, it has been well documented in the literature that, in patients with established AMI, even marked conduction disturbances are frequently not accompanied by significant lesions of the cardiac conduction system.24-27 In posterior AMI with complete heart block, extensive to total necrosis of the A-V node was seen in two out of nine patients in the series reported by Blondeau, in none of Sutton and Davies' ten patients, and in only three of the 36 patients studied by Ekelund et al. These same authors describe a higher incidence of ischemic necrosis of the bundle branches in patients with anterior AMI complicated by complete A-V block. Hackel et al. have suggested several factors which may explain the lack of histologically demonstrable acute lesions of the conduction system in patients with clinically documented heart blocks complicating AMI, including higher glycogen content and lower oxygen consumption of the conduction tissue of the heart as compared with the contractile myocardium. Hackel et al. attribute the possible mechanism of transient conduction defects in AMI to altered ionic milieu, the release of lysosomal enzymes by leukocytes, or hypersensitive vagal reflexes following ischemic injury to the myocardium.

Because of the vulnerability of ischemic myocardium to ventricular fibrillation, our finding of positive HBFP staining and myofibrillar degeneration, both of which are histologic markers of acute injury to the myocardium, in the hearts of about 80% of SCD is highly significant. This observation correlates well with the clinical finding of electrocardiographic changes of myocardial ischemia in about three-quarters of successfully resuscitated "would-be SCD" survivors, and with the postmortem detection of lowered potassium/sodium ionic ratios in coronary heart disease victims who had no histologically demonstrable AMI.31 By the use of similar histochemical methods, Lee et al. have also been able to define "early" or "inapparent" ischemic injury consistently, involving or surrounding the conduction tissue of the heart in an experimental pig model of sudden death from severe coronary atherosclerosis. In their experiment, electrocardiographic equipment was placed in close proximity and terminal electrocardiograms were obtained in some of the swine within a few minutes after the first recognizable signs of illness. The terminal electrocardiograms of 18 swine that died suddenly showed ventricular asystole in 13 cases and ventricular asystole in five animals.

If myocardial ischemia, not necessarily directly involving the conduction tissue of the heart, is the anatomical basis of SCD manifested by electrical instability and the development of ventricular fibrillation, then the tedious histologic study of the conduction system may not be as revealing as has been anticipated in the clinicopathologic correlation of SCD.33 While the mechanism which precipitates the seemingly abrupt onset of fatal myocardial ischemia may be multifactorial, it seems more profitable to continue the search for more sensitive and reliable histopathologic markers of acute injury to the myocardium.

References
6. Lie JT, Titus JL: Inapparent early myocardial ischemia in


17. Smith HL: The relation of the weight of the heart to weight of the body, and of the weight of the heart to age. Am Heart J 4: 79, 1925-29


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