Precursors of Sudden Coronary Death

Factors Related to the Incidence of Sudden Death

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SUMMARY

Precursors of sudden death were sought in men — 1838 civil servants in Albany, New York, and 2282 residents of Framingham, Massachusetts — under continuous surveillance for 16 years. In men 45–74 years old there were 234 deaths attributed to coronary heart disease (CHD) of which 109 occurred within one hour of onset of symptoms. More than half of all deaths due to CHD occurred outside the hospital and about 80% of these were sudden. Most were unheralded by prior symptoms of CHD.

Persons at high risk of death from CHD, including sudden death, can be identified long before the terminal unexpected catastrophe. The same precursive stigmata exist in persons subject to coronary attacks whether or not immediately fatal. The risk of sudden death in these two populations was positively correlated with high blood pressure, the electrocardiographic pattern of left ventricular enlargement, obesity, and heavy cigarette usage.

Sudden death is a common and possibly incidental expression of lethal coronary heart disease. The potential candidate for sudden death cannot be confidently distinguished from the individual who succumbs more slowly of myocardial infarction. The inescapable conclusion is that the prevention of sudden death requires the prevention of coronary attacks.

Additional Indexing Words:

Sudden death          Coronary heart disease          Myocardial infarction
Risk factors          Hypertension                  Left ventricular enlargement
Obesity               Cigarette smoking            Physical activity

A REVIEW OF THE NATURAL HISTORY of coronary heart disease (CHD) leads to the inescapable conclusion that a substantial reduction in the rate of premature mortality from this disease requires the early detection of persons particularly susceptible to coronary attacks as well as the identification of those factors predisposing to sudden death which could be modified. This report examines the circumstances under which sudden coronary deaths occurred in two population samples in Albany, New York, and Framingham, Massachusetts, which have been under continuous medical surveillance for 16 years. Precursors of sudden death are dealt with in particular.

Study Procedure

Observations have been made on the 4120 men of the original cohort who were found to be free of CHD at first examination: 1838 civil servants in Albany 39–55 years of age at entry and 2282 men residing in Framingham 30–62 years of age at entry. A detailed cardiovascular examination was carried out annually in Albany and biennially in Framingham. At the first examination, information was obtained concerning current form and amount of daily tobacco consumption; relative body weight and arterial blood pressure were measured; an electrocardiogram was done as well as a variety of biochemical assays. Details for Framingham are available elsewhere. The methods used at Albany were essentially the same. At Framingham about 85% of participants reported for the last possible examination and about 2% were completely lost to follow-up. The experience at Albany was similar. Analysis is restricted to sudden deaths in men aged 45–74 years at the time of death. Too few sudden deaths outside this age range occurred for meaningful analysis. Furthermore, all persons with definite and suspect CHD at entry are excluded from all analyses. This was done to avoid the possibility that the pre-existence of CHD affected the characteristics under study.

Diagnostic Criteria

The diagnostic criteria employed by each study for the various clinical manifestations of CHD have been previously reported in detail.1–3

Sudden death was attributed to CHD when an apparently well person was observed to collapse and expire within one hour of onset of symptoms, usually in a matter of minutes, where no other cause was suggested by the medical history. Two categories were distinguished: sudden unexpected death without prior CHD, and sudden death in subjects in whom CHD had been detected after entry into the study.
(more than 30 days prior to death). Deaths occurring within 30 days in the course of a diagnosed, established acute coronary attack are not included as sudden deaths. Men found dead in bed without explanation are also excluded from analysis. Eleven hospitalized sudden deaths—five with prior CHD—included those who reached the emergency room alive but died within one hour of onset of symptoms.

By a coronary attack is meant any major manifestation of CHD (i.e., myocardial infarction, CHD fatality—sudden and nonsudden—and the coronary insufficiency syndrome) other than angina. A coronary fatality includes only fatalities within 30 days of an acute coronary attack. The professional personnel of the Albany and Framingham studies have met periodically since 1952 and are well acquainted with each others' viewpoints on the classification of CHD and are in close agreement.

Cardiovascular Surveillance

In Albany, transcripts of all hospital records are systematically secured for all participants. Death certificates are also routinely obtained. A specially trained nurse interviews the widow or other close relative of all individuals who expire suddenly outside of hospital. In Framingham, in addition to periodic cardiovascular examinations, all interim cardiovascular illnesses are monitored by daily surveillance of hospital admissions. Hospital protocols and medical examiners' reports are reviewed. Death certificates are obtained and reports from physicians are routinely scrutinized. The circumstances of sudden death are derived from information from the medical examiner, the witness to the death, close relatives and from the attending physician.

Where it was not possible to ascertain that death had actually occurred in less than one hour and where some lethal condition was known to have been present, the case was excluded from the category of "sudden death."

Analysis

The risk of sudden death was related to characteristics measured at the time of initial examination by calculating the annual age-specific incidence of sudden death against person-years exposure to a risk factor. Where the number of deaths was small, as it often was, the age-adjusted incidence for the entire age band was calculated.

In calculating person-years experience each person still alive on any specified examination was considered to be at risk until the next biennial examination and for that interval to contribute two years experience to the age group he was then in. This experience was summed to yield person-years experience. Age-adjusted rates were computed separately for each of the studies and for the pooled data from both studies, as follows: if \( P_i \) is the proportion of all the sudden deaths in the specified study in age group \( i \) and \( r_j \) is the rate for level \( j \) of age group \( i \) then \( \Sigma P_i r_j \) is the age-adjusted rate for level \( j \).

In figures 4–7 each age-adjusted rate has an accompanying ratio of the number of cases/person-years experience. While the age-adjusted rate is, of course, not calculated directly from these two numbers they do indicate the amount of pooled experience available. Each study contributed roughly half the person-years experience at each level.

Justification for pooling the data from the two studies is based primarily on similarities in study techniques and similarity in findings. While there are some differences in characteristics as measured, the study similarities are much more striking (table 1). Sudden death rates are also similar in the two populations, and except for the age group 65–74, the two studies contribute a similar amount of experience (table 2). These facts, together with the close similarity in study methods, warrant pooling data.

**Results**

Size and Nature of the Problem

Sudden and unexpected death is a striking feature of CHD. If it is assumed, as it is assumed in this article, that all sudden deaths without other explanation are, in fact, attributable to CHD, then 16% of first coronary attacks are manifested in this way. Thus sudden death is not infrequently the first and terminal clinical manifestation of coronary disease.

Sudden death is the commonest mode of exitus of victims of either symptomatic or silent CHD. An examination of the prior medical status of men 45–74 years of age who died suddenly showed that about 60% had no prior evidence of CHD. Variation in the proportion of unexpected sudden deaths with age was not statistically significant, although there was some indication that in those over 65 the proportion may be smaller.

In men with known CHD and presumably but not

**Table 1**

| Average Values for Specified Characteristics by Age (Population at risk in Framingham and Albany, aged 45-64) |
| ----------------- | ----------------- | --------------------------------- | --------------------------------- |
|                  | 45-54             | 55-64                           |
|                  | Albany Mean       | Framingham Mean                 | Albany Mean                      | Framingham Mean                 |
| Systolic blood pressure (mm Hg) | 133.1             | 135.1                           | 134.9                             | 139.7                           |
| Serum cholesterol (mg/dl)        | 228.5             | 226.4                           | 228.1                             | 228.4                           |
| Metropolitan relative weight*    | 114.0             | 118.9                           | 114.5                             | 119.6                           |
| LVH-ECG                  | 2.2               | 2.2                             | 2.7                               | 3.5                             |
| 20 or more cigarettes/day      | 44.0              | 51.0                            | 41.5                              | 39.9                            |

LVH-ECG = Electrocardiographic evidence of left ventricular hypertrophy.

*Based on Metropolitan Life Insurance Tables.

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necessarily under some sort of medical management, about 40% of coronary deaths were sudden, a figure not substantially lower than that in men without known CHD (fig. 1). Most sudden deaths occurred outside the hospital and out of reach of possible resuscitation (fig. 2). Forty percent of all deaths from CHD but only 10% of sudden deaths occurred in hospital. Even in those men with known CHD only 10% (5/47) of sudden deaths were in hospital. Lethal coronary attacks are too often sudden, whether or not CHD has been previously recognized.

Factors Related to Sudden Death Incidence

A substantial reduction in coronary mortality can be achieved only by the prevention of sudden and unexpected coronary death. Identification of the candidate for sudden death, as well as the factors which render him vulnerable, are prerequisites. In general, the same factors associated with an increased risk of morbidity and mortality from CHD are also correlated with liability to sudden and unexpected death.

Age

In men aged 45–74 years, 119 deaths in Framingham and 115 deaths in Albany were attributed to CHD in the 16 years of observation. Of these deaths, 60 in Framingham and 49 in Albany were sudden. The 16-year incidence rate for sudden death rose steeply with age up to age 65, and then declined. This decline, based on average annual rates, appeared to be steeper for unexpected sudden death without prior CHD (fig. 3). Because the numbers involved are small, this trend is only suggestive.

Prior CHD

It has long been recognized that persons with clinically overt CHD are particularly liable to sudden death. The incidence was about four times that of the general population without CHD.

However, 85% (62/109) of men dying suddenly in this study had no prior evidence of CHD. At any age, men more vulnerable to sudden death could be identified, even in the absence of overt CHD.

Precursors of Sudden Death

The annual rate of sudden death rose progressively with the blood pressure in both cohorts. Men with systolic pressures of 160 mm Hg or greater had three times the incidence of sudden death as men with systolic pressures under 140 mm Hg (fig. 4).

The relationship of antecedent serum cholesterol levels to the incidence of sudden death was less clear. No stepwise trend proportional to the serum cholesterol value was seen for coronary mortality in either population sample (fig. 5).

In neither study was there an excess of sudden death among diabetics but the number of diabetics and the number of sudden deaths among them was

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**Table 2**

<table>
<thead>
<tr>
<th>Age at exam</th>
<th>Number of deaths</th>
<th>Population at risk*</th>
<th>Annual rate/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>12</td>
<td>13,208</td>
<td>0.90</td>
</tr>
<tr>
<td>55–64</td>
<td>36</td>
<td>8,741</td>
<td>4.11</td>
</tr>
<tr>
<td>65–74</td>
<td>1</td>
<td>523</td>
<td>1.91</td>
</tr>
<tr>
<td>75–84</td>
<td>2</td>
<td>1,445</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Person-years experience.

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**Figure 1**

Proportion of total sudden coronary deaths associated with prior evidence of coronary heart disease, men aged 45–74 at death. The fraction alongside the bars relates the actual number of deaths to the number of cases.

**Figure 2**

Hospitalization status of CHD deaths.

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too small to provide a reliable estimate of an age-specific rate for sudden death.

The risk of CHD has, in general, been shown in prospective studies to be related to the level of each of the foregoing atherogenic traits, and further, to be compounded by the number of antecedent atherogenic factors simultaneously present.4,6

Living Habits

The amount of overweight was distinctly related to the rate of sudden death in all age groups. Risk was particularly marked in grossly overweight men but also appeared to rise progressively with the degree of overweight (fig. 6). The apparent difference in trends between Albany and Framingham could have arisen by chance.

Sudden death was also clearly related to cigarette habit. Non-smokers were spared. In all but the oldest group a marked increase in the incidence of sudden death was observed in cigarette smokers. In young men dying prior to the age of 55 years there were 29 sudden deaths out of the 15832 person-years experience for cigarette smokers but only two in non-smokers despite their 9562 person-years exposure to risk. In the entire cohort, smokers had a three fold higher rate of sudden death than non-cigarette smokers (fig. 7).

ECG-LVH

The electrocardiographic pattern of left ventricular enlargement (ECG-LVH) was examined in relation to sudden death. (The electrocardiographic observations will be dealt with in detail in a later report.) The appearance of the electrocardiographic pattern of left ventricular hypertrophy in a man with one or more atherogenic traits and without valvular disease strongly suggests the existence of occult ischemic

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**Figure 3**
Annual incidence of sudden death (SD) according to age. The number of sudden deaths and person-years corresponding to the above bars (from left to right) are as follows:

- No. of SD: 31, 68, 10, 17, 42, 3
- Person-years: 25554, 17605, 3305, 25554, 17605, 3305

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**Figure 4**
Age-adjusted incidence of sudden death according to systolic blood pressure. The number of sudden deaths associated with each group's incidence rate are 43, 32, 22, and 12.

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**Figure 5**
Age-adjusted incidence of sudden death according to serum cholesterol. The number of sudden deaths associated with each group were 46, 17, 11, and 32.

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**Figure 6**
Age-adjusted incidence of sudden death according to relative weight. The number of sudden deaths associated with each group were 9, 12, 24, and 64.

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*Metropolitan tables*
heart disease. Sudden death occurred significantly and strikingly more frequently in each age group when there was prior ECG-LVH. Men with this abnormality had a five fold increase in risk of sudden death. Age-adjusted annual rates were 14.0 and 2.7 per 1,000, respectively, for those with and without LVH.

Multivariate Results

An examination of the net effect of variables under consideration in relation to sudden death employing multivariate regression analysis reveals that for the variables listed in table 3 all but cholesterol make a significant, independent contribution to risk. This analysis is restricted to the age groups 45-54 and 55-64. Judging from the size of the value of the t-test, the cigarette habit would appear to be the most potent contributor in these age groups (i.e., the P value associated with a t(B) of 5.52 is extremely low).

Thus, at any age the incidence of sudden death was distinctly greater in persons with antecedent coronary risk factors. Risk increased with the number of these risk factors categorically defined. However, more moderate abnormalities were also associated with an increased risk and combinations of these add up to an ominous coronary profile presaging sudden coronary death. An examination of risk of sudden death according to risk function score computed from ingredients related to coronary attacks (i.e., cholesterol, systolic blood pressure, ECG-LVH, cigarette habit, and relative weight) revealed that risk varied over a 14-fold range in proportion to the score (table 4). Thus, it is possible to identify a tenth of the general population from which a third of the sudden deaths will emerge using only established coronary risk factors. This is true whether persons with or without prior CHD are considered.

Discussion

These data on the incidence of sudden death agree in general with previously published information. When these other data are examined closely, however, some discrepancies are not easily resolved.

Few published studies deal with the population at large and even fewer are prospective. Thus, reliable estimates of the real incidence of sudden and unexpected death are difficult to arrive at. Serious bias exists in studies restricted to deaths certified by the medical examiner. The frequency of certification by the medical examiner is greatly influenced by ethnic, religious, and cultural factors.

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>0.0125</td>
<td>0.0044</td>
<td>2.82</td>
</tr>
<tr>
<td>ECG-LVH</td>
<td>2.32</td>
<td>0.352</td>
<td>6.64</td>
</tr>
<tr>
<td>Metropolitan relative weight</td>
<td>0.0227</td>
<td>0.0058</td>
<td>3.95</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>0.0376</td>
<td>0.0068</td>
<td>5.52</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.0025</td>
<td>0.0023</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Estimates by the method of Walker-Duncan derived separately for the age groups 45-54 and 55-64 at biennial exam preceding death.

Table 4

<table>
<thead>
<tr>
<th>Decile of multivariate risk*</th>
<th>No. of sudden deaths</th>
<th>2-year incidence of sudden death/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>97</td>
<td>4.34</td>
</tr>
<tr>
<td>Prior CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>10.80</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.80</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>2.52</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2.52</td>
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<td>2.69</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>5.37</td>
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<tr>
<td>8</td>
<td>10</td>
<td>4.48</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>7.61</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>14.32</td>
</tr>
</tbody>
</table>

*Multivariate function includes systolic blood pressure, ECG-LVH; relative weight, cigarettes smoked/day, and serum cholesterol (see table 3). Ranking is based on specific functions for the age groups 45-54 and 55-64.
social, racial, and economic factors and often, doubtless, by expediency. These considerations probably account for estimates of the frequency of sudden death from "natural causes" which vary from 15–30%.10,13 The proportion of sudden deaths attributed to CHD also varies widely, particularly in autopsy series. These different estimates depend both on the source of the information as well as the definition of the suddenness of death. It is felt that the prospective observations of the combined Albany-Framingham studies provide a more nearly representative sample of sudden death in adults.

The present observations compared with other prospective population studies reveal obvious differences but these may be more apparent than real. A community-based study in Tecumseh, Michigan, using essentially the same methodology as the Albany-Framingham studies, reported that 52% of CHD deaths occurred outside the hospital, compared to the Albany-Framingham percentage of 60.13 A death certificate study in Belfast, Ireland, reported that 60% of CHD deaths occurred outside hospital.14 In a death certificate study in King County, Washington, it was found that 63% of CHD deaths among men 50 years of age or younger occurred within one hour.15 In the HIP study in New York City roughly 55% of the unexpected CHD deaths were sudden, a figure almost identical with that of Albany-Framingham.16 In Baltimore, on the other hand, the percentage of deaths due to atherosclerotic heart disease occurring in less than two hours (there is no figure for death occurring in less than one hour) was only 27%.17

Despite differences in age-sex distribution, criteria for CHD, definition of sudden death, and case-finding procedures, the proportion of coronary attacks first presenting as sudden death, nevertheless, varies within the narrow range of 19–26% in eight out of the ten studies reviewed.17

The proportion of sudden deaths truly unexpected may possibly not be as large as it appears. The Baltimore study reported that 36% of those dying suddenly of CHD had seen a physician within the preceding month.17 On the other hand, so had 22% of the general population of Baltimore who died of other causes.17 No information is provided as to why these people consulted a physician or what was found.

It is well documented that many people postpone seeking medical assistance, sometimes for many hours after a heart attack begins.18-21 Symptoms suggestive of coronary insufficiency, unrecognized or denied, are sometimes present in individuals for considerable periods immediately preceding the overt attack.22 Our only source of information on the incidence of this tendency comes from persons who survive long enough to enter a coronary care unit. Such observations provide no useful basis for developing techniques to prevent more than a small number of the CHD deaths designated sudden and unexpected.

In several studies it has been noted that the proportion of sudden CHD deaths decreases with age. This is sometimes expressed as an increasing average length of survival after a heart attack among older people.14,17,23,24 The combined data for Albany and Framingham are moot on this point, although not inconsistent with the conclusion.

The catalog of possible precursors of sudden death considered in this report is by no means complete. Other factors have been implicated. For instance, myocardial "irritability," evidenced by ventricular premature beats, has been found to be associated with an increased risk of sudden death both in coronary care units and in population studies.13 This is not a significant prognostic finding in persons without clinically manifest heart disease and without ECG abnormalities in the experience reported here.

Lack of physical activity has been implicated in lethal coronary attacks. An "activity index" was computed for each subject at the time of the fourth biennial examination in Framingham, based on a weighted estimate of hours spent at various levels of physical activity both at work and during leisure hours. Similar data are not available in the Albany cohort. In ten years of follow-up subsequent to this assessment of activity, 26 sudden deaths occurred. The most sedentary men appeared to have more than double the risk of sudden death compared with the more active.25

CHD has for several decades been the leading cause of death in the United States, accounting for nearly one death in three in the age group 35–64 years. More than 80% of the cardiac mortality in this age group is due to CHD. While the rate of CHD increases inexorably with advancing age, it is also the chief cause of death in younger adults. Half of all deaths due to CHD are sudden.

There are compelling reasons for believing that many of these premature coronary deaths could be delayed or avoided. Atherosclerosis is not an inevitable consequence of growing old. Epidemiologic investigations have repeatedly delineated the precursors of coronary attacks. At all ages certain persons can be identified who are distinctly more vulnerable than others to CHD.5,6 It is, therefore, reasonable to suppose that modification of identified "risk factors" can delay or prevent morbidity or mortality due to coronary atherosclerosis if initiated early enough in life to forestall the development of fibrocalcific and ulcerative plaques.

Effective means for coping with life-threatening dysrhythmias are available. Even heart failure and cardiogenic shock due to acute myocardial infarction

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may yet become amenable to treatment. Unfortunately, however, an examination of the natural history of CHD fails to support the contention that a substantial proportion of premature coronary mortality could be avoided by effective treatment of these complications. All too often deaths from CHD occur with little or no warning, outside hospital, and the terminal event lasts only a few minutes. This will remain a large and irreducible mortality rate as long as attention is directed exclusively to the management of already recognized, symptomatic and usually far advanced CHD.

A substantial reduction in premature coronary mortality can be achieved only by prophylactic measures directed either to the general population or to that segment of the population identified as especially vulnerable to coronary attacks.

The majority of persons dying suddenly of CHD have identifiable precursor traits. The prevention of sudden coronary deaths means the prevention of coronary attacks. The incidence of fatal CHD, including sudden death, is correlated with definable antecedent attributes which are almost identical with those predisposing to coronary attacks in general. It is impossible to estimate the number of men dying suddenly who had some warning of impending disaster. However, contrary to the experience reported by Kuller, there is no evidence in Albany or Framingham that significant numbers of the decedents had consulted a physician shortly before death.

While most sudden coronary deaths appear to be truly unexpected and occur in persons who believe themselves to be well, potential victims of this catastrophe can be identified long before. They are, indeed, no different from the rest of the coronary-prone population. Most of those men who died suddenly could have been identified many years before the terminal event. Removal or amelioration of the precursor traits might, in theory, have delayed or altogether prevented the final outcome.

**Pathogenic Implications**

Victims of sudden death share atherogenic traits with those who survive or succumb less abruptly to coronary attacks. These factors, singly or in combination, do not, however, predict the candidate for sudden death.

Youth may predispose to sudden death in coronary attacks since the fraction of coronary deaths which are sudden is higher in the young coronary victim. Older persons in general have more advanced coronary atherosclerosis, the most potent stimulus to the development of a collateral circulation. Older persons may for this reason be less subject to sudden death since their coronary collaterals protect them at the time of occlusion. Those more susceptible to sudden death have, of course, already been removed from the population at risk.

Excepting youth and a presumably minimal or non-existent coronary collateral circulation, the characteristics of men especially prone to sudden, rather than delayed, coronary death have not yet been identified. More prospective experience in populations with identified coronary risk factors is urgently needed to determine what role age, electrocardiographic abnormalities, obesity, and possibly other as yet unidentified factors play. Such knowledge can be acquired only by time-consuming and expensive epidemiologic studies.

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