JACC Vol. 23, No. 3
March 1, 1994:741–6



# Conduction System Findings in Sudden Death in Young Adults With a History of Bronchial Asthma

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***Objectives.*** **This study was conducted to determine whether there are any pathologic changes in the conduction system when death occurs suddenly in young adults with a history of bronchial asthma.**

***Background.*** **There is a worldwide increase in sudden death, especially in young adults with a history of bronchial asthma.**

***Methods.*** **We studied the conduction system by serial section examination in six male patients (16 to 23 years old) with a history of bronchial asthma who died suddenly.**

***Results.*** **The sinoatrial node artery was narrowed in two patients, with chronic inflammatory cells in three; it was fibrosed in one. The atrioventricular (AV) node was within the central fibrous body in three patients and isolated by fat in one. The AV bundle was markedly fragmented in five patients and fibrosed in two. The right and left bundle branches showed fat, fibrosis and disruption in five patients. Increased fibrosis on the summit of the ventricular septum with patchy fibrosis was present in five patients, and inflammatory cells in the conduction system were found in one.**

***Conclusions.*** **1) There are distinct pathologic findings in the conduction system of young adults with a history of bronchial asthma who die suddenly. 2) The significant findings appear to be a markedly fragmented bundle and changes in the sinoatrial node that are not found in normal healthy young adults. 3) The changes in the conduction system may create an arrhythmic event, and sudden death may occur in some persons during an altered physiologic state. 4) We hypothesize that bronchial asthma may be associated with an alteration in immune complexes that affects the conduction system in some patients.**

***(J Am Coll Cardiol 1994;23:741–6)***

There is an increased mortality rate in the young and the elderly with a history of bronchial asthma, not only in this country but globally, and death may indeed be sudden and unexpected in the young (1–3). There is also a dramatic increase in the worldwide incidence of asthma, resulting in an increase in the rate of emergency care visits, hospital admissions and, obviously, in the total cost of treatment (1,2,4). It has been suggested that adult women are more severely affected, raising the possibility that hormonal or biochemical differences related to gender may play a role in the pathophysiology of asthma (5). The incidence of death due to bronchial asthma is also increasing in all age groups. At present, the reasons for the increased incidence of death related to asthma are not clear. It has been suggested that asthma medications may contribute to the incidence of death in some patients, and asthmatic black male patients living in an urban environment, especially those <15 years of age, are at greater risk (1,2). Myocardial contraction band necrosis has been associated with catecholamine toxicity in some patients with fatal asthma (6). It is conceivable that sudden death, especially when it occurs in young persons with a history of bronchial asthma, may be an arrhythmic event related to disease in the conduction system. It is also possible that some young people who are prone or susceptible to cardiac arrhythmias are also susceptible to asthma or vice versa. Nevertheless, to the best of our knowledge, the conduction system in bronchial asthma has not thus far been studied, especially when death occurs suddenly. We therefore studied the conduction system by serial section examination in six males with history of bronchial asthma who died suddenly to determine whether there were any anatomic abnormalities in this system that might give rise to an arrhythmic event during an altered physiologic state.

## Clinical History and Gross Findings in the Heart

The hearts of six young adults with a history of bronchial asthma who died suddenly were sent to us by medical examiners in this country. The medical examiners were unable to determine the cause of death in all six persons. Because all six had been living a normal life up to the time of death, we briefly describe the manner in which each person died.

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Manuscript received July 8, 1993; revised manuscript received September 10, 1993, accepted October 14, 1993.

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0735-1097/94/$7.00

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**Case 1.** A 16-year old black young man collapsed after playing basketball and could not be resuscitated. He had been treated for bronchial asthma some time previously.

*The heart* weighed 261 g. There was a distinct right ventricular septal bulge with right ventricular hypertrophy and an accessory tricuspid orifice. There was also a left ventricular bulge with hypertrophy and distinct fibrosis of the summit of the septum.

**Case 2.** A mother found her son (a 17-year old black man) standing in the kitchen doorway saying, "I cannot breathe." He then collapsed to the floor. He had been diagnosed as having asthma, and 2 months before death he was taking theophylline and using a Ventolin inhaler (albuterol; Allan & Hanburys) for his asthmatic condition.

*The heart* weighed 397 g. The left main coronary artery originated close to the junction of the right and the left anterior commissures. There was abnormal formation of the posterior crest close to the region of the sinoatrial node, with distinct hypertrophy and enlargement of the right and left ventricles. The coronary arteries were widely patent.

**Case 3.** This 18-year old white young man suddenly lost consciousness while driving a car. Cardiovascular collapse followed and, according to the history, a terminal asthmatic attack.

The history revealed he had been taking theophylline, a Proventil Breathair inhaler (albuterol, as needed; Schering), an Alupent inhaler (metaproteronal, as needed; Boehringer Ingeheim) and Asthmacort (three puffs three times a day after the Breathair or Alupent) and was being weaned from prednisone as well as Seldane (terfenadine; Marion Merrell Dow) for allergic rhinitis. The process of weaning from prednisone had been completed 1 week before his collapse. The mother stated that her son had taken his asthma medication shortly before midnight but not the next morning. He worked at a fast food restaurant and at 11:30 PM had complained that he did not have the necessary energy to do the work and later said he felt sick, without giving particulars. He felt he had to sit down while cleaning dishes at the sink and later described pain and numbness of the left arm. However, he continued to work, denied that the pain was severe, showed no symptoms or signs of asthma and was not seen to take any asthma medications. He left the restaurant and, while driving, struck another car and was found unconscious. The rescue team recorded a pulse of 115 beats/min, blood pressure 200/90 mm Hg and respirations 24/min. While he was being transferred to the trauma room, he developed bradycardia with premature ventricular complexes followed by cardiorespiratory arrest and could not be resuscitated. His blood theophylline level was 1.02 mg/liter.

*The heart* weighed 317 g, with mild hypertrophy of the right and left ventricles and a right ventricular septal bulge close to the region of the atrioventricular (AV) node and the His bundle.

**Case 4.** An 18-year old apparently healthy young white man who had no current complaints died suddenly while taking a shower. His past history revealed some orthopedic problems and a history of allergies consistent with asthma. Antigen testing revealed only minimal sensitivities, yet on many occasions he had experienced severe hyperventilation and shortness of breath, almost to the point of syncope.

*The heart* weighed 400 g, with mild to moderate left ventricular hypertrophy and fine endocardial fibroelastosis with considerable thickening in the sinoatrial node area.

**Case 5.** This 18-year old black young man collapsed while playing basketball for 5 min. He had a prior history of asthma and was using an inhaler and other unknown medication. According to his mother, he had collapsed 2 years previously while playing basketball.

*The heart* was enlarged, weighing 410 g, with hypertrophy and enlargement of all the chambers. The coronary sinus was displaced close to the central fibrous body, receiving a left superior vena cava, with an enlarged tricuspid valve, elongated chordae and possible insufficiency.

**Case 6.** This 23-year old white male college student went drinking with friends and had approximately seven beers. He returned to his apartment a little after midnight and was found dead a few hours later. He was known to have asthma and apparently had not felt well in the past week. He also had a cold.

*The heart* weighed 400 g and the right coronary ostium was smaller than the left. However, all the coronary arteries were patent, with mild hypertrophy and enlargement of all the chambers.

## Methods

Blocks containing the sinoatrial node and its approaches, the AV node and its approaches, the AV bundle (the penetrating, branching and bifurcating portions) and the bundle branches up to the region of the moderator band were serially sectioned and every 20th section was retained. Every 40th section from the block containing the atrial preferential pathways, the block with the approaches to the AV node and the block containing the peripheral bundle branches was retained. In addition, several sections were taken from the right atrium, right ventricle, left atrium, left ventricle and the posterior septum apex. In this manner, 1,426 sections from Case 1, 1,370 from Case 2, 1,420 from Case 3, 1,244 from Case 4, 1,368 from Case 5 and 1,414 from Case 6 were examined and compared with those from the conduction system in patients from a similar age group.

**The conduction system.** The findings in the conduction system in each case are summarized here. In addition, the pathologic observations in each case are listed in Table 1.

*Case 1*

1) Mononuclear cells in and around the sinoatrial node.
2) Markedly fragmented AV bundle, penetrating (Fig. 1) and branching portions, with fibrosis and mononuclear cells.
3) Atrioventricular node draped over the central fibrous body, with fibrosis and mononuclear cells.

Table 1. Pathologic Findings in the Conduction System

| | Case No. | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Mononuclear cells in SA node and/or its approaches | + | + | + | – | + | + |
| Arteriolosclerosis of SA node | + | – | + | – | – | + |
| Fat and fibrosis in SA node and/or its approaches | – | – | + | + | + | + |
| Fat, fibrosis or mononuclear cells in atrial preferential pathways and approaches to AV node | + | + | + | + | + | + |
| Fat and/or fibrosis in the AV node | + | + | – | + | + | + |
| Mononuclear cells in the AV node | + | + | + | + | + | + |
| AV node in part in central fibrous body | + | – | – | + | – | + |
| Fragmented AV bundle | + | + | + | + | + | – |
| Fat and/or fibrosis of AV bundle | + | + | + | + | + | + |
| Mononuclear cells in AV bundle | + | + | – | – | + | + |
| Fibrosis and fat and/or mononuclear cells in left bundle branch | + | + | + | + | + | + |
| Fibrosis and fat and/or mononuclear cells in right bundle branch | + | + | + | + | + | – |

AV = atrioventricular; SA = sinoatrial; + = present; – = absent.

4) Partial disruption of the left bundle branch, with atrophy and hemorrhage.
5) Fibrosis of the summit of the ventricular septum.

*Case 2*

1) Marked right atrial and right ventricular hypertrophy.
2) Distinct fibrosis of the nerves.
3) Sinoatrial node artery outside the sinoatrial node.
4) Fatty infiltration of atrial preferential pathways.
5) Tenuous connection of the AV node with the surrounding atrial musculature due to marked fatty infiltration (Fig. 2), and chronic inflammation and moderate fibrosis of the node.
6) Marked fragmentation of the penetrating AV bundle.
7) Left-sided AV bundle with vacuolization.
8) Fragmentation and vacuolization of the beginning of the left bundle branch.
9) Fibrosis of the beginning of the right bundle branch.
10) Origin of the conal branch from the right bundle branch.
11) Arteriolosclerosis of the myocardium.
12) Fibrosis of the summit of the ventricular septum.

*Case 3*

1) Moderate arteriolosclerosis in the sinoatrial node, accompanied by chronic inflammation in the epicardial area.
2) Focal hemorrhage and fibrosis of the atrial preferential pathways.
3) Moderate to marked mononuclear cell infiltration of the AV node and Mahaim fibers.
4) Left-sided branching bundle with moderate lobulation and fibrosis.

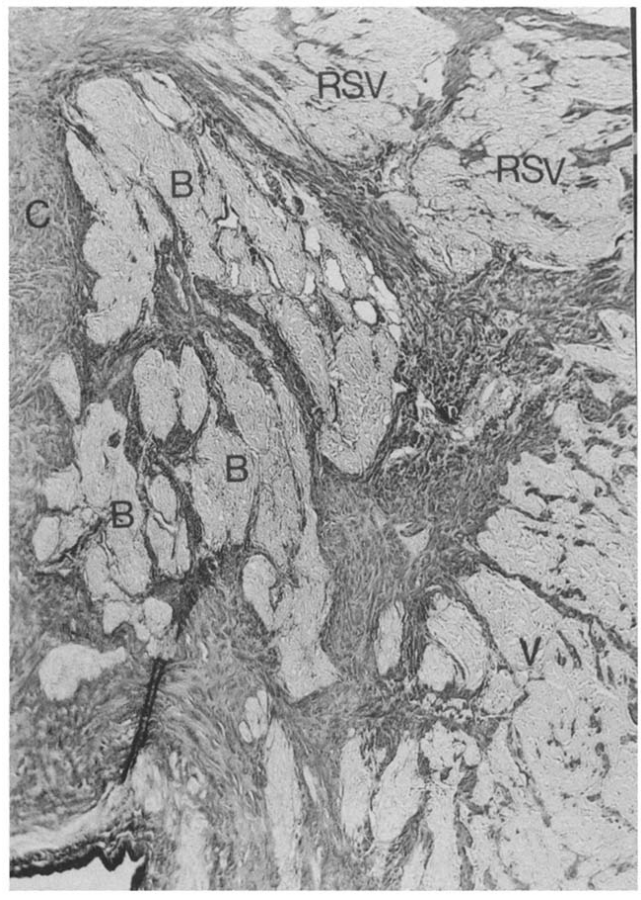


Figure 1. Case 1. Markedly fragmented penetrating atrioventricular (AV) bundle, in part pressed by the right ventricular septal hypertrophy. B = fragmented AV bundle; C = central fibrous body; RSV = right ventricular septal hypertrophy pressing on the bundle; V = ventricular septum. Weigart-van Giesen ×60, reduced by 28%.

5) Posterior radiation of the left bundle branch, encircling large pieces of myocardial fibers, with occasional interruption and fibrosis.
6) Large right bundle branch with segmentation or division on and off several times intramyocardially.

*Case 4*

1) Hypertrophy and enlargement of the heart (all chambers).
2) Abnormal shape of the sinoatrial node.
3) Marked fatty metamorphosis of the right atrium.
4) Fibrosis of the nerves.
5) Hemorrhage in the atrial and ventricular myocardium.
6) Partial inclusion of the AV node in the central fibrous body, with thickening of the central fibrous body.
7) Fatty metamorphosis of the AV node and its approaches (Fig. 3).
8) Fragmentation of the AV bundle, with fatty metamorphosis and fibrosis (Fig. 4).
9) Fatty metamorphosis of the right bundle branch and part of the left bundle branch (Fig. 4).

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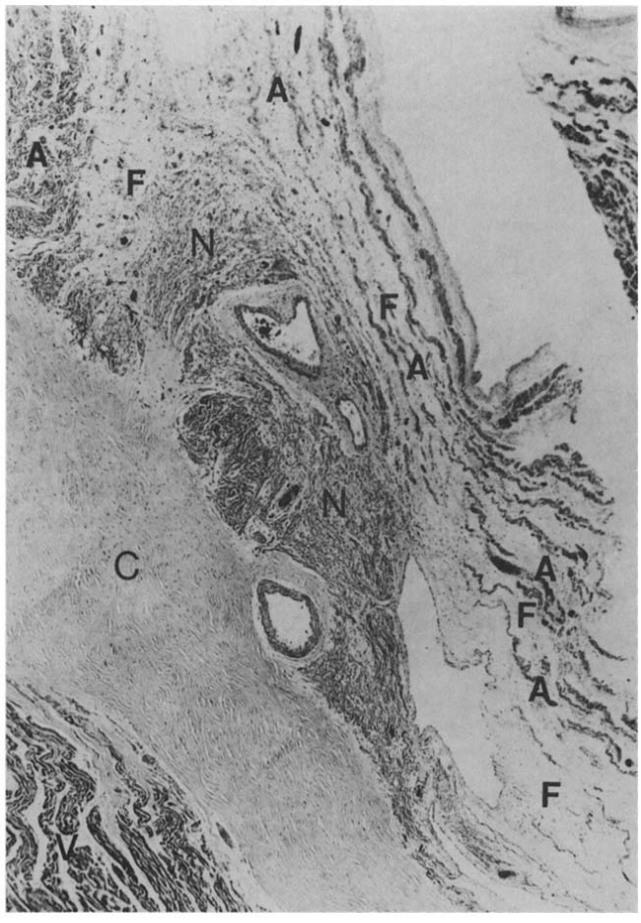


**Figure 2.** Case 2. Tenuous connection of the atrioventricular (AV) node with the surrounding atrial myocardium due to marked fatty infiltration, with chronic inflammation and moderate fibrosis of the node. A = approaches to the AV node; C = central fibrous body; F = fat isolating the node from the approaches; N = AV node; Hematoxylin-eosin ×30, reduced by 28%.

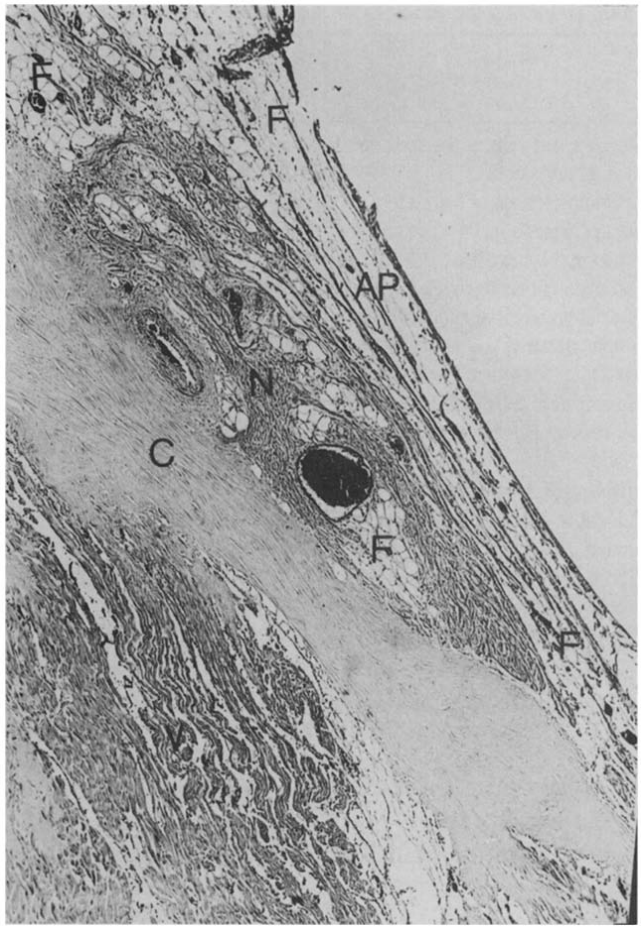


**Figure 3.** Case 4. Marked fatty metamorphosis of the atrioventricular (AV) node and its approaches. AP = approaches to the AV node; F = fat in and around the node; N = AV node; V = summit to the ventricular septum. Weigert-van Gieson ×45, reduced by 28%.

10) Moderate fibrosis and fatty metamorphosis of the summit of the ventricular septum.
11) Moderate fibrosis and hemorrhage of the right ventricle.

*Case 5*

1) Infiltration of mononuclear cells in the sinoatrial node.
2) Fatty metamorphosis of the atrial preferential pathways.
3) Atrioventricular node on top of the central fibrous body with an infiltration of mononuclear cells, with part of the AV node entrapped within the central fibrous body.
4) Segmented penetrating part of the AV bundle, with mononuclear cell infiltration.
5) Increase in fibrosis of the branching bundle, with linear formation of the posterior radiation of the left bundle branch and mononuclear cell infiltration.
6) Division of the right bundle branch into two components, with mononuclear cell infiltration and some fibrosis.
7) Focal areas of fibrosis in the mid-part of the ventricular septum.

*Case 6*

1) Sinoatrial node in part intramyocardial with fat, fibrosis (Fig. 5) and infiltration of mononuclear cells.
2) Atrioventricular node located at the aortic-mitral annulus and in part in the central fibrous body or the atrial septum, with infiltration of mononuclear cells.
3) Atrioventricular bundle (penetrating, branching and bifurcating portions) showing fibrosis and mononuclear cell infiltration.
4) Left bundle branch disrupted at various levels, especially in the posterior radiation, and replaced by fibrosis.
5) Ventricular septum with patchy fibrosis and arteriolosclerosis.

## Discussion

The incidence of death related to asthma is increasing throughout the world. It has been suggested that this may be related to asthma medications. It has also been suggested (1,2) that the risk is much greater in blacks <15 years of age.

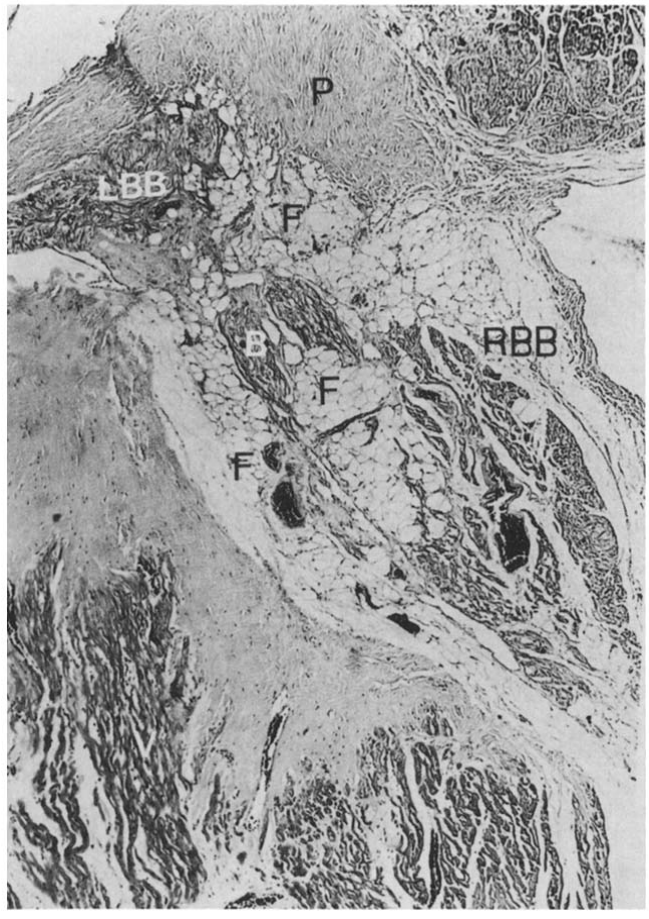


**Figure 4.** Case 4. Marked fatty infiltration of the bifurcating atrioventricular bundle (B) with loss of right bundle branch (RBB) and left bundle branch (LBB) fibers. F = fat; P = pars membranacea; Weigert-van Gieson ×45, reduced by 28%.

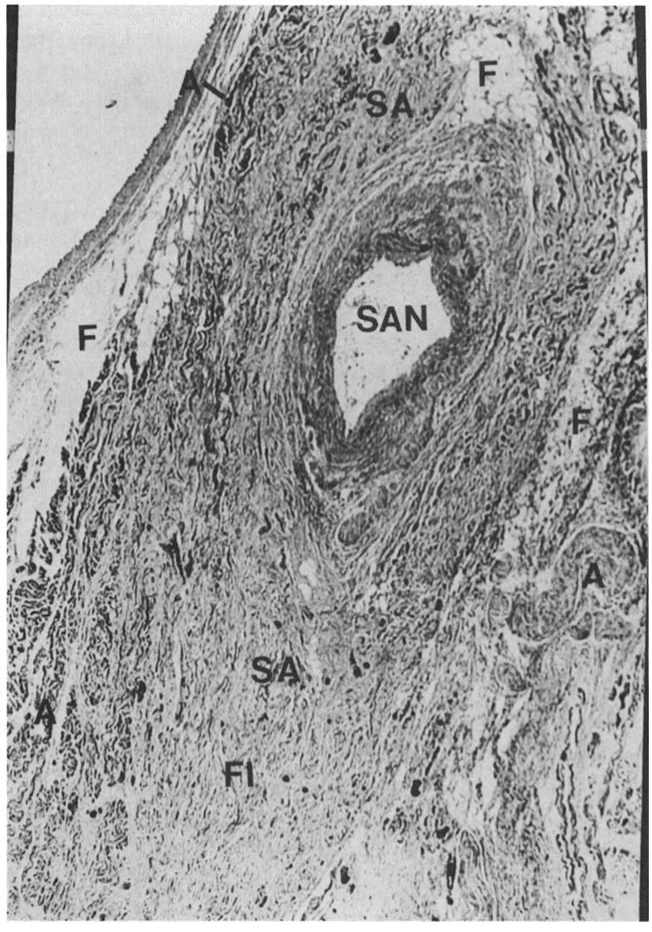


**Figure 5.** Case 6. Sinoatrial node, in part intramyocardial, with fat and fibrosis. A = approaches to the sinoatrial node; F = fat; FI = fibrosis; SA = sinoatrial node; SAN = sinoatrial node artery. Hematoxylin-eosin ×45, reduced by 28%.

Our study of the pathologic features of the conduction system demonstrates that there are indeed significant findings in this system. The pathologic findings in this system may shed some light or give new insight as to the possible causes of sudden death in those with bronchial asthma, especially the young.

**Conduction system.** The sinoatrial node artery was outside the node in one patient, markedly narrowed in two, with inflammatory cells in and around the sinoatrial node in five and small and fibrosed in one patient each. The AV node was within the central fibrous body in three patients, and at the aortic mitral annulus in one. It was isolated by fat from the surrounding atrial muscle, with marked fat within the node in one patient. Mild to moderate fat, fibrosis and mononuclear cells to a varying degree were present in all. The AV bundle was markedly fragmented in five patients (left-sided in one) and fibrosed in two (one left-sided). In addition, inflammatory cells were present in two patients and fat in one. The right and left bundle branches showed either fat, fibrosis or disruption in all. Increased fibrosis of the summit of the ventricular septum with patchy fibrosis was present in all, with arteriolosclerosis in two. These are distinct pathologic findings in young adults that are not found in normal healthy adults of similar age. The findings are seen in the sinoatrial node, AV node, AV bundle, the bundle branches and ventricular septum. These pathologic changes are quite similar to those found after sudden death in young healthy persons with no history of bronchial asthma (7). The anatomic and pathologic changes in the conduction system may form a milieu for an arrhythmic event during an altered physiologic state. Any one of these findings or any of their combination may promote a reentrant mechanism that may induce ventricular tachycardia, fibrillation and sudden death.

**What causes the pathologic findings in the conduction system?** We hypothesize that there is a group of individuals with asthma who may have abnormalities of the conduction system. Conversely, we may be dealing with a group of young people who are born with a susceptibility for an abnormal conduction system who may also be prone to asthma. The pathologic changes, especially the fibrosis, inflammatory cells and fat, may represent the end result of reactions related to the associated infections or the immune complex or system or that part of the immune system related

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to asthma. In some susceptible individuals, the immune mechanisms or hypersensitivity state responsible for asthma may also be related to the pathogenesis in the conduction system. This relation may not be the same in all cases of asthma at all ages. An epidemiologic study (8) has shown a statistically significant independent association between idiopathic dilated cardiomyopathy and a history of asthma, especially in persons <55 years of age. These findings support the theory that hypersensitivity mechanisms may play a role in the development of cardiomyopathy. Further studies are indicated to explore the exact mechanism and relation, if any, between asthma, arrhythmias, cardiomyopathy and sudden death in young adults.

We are indebted to Maryellen Kurek, Deborah Nichols and Chris James for technical assistance and Kay Pinson for secretarial assistance.

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