The Relevance of Platelet and Fibrin Thromboembolism of the Coronary Microcirculation, with Special Reference to Sudden Cardiac Death

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SUMMARY The coronary microcirculation was examined for platelet and fibrin thrombi in hearts from 21 normal subjects and 244 cardiac patients, including 168 with ischemic heart disease (IHD) and 76 with other types of heart disease. Seventy-seven cases were sudden cardiac death (SCD). No microthrombi were present in any of the normal hearts, whereas platelet and fibrin thrombi were present in the coronary microcirculation in 32 of 244 cardiac cases (13.1%), including 19 with IHD and 13 with other types of heart disease and after cardiac surgery. The microthrombi were either embolic or represented in situ thrombosis, depending upon the underlying pathologic process.

There was no significant difference in the incidence of microthrombi in SCD patients with IHD (10 of 50, 20%) compared with patients who survived longer (nine of 93, 10%). In SCD patients, however, platelet microthrombi were more frequent in patients less than 45 years of age compared with those older than 45 years of age ($p = 0.0002$).

We concluded that coronary microcirculatory thrombi are not uncommon in heart disease. A subgroup of SCD in young patients with IHD has been identified in whom microcirculatory platelet thrombosis is the main cardiac pathologic process. The significance of this process is emphasized by the associated myocardial damage.

INTEREST in the significance of alterations in the coronary microcirculation in cardiac disease is relatively recent. Initially, this interest related mainly to the role of degenerative or inflammatory changes in the small vessels of the heart, including those supplying the conduction tissue.\(^1\)\(^4\) Subsequently, reports of platelet aggregates in the coronary microcirculation in some cases of sudden death from cardiac disease\(^6\)\(^8\) led to speculation that such lesions might play a significant and possibly primary role in these cases.\(^9\) This hypothesis has gained some support from experimental evidence that suggests that emboli arising from proximal thrombi might provoke sudden death by initiating ventricular fibrillation.\(^10\)\(^11\) The significance of such microcirculatory platelet aggregates is further emphasized by their association with myocardial damage in patients with various disease states, including coronary atherosclerosis,\(^12\)\(^13\) thrombotic thrombocytopenic purpura\(^14\) and primary thrombocytosis.\(^15\)

It is important to clarify the role of microcirculatory thromboembolism in heart disease to achieve a better understanding of the pathophysiology of the conditions in which the lesions are found as well as to evaluate the possibility of treating these conditions. Several drugs that alter platelet reactivity are available and have reduced platelet aggregates in the microcirculation and mortality in experimental animals.\(^16\)\(^17\) In clinical trials of these drugs, decreased mortality has been observed in patients with cerebrovascular disease\(^18\)\(^19\) and coronary arterial disease,\(^20\)\(^21\) presumably through a platelet-inhibiting mechanism.

In recent clinical studies, an increased incidence of circulating platelet aggregates\(^22\) and enhanced platelet activation and release reaction\(^23\)\(^24\) have been linked to poor prognosis in patients with acute myocardial infarction, probably by promoting myocardial damage. However, there have been no documented morphologic studies of the actual incidence and sequelae of coronary microcirculatory thromboemboli in patients who die from cardiac causes. In this study, we attempted to determine the incidence and significance of postmortem platelet and fibrin thromboembolism of the small intramyocardial vessels in heart disease in general, and sudden cardiac death in particular, topographically assessed the distribution of such lesions in relation to proximal thrombosis of the main coronary arteries and simultaneously appraised the state of the myocardium.

Autopsy Material

We examined 265 hearts from adult patients who came to autopsy at the Hamilton General Hospital over a 3-year period. The cases were divided into two groups.

Cardiac Group

This included 244 patients with heart disease, 165 males and 79 females, ages 21–95 years. Sudden cardiac death (within 24 hours after the onset of the terminal clinical episode) occurred in 77 patients. In the other 167 patients who died after symptoms lasting more than 24 hours, cardiac disease was either the primary or a contributory cause of death. This group included 41 patients who underwent open heart sur-
surgery for aortocoronary bypass or valve replacement (table 1).

Control Group

This included 21 patients with normal hearts, 15 males and six females, ages 20-59 years. Death was due to noncardiac causes, and sudden death occurred in 12 cases.

Methods

At autopsy, the heart was removed intact from the body, examined externally and weighed. A control plain x-ray of the heart in the anteroposterior position was routinely taken for assessment of calcification of the coronary arteries or heart valves.

The coronary ostia were gently probed for evidence of ostial stenosis, using metal catheters of various calibers. Appropriate-sized catheters were inserted in the proximal 1.0 cm of the main coronary arteries and tied in place. Each coronary artery was injected in turn by contrast medium composed of 50% mixture of water and colloidal suspension of barium sulphate (60% W/W). The contrast medium was delivered from a reservoir at a constant pressure of 120 mm Hg for 2 minutes. The catheter was then clamped and the heart radiographed in the anteroposterior and left lateral positions. Kodak XM-2 x-ray films were exposed for 15 seconds at a kilovolt peak of 60-70.

After angiography, the main coronary arteries were dissected free of the heart. Where necessary, calcified vessels were decalcified in a mixture of 410 ml of 17.5 g/l of sodium formate and 90 ml of formic acid. All vessels were then sectioned at 3-mm intervals, any stenosis or thrombosis was recorded, and the sections were submitted for histologic examination. Histologic findings from the vessels were correlated with the postmortem angiographic appearance.

The ventricular myocardium was serially sectioned into 1-cm-thick slices starting at the apex and proceeding basally to within 3 cm of the atrioventricular plane and valvular rings. The myocardium was inspected for gross evidence of acute infarction or fibrosis. At least one section including any area of suspected infarction was used for enzymatic mapping of the infarct. Where no infarct was seen, the second basal section was used for routine enzymatic staining.

The fresh thick-heart section was placed in 250 ml of 1% 2,3,5-triphenyl-tetrazolium chloride reagent (Fisher Brand T. 413) in Sorenson's phosphate buffer at pH 8.5, in a water bath at 37°C for 30 minutes. At the end of the incubation the heart section was removed and stored in buffered 10% formalin solution. Blocks, 2.0 cm wide, passing from the endocardial to the epicardial surface of the ventricular myocar-
dium were selected for histologic examination. Twelve blocks were taken from the proximal and middle thirds of the ventricular myocardium. These were from the anterior, lateral and posterior left ventricular wall, anterior and posterior right ventricular wall, and the ventricular septum. In addition, two blocks were taken from the apical myocardium, for a total of 14 blocks from each heart.

One section from each of the 14 ventricular blocks was stained with hematoxylin and eosin and examined for platelet and fibrin thrombi in the small intramyocardial vessels. The composition of all thrombi was confirmed by special stains, and all thrombi were counted and recorded in relation to the area of the ventricular wall in which they were found. Correlation was then made to the presence or absence of any thrombosis of the main coronary artery supplying this area and to any associated myocardial lesions.

The microthrombi were characterized according to their composition. A platelet thrombus consisted predominantly of a mass of identifiable platelet aggregates and frequently included a small amount of fibrin, whereas a fibrin thrombus consisted predominantly of a hyaline or fibrillary mass that stained positively for fibrin (figs. 1A and B). A mixed thrombus contained variable proportions of platelets and fibrin (fig. 1C). An organizing or totally organized thrombus was partially or completely replaced by fibrous granulation tissue (figs. 1D and E).

<table>
<thead>
<tr>
<th>Type of heart disease</th>
<th>Male</th>
<th>Female</th>
<th>Open heart surgery</th>
<th>Sudden death</th>
<th>Total number of cases</th>
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<td>57</td>
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<td>59 (9)*</td>
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<td>Valvular and endocarditis</td>
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<td>12</td>
<td>16</td>
<td>9 (6)*</td>
<td>32</td>
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<td>0</td>
<td>1</td>
<td>5</td>
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<td>3</td>
<td>0</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
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<td>16</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>165</td>
<td>79</td>
<td>41</td>
<td>77 (15)</td>
<td>244</td>
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*Numbers in parentheses indicate cases of sudden death after open heart surgery. Abbreviation: DIC = disseminated intravascular coagulation.
Results

Platelet and fibrin microthrombi were found in the small intramyocardial vessels in 32 of the 244 cardiac cases (13.1%) (fig. 2), whereas no such lesions were present in any of 21 hearts in the control group. Of the 32 cases in which microthrombi were present in the coronary microcirculation, 19 had ischemic heart disease (IHD), six were associated with endocarditis and one had cardiac scleroderma and disseminated intravascular coagulation. Six of the 32 patients died in the immediate postoperative period after open heart surgery for coronary bypass or valve replacement. The number of microthrombi varied considerably in each group (table 2). The distribution of all observed microcirculatory thrombi according to the type of vessel involved was: 62% in the intramyocardial arterioles, 26% in the capillary vessels and 12% in

Figure 1. Intramyocardial arterioles. (A) Platelet thrombus with little fibrin. Martius yellow, brilliant scarlet red and aniline blue (MSB) stain; magnification × 158. (B) Fibrin thrombus associated with necrosis of the vessel wall. Hematoxylin and eosin stain; magnification × 240. (C) Mixed platelet and fibrin thrombus. MSB stain; magnification × 386. (D) Partially organized thrombus. MSB stain; magnification × 280. (E) Completely organized thrombus with foamy cells. MSB stain; magnification × 96.
venules; 11% of the microthrombi showed partial or complete organization. Regardless of the underlying type of heart disease, most vessels (58%) that contained the microthrombi were situated in the middle layer of the myocardium, particularly at the site of branching of the intramyocardial arterioles, to a lesser extent in the outer or subepicardial layer of myocardium (34%), and least in the inner or subendocardial layer of myocardium (8%). Marked differences in the distribution and composition of the microcirculatory thrombi were found between the various groups according to the type of heart disease and the duration of survival after the onset of the terminal clinical episode (table 2).

Ischemic Heart Disease

Excluding the operative cases, 10 of 50 patients (20%), ages 25–53 years, who died suddenly had platelet thrombi in the coronary microcirculation. Of these, eight of 14 patients were under 45 years of age and only two of 36 were older than 45 years of age. This difference in incidence was highly significant (p = 0.0002, Fisher’s exact test). The mean survival time was 9.3 hours from the onset of the terminal clinical episode. A recent thrombus was found in at least one major coronary artery, with underlying intimal fibrosis or mild atheromatous stenosis (< 50%) in eight cases; these thrombi were mostly nonocclusive and consisted predominantly of platelets. In five of the 10 cases (50%), the thrombi in the microcirculation were correlated with a thrombosis of the major coronary artery supplying the area and were, therefore, probably embolic in origin. In two of these, fragments of thrombus were also present in the lumina of some epicardial coronary branches distal to the site of the main thrombus. There was, however, no such correlation in the other five cases (50%), in which the microcirculatory involvement was diffuse and not related to a thrombosed coronary artery (figs. 3A and B). In two cases, some intramyocardial arterioles, particularly in the subendocardial layer, showed marked intimal fibrous hyperplasia. Only four of the 10 cases (40%) showed an acute myocardial infarction on enzymatic staining of a thick-heart section. Four others (40%) showed healed chronic infarcts associated in three with organized thrombosis of the corresponding coronary artery and in one with arterial stenosis. Microscopically, all 10 cases showed focal myocardial lesions that were either scattered or coalescing and consisted mainly of myofibrillar lesions (figs. 4A and B), focal myocyte lysis (fig. 4C), or organized microinfarcts. The intramyocardial capillary vessels in which platelet thrombi were present showed endothelial damage. The gross infarcts in cases with diffuse involvement of the coronary microcirculation were usually extensive or circumferential, had ill-defined borders and were not localized to the area of

<table>
<thead>
<tr>
<th>Type of heart disease</th>
<th>Terminal clinical episode</th>
<th>Number of cases</th>
<th>Acute coronary thrombosis</th>
<th>Thrombi in coronary microcirculation</th>
<th>Acute infarction</th>
<th>Focal myocardial lesions</th>
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</thead>
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<tr>
<td>Ischemic heart disease*</td>
<td>Sudden death</td>
<td>10</td>
<td>8</td>
<td>31 ± 31</td>
<td>++</td>
<td>4</td>
</tr>
<tr>
<td>Ischemic heart disease*</td>
<td>Over 24 hr</td>
<td>9</td>
<td>7</td>
<td>11 ± 17</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>After cardiac surgery†</td>
<td>Sudden death</td>
<td>6</td>
<td>4</td>
<td>15 ± 5</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Over 24 hr</td>
<td>5</td>
<td>0</td>
<td>36 ± 49</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>sudden death</td>
<td>1</td>
<td></td>
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</tbody>
</table>

*Excluding operative cases.
†Coronary bypass graft or valve replacement.
‡Semiquantitative assessment of relative amount of thrombus components: maximum = +++; minimum = ±.
Abbreviation: DIC = disseminated intravascular coagulation.

![Figure 2. Incidence of microcirculatory platelet and fibrin thrombi according to the type of heart disease and operative treatment. *Excluding operative cases; †complicated by endocarditis or disseminated intravascular coagulation; ‡aortocoronary bypass or valve replacement.](http://circ.ahajournals.org/).
supply of one main coronary artery.

Excluding operative cases, nine of 93 patients (9.6%) with IHD, ages 28–83 years, who survived longer had thrombi in the coronary microcirculation. The mean survival time was 5.3 days after the onset of an acute myocardial infarction. Four of these patients also had previous old infarcts. In eight of the nine cases, advanced atherosclerosis with more than 75% stenosis was present in at least one major vessel, with acute thrombosis in seven cases and organized thrombosis in four cases. In eight cases, only a few fibrin thrombi were present in the small intramyocardial vessels. The affected vessels were situated within the area of infarction and appeared to be part of the infarction process because the vessel walls were necrotic. Thus, the lesions were suggestive of in situ thrombosis rather than embolization. In two of the eight cases, platelet thrombi were also present in a few vessels in the area of viable myocardium adjacent to the infarct. These were within the distribution of the thrombosed main coronary artery and were therefore probably due to a terminal embolic event. The ninth case, a 28-year-old woman with no history of heart disease, is of special interest. She was admitted to hospital after sudden collapse with severe chest pain and survived for 5 days on life support measures in the intensive care unit. Autopsy examination showed an extensive acute myocardial infarction with ill-defined borders. Histologically, coagulative necrosis and myofibrillar lesions of the myocardial fibers were seen, associated with recent interstitial hemorrhage. All main coronary arteries were patent and normal, but the coronary microcirculation was extensively and diffusely obstructed by fibrin microthrombi. A few of these vessels also showed evidence of acute vasculitis, but there was no evidence of vasculitis or microthrombi in other organs.

In the IHD group, there was no statistically significant difference in the incidence of microcirculatory thrombi between the patients who died suddenly and those who survived longer \( p = 0.0721 \), Fisher's exact test). However, the extent of the myocardial damage was proportional to the number of microthrombi in the sudden death patients, whereas there was no direct relationship between the size of the acute infarct and the number of microthrombi present in those who survived longer.

**Figure 3.** (A) Angiogram of coronary microcirculation showing diffuse occlusion of the small intramyocardial vessels, which histologically contained platelet thrombi. The main coronary arteries showed recent thrombosis of the left anterior descending artery, and all other main vessels were patent (40-year-old female with ischemic descending disease who died suddenly). (B) Angiogram showing normal coronary microcirculation in a postmortem thick-heart section from a 39-year-old male with a normal heart.

**After Cardiac Surgery and Other Types of Heart Disease**

Of 41 fatalities after open heart surgery for coronary bypass or valve replacement, 15 patients
(37%) died suddenly in the immediate postoperative period. Of the latter, six patients (40%), ages 54–65 years, had mixed platelets and fibrin thrombi in the coronary microcirculation. In four cases, the microcirculatory thrombi were associated with acute myocardial infarction and proximal acute thrombosis of a coronary artery or bypass graft. In the remaining two cases, the microthrombi were not related to proximal arterial thrombosis but were associated with focal myocardial necrosis and myofibrillar lesions. However, there was no constant relationship between the number of microthrombi observed and the extent of the myocardial injury.

All six patients with endocarditis had diffuse microcirculatory thrombi in the coronary microcirculation, with normal and patent main coronary arteries. Five cases were due to infective endocarditis, and one case was due to noninfective thrombotic endocarditis. Of the five patients with infective endocarditis, ages 47–67 years, the aortic valve was involved in
two and the mitral valve in two. The fifth case had asymmetrical hypertrophic cardiomyopathy with endocardial vegetations superimposed on fibrous plaques on the base of the papillary muscle of the mitral valve and the opposite ventricular septum. One patient died suddenly out of the hospital, whereas the other four patients had been hospitalized for an average of 6 days. In all five cases, the microcirculatory thrombi were composed mainly of fibrin similar in composition to the endocardial vegetation; some thrombi were organized, indicating repeated embolic episodes. Microorganisms were detected by special histologic stains in only four of 148 microthrombi observed in this group.

The only case of noninfective thrombotic endocarditis involving the mitral valve occurred in a 69-year-old woman who died after being hospitalized for 10 days. At autopsy, multiple small vegetations composed of large masses of platelets, including a small quantity of fibrin, were found at the free margin of the mitral valve leaflets. The vegetations caused extensive platelet embolization to the coronary microcirculation.

In patients with endocarditis, the thromboemboli were associated with focal myocardial necrosis, either recent or old, and in two cases, the myocardial damage was extensive and resulted in transmural myocardial infarction. The extent of the myocardial necrosis was directly proportional to the number of the small vessel thromboemboli. In all six cases of endocarditis, similar embolic phenomena and tissue damage were observed in other organs of the body, particularly in the brain, spleen and kidneys.

The single patient with disseminated intravascular coagulation was a 29-year-old woman with systemic sclerosis who died suddenly and unexpectedly in the postpartum period. At autopsy, several small vessels were occluded by fibrin microthrombi, resulting in multiple foci of acute myocardial fiber necrosis. The intravascular coagulation process was widespread throughout the organs of the body, particularly in the kidneys.

Discussion

The results of this study confirm that platelet and fibrin thromboembolism of the coronary microcirculation and associated myocardial damage are not uncommon in various types of heart disease, but are encountered mainly in IHD and endocarditis and after cardiac surgery. The coronary microthrombi were either embolic or in situ thrombosis, depending upon the underlying pathologic process.

In IHD, coronary microcirculatory thrombi were present in patients who died suddenly and those who survived longer. However, the distribution and composition of the microthrombi varied in the two groups. In half the patients who died suddenly with IHD, microcirculatory lesions were diffusely distributed throughout the coronary microcirculation and were not limited to being downstream of a proximal coronary thrombus. The microthrombi consisted predominantly of platelets, and the extent of the myocardial damage was proportional to the observed number of microthrombi. The patients with IHD who survived longer had microcirculatory lesions that were predominantly fibrin and were, with one exception, localized to an area of established infarction. Possibly, these patients originally had platelet microthrombi that underwent fibrinous transformation. In animal studies, microthrombi were rapidly transformed from platelet aggregates to fibrinous masses within 24 hours. This mechanism may be applicable to the only young patient in this group who had diffuse microcirculatory thrombi. However, in most patients who survived longer, the microthrombi probably represented in situ thrombosis and from their initiation were predominantly fibrin.

Our observation that the incidence of microcirculatory thrombosis in IHD was not significantly different in the patients who died suddenly compared with those who survived longer is consistent with the data presented by Haerem. However, the finding in that series of significantly greater numbers of platelet aggregates in the intramyocardial arterioles in 27 cases of sudden death compared with 16 chronic coronary cases is at variance with our results. The present study may not be directly comparable to Haerem's series, because in that author's patients, all of whom were above 40 years of age, sudden death was defined as occurring within minutes of the onset of the terminal clinical episode, whereas in the chronic coronary cases, death occurred several months after a myocardial infarction. Further, it is not clear whether Haerem counted fibrin as well as platelet thrombi.

The mechanism of formation of the microcirculatory lesions in sudden death due to IHD is not certain. One explanation is that the lesions represent downstream embolization from proximal platelet aggregates on atherosclerotic plaques. Jørgensen showed experimentally that platelet mural thrombi in proximal vessels embolized distally to the microcirculation over an extended period of time. This mechanism could explain not only the lesions downstream of the proximal occlusion, but also the microcirculatory lesions without proximal thrombi seen at autopsy, if such thrombi had previously existed but shattered and embolized totally into the microcirculation. Considering the lack of evidence of significant atherosclerotic disease in the proximal vessels in areas of involved myocardium, this seems an unlikely explanation for most cases. The second possibility is that the thrombi occurred as in situ lesions in the microcirculation. It has been shown that myocardial ischemia in dogs produced capillary endothelial damage with subsequent stasis and platelet aggregation in the coronary microcirculation. If ischemia were generalized, as would occur if coronary arterial spasm involved more than one main coronary artery, diffuse distribution of platelet aggregates might be expected.

Enhanced platelet reactivity may also lead to microcirculatory platelet thrombosis in certain subjects. In a recent study, a subset of patients with IHD
showed transient increased levels of platelet factor 4 during periods of exercise-induced myocardial ischemia. Enhanced reactivity may also result from the effect of hormones or chemicals. Haft et al. showed that infusion of catecholamines into the coronary microcirculation resulted in diffuse microcirculatory platelet aggregates. The circulatory lesions so produced were associated with myofibrillar lesions and resulted in permanent ischemic myocardial damage. The formation of aggregates by this mechanism would produce stimulation of platelets, leading to the formation of endoperoxides, which are converted to thromboxane A2, perhaps resulting in coronary vasospasm and stimulation of further platelet aggregation. The possibility that the lesions observed were the result of drugs used in the treatment of cases during their terminal phase was considered an unlikely explanation because not all patients who had microcirculatory thrombi received catecholamines. In addition, several patients in this study who received similar treatment had neither microcirculatory platelet thrombi nor myofibrillar lesions.

The present findings, supported by the experimental data, suggest that the distribution of microcirculatory thromboemboli in patients who died suddenly with IHD might be explained by a two-stage mechanism. Initially, all or part of a proximal coronary mural thrombus may disintegrate and shower the distal microcirculation in the area of supply of the vessel. The resulting myocardial damage might then induce the formation or release of chemical mediators, as shown in man, which stimulate further platelet aggregation and myocardial damage in areas of the heart remote from the initial lesion. Support for this type of mechanism is available from experiments in dogs, in which acute occlusion of the left anterior descending artery resulted in focal myocardial necrosis of the posterior ventricular wall. The sudden death patients with IHD who sustained extensive myocardial damage most likely died of pump failure of the ventricular myocardium. Ventricular arrhythmia is a possible cause of death of other patients with less extensive myocardial damage. In animal experiments, platelet aggregates induced in the coronary microcirculation by catecholamines or stress were associated with a high incidence of death from ventricular arrhythmia. In dogs, the administration of drugs that block platelet reactivity reduced the incidence of both microcirculatory lesions and arrhythmia. However, these data require cautious interpretation in view of the results of recent experiments that suggest that some antiplatelet drugs may possess an antiarrhythmic effect independent of their platelet-inhibiting action.

The important finding in this study is that in one-half of fatal cases of IHD in patients less than age 45 years, predominantly platelet coronary microcirculatory thromboemboli were associated with and presumably produced significant myocardial damage. Of six cases of sudden death in men less than 45 years old, Frank et al. observed platelet microemboli in the small intramyocardial vessels in four cases, which were associated with nonobstructive mural thrombi in the proximal coronary arteries. These observations support the potential importance of the process described and suggest that it might contribute significantly to sudden death in young patients with coronary artery disease, often as the first evidence of the presence of heart disease. Although the incidence of IHD increases with age, there is ample evidence that in the younger age group, IHD carries a relatively more serious prognosis with a higher risk of sudden cardiac death. IHD has also been associated with abnormal platelet reactivity.

In conclusion, a subgroup of sudden death patients with IHD has been identified in whom microcirculatory platelet thrombosis appears to be the main cardiac pathologic process. Studies of larger populations are necessary to obtain further information on this important subject.

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