Sudden Cardiac Death

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Over the past decade, there has been a significant decrease in the hospital mortality of patients with coronary artery disease. However, sudden cardiac death, which accounts for the majority of deaths from coronary artery disease, has been little affected. This report reviews the pathology, electrophysiology, demographics and clinical presentation of sudden cardiac death. Emergency care and possible preventative measures are examined.

INTRODUCTION

The management of the hospitalized patient with coronary artery disease has been much improved over the past decade. The development of coronary care units, more aggressive treatment of rhythm disturbances, and recent medical and surgical treatments for pump failure and unstable angina are all significant advances. Accordingly, national statistics have shown a significant decrease in the hospital mortality of these patients [1]. Despite these advances, the incidence of sudden cardiac death, which almost always occurs outside the hospital, has been little affected. This report will review our present understanding of sudden cardiac death, and attempt to outline an approach to this important problem.

Definition and Statistics

The definition of sudden cardiac death varies from study to study [2]. The criteria used in the Albany and Framingham studies [3] were: "when an apparently well person was observed to collapse and expire within one hour of onset of symptoms, where no other cause was suggested by the medical history." A large study by the Baltimore City Health Department [4] used the time interval of 24 hours from onset of symptoms to death. In autopsy studies of sudden death [5,6] the lack of noncoronary causes of sudden death at postmortem is an added criterion. A greater proportion of deaths will be noncardiac if a time limit of 24 hours is used [4,7]. For this reason, the one hour interval from onset of symptoms to death would appear more specific for sudden cardiac death.

A reasonable estimate based on mortality data would indicate that 300,000 to 400,000 sudden, nontraumatic deaths occur in the United States each year [1,7]. A small percentage of these are noncardiac such as asphyxia, status asthmaticus, acute pulmonary embolism, sudden infant death, and aortic dissection. However, the vast majority are cardiac. Within the cardiac group, a very high percentage are due to...
coronary artery disease. Other cardiac causes include: aortic stenosis, IHSS, myocarditis, prolonged Q-T interval syndrome and those due to congenital heart disease [7,8]. The large majority of all sudden deaths are thought due to coronary artery disease.

Pathology

There have been a number of autopsy studies of victims of sudden death [5,6,9–13]. While these studies also use varying definitions of sudden death, some generalizations can be made. The majority of the cases are male (60–85%) with a mean age of 58 years. A history of prior cardiac symptoms has been found in 36–97% of the cases. Activity at the time of collapse has been variable, but most studies show a preponderance of light activity or rest. The study by Friedman et al [10], however, was an exception. They separated instantaneous (less than 30 seconds) from sudden (minutes to 24 hours) death. Of the 27 instantaneous deaths, 14 occurred during or directly after severe or moderate physical activity. In the sudden death group, only 3 of 37 were associated with such activity.

Autopsy examination of the heart showed hypertrophy of the heart in nearly half the cases in one study [13]. The outstanding common denominator in all studies is the high percentage of significant coronary artery disease found at autopsy [6,9,10]: In over 90% of cases there is greater than 75% narrowing of at least one coronary artery. Moreover, 3 vessel disease is found in 36–64% of the hearts [6,13]. By comparison, only 8% of sudden deaths from other causes had triple vessel disease [11].

Old myocardial infarction (MI) has been found in approximately one half of hearts studied [6,10,13]. The data concerning acute events is more variable. Acute thrombi were found in 59% of Friedman's sudden deaths as compared to only 4% of his instantaneous deaths [10]. Scott and Briggs [13] noted acute thrombi in 84 of 183 [46%] subjects. Furthermore, 55 of 118 [47%] of their patients dying within one hour of symptoms had recent thrombi. Data on acute MI (6 hours to one week) followed a similar disparate pattern in the two studies. Friedman et al had a 21% and 0% incidence of acute MI in the sudden and instantaneous groups, respectively. Scott and Briggs showed acute MI in 47% of their cases, and a 49% rate in victims dying within an hour. A study from Seattle [6] showed recent thrombi in 10% and acute MI in 5% of cases. Thus, over 90% of patients have significant CAD and one-half have evidence of old MI. The majority of deaths do not appear to be associated with recent thrombi or infarction.

The lack of tissue change in many of the autopsy specimens raises the possibility of arrhythmia as a cause of death. As will be shown later, ventricular fibrillation (VF) or asystole are the predominant rhythms seen in those who suddenly collapse [14–16]. Lie [5,12] has examined the conduction system in sudden death victims. No patient had an acute lesion of the SA node or the His bundle. Only 2 of 39 patients with MI and sudden death had AV node necrosis—both with thrombosis of the right coronary artery and massive anteroseptal MI. In a group of patients dying suddenly without infarction, none had AV nodal necrosis. Examination of the His bundle and proximal bundle branches showed fibrosis or fatty replacement in nearly half of Lie's cases. However, the author points out that these changes are not uncommon in patients over 40 dying of noncardiac causes [12].

Lie also studied the microcirculation of 120 patients [12]. Only 3 cases showed thromboemboli in small intramural vessels. In each case there was thrombosis of a major coronary artery proximally, with an associated acute MI. Finally, using sensitive methods for detecting myocardial ischemia, 52 to 81% of cases had evidence
of ischemia. An unanswered question is whether these changes were a cause or a consequence of a presumed terminal arrhythmia.

In summary, pathologic studies have shown that victims of sudden death have a high incidence of significant coronary artery disease, and that half have evidence of prior infarction. Acute infarction or thrombosis is not present in the majority of cases. The conduction system and the microcirculation are usually spared of acute disease.

**Electrophysiology**

**A. Clinical Data**

The lack of evidence of profound myocardial damage at autopsy, coupled with the rapidity of collapse often seen in sudden death victims points to ventricular arrhythmia as the terminal event. Recent data obtained from CCU [17–21] and mobile rescue units [9,14,22–25] have confirmed this hypothesis. Data from coronary care units show that primary ventricular fibrillation, defined as ventricular fibrillation (VF) not associated with heart failure, shock or as an agonal event [26], occurs in 2.3 to 10% of monitored MI patients [19,20,27]. Lawrie et al [19] showed that 80% of episodes of primary VF in infarct patients occur within four hours of symptoms, and that in the majority of cases there was no warning arrhythmia.

With the development of the mobile CCU in 1966 data were obtained on patients in the early stages of MI. In Pantridge and Geddes’ study [24] the risk of developing VF was 15 times greater in the first four hours than in the period from 4 to 12 hours after the onset of symptoms. Further work [28] documented that patients resuscitated from VF had similar functional capacity and survival rates as those sustaining infarction without VF.

Recent experience collected from the Seattle Medic 1 Unit has added new information on victims of VF [16]. These authors reported on 234 survivors of out-of-hospital ventricular fibrillation. Of note is that only 45% of these patients had evidence of myocardial infarction as judged by LDH isoenzymes or ECG. Thus, over one half of survivors of VF had no evidence of MI. Furthermore, long term follow-up of these patients showed that those whose episode was associated with an acute transmural MI had significantly higher survival rates when compared to all other patients [29].

Thus, there appear to be two subsets within the group of patients who develop VF. One group has VF in association with acute MI. In general, the arrhythmia is most likely to develop within four hours of symptoms and is responsive to defibrillation. Warning arrhythmias are often not present. Residual activity and prognosis of patients with VF associated with transmural MI is similar to patients with transmural MI without VF. A second group of patients appear to sustain VF without myocardial necrosis. In general, their prognosis is poor—with a 2 year mortality of 47% [14,29].

**B. Possible Mechanisms**

Some insight into initiation of VF can be gleaned from experimental models of coronary artery occlusion in the dog. In this model, ventricular arrhythmias appear in two phases [30,31].

1. **Early Phase** Ventricular arrhythmias during this phase occur immediately after occlusion and can last for several hours. The theories as to why these arrhythmias occur has been recently reviewed [30–33]. Ventricular muscular ischemia is thought responsible for the rhythm disturbances seen during this period. Local
muscular hypoxia is thought to lead to extracellular hyperkalemia through malfunctioning of the sodium-potassium pump, and eventual loss of cellular potassium. Extracellular hyperkalemia interferes with the entrance of sodium into the cell. Although sodium and calcium can still enter the cell they do so at a slower rate leading to delayed conduction through the ischemic area. Depending on local metabolic factors, conduction is slowed to varying degrees within the ischemic area. Impulses delayed in the ischemic area eventually emerge and can stimulate surrounding normal myocardium. The above sequence leads to a re-entry premature ventricular contraction (PVC).

2. Late Phase These arrhythmias occur from 12 to 48 hours after coronary arterial occlusion. They are thought to be related to ischemia of Purkinje fibers. Ischemia of these fibers leads to re-entry in this system through mechanisms similar to those of the early phase.

Thus, myocardial ischemia can lead to varying degrees of refractoriness of the conduction tissue of the ventricle. This nonhomogeneous refractoriness has been shown experimentally to decrease the fibrillation threshold [33]. The occurrence of ventricular fibrillation is favored by nonhomogeneity of myocardial refractoriness [31,34].

It has long been known that maximum asynchrony of refractoriness in the normal heart occurs within a 30 msec period preceding the apex of the T wave [31,34]. This is sometimes called the vulnerable period. Smirk and Palmer [35] noted that early ectopic beats interrupting the T waves predisposed post-infarction patients to sudden death. Recently, two episodes of sudden death have been recorded on Holter monitor [36,37]. In both instances, a PVC in the vulnerable period led to terminal ventricular fibrillation.

It should be added that a late coupled PVC (QR’/QT greater than 0.85) can also initiate runs of ventricular tachycardia and VF. Lie [21] showed that in 11 of 20 cases of primary VF a late PVC initiated the arrhythmia. Williams et al [38] have shown in the dog that the ability of a PVC to lead to VF is not always related to the portion of the cardiac cycle during which it occurs. The degree of delay of conduction of ischemic epicardium appears to be more important.

In summary, experimental and clinical data indicate that myocardial ischemia can lead to nonhomogeneity of ventricular conduction and excitability. This makes it more likely for a PVC to initiate VF. The vulnerable period around the apex of the T wave is one time when this can occur. Recent data have also indicated that a late-coupled PVC can similarly lead to VF.

Risk Factors and Prodromes

A. The Susceptible Patient

A meaningful attack on the problem of sudden death calls for the identification of those individuals at risk. The Albany-Framingham Studies [3,39,40] have followed, at regular intervals, large numbers of patients initially free of clinical coronary artery disease. Other studies [41–48] have examined the risk of sudden death in patients with known CAD.

The following data has been noted in The Albany-Framingham Studies [3,39,40].

1. Age: In general death rates rose from age 45 to 64 and then declined in Framingham. This decline in the older group was not noted in Albany.

2. Prior Coronary Artery Disease: Patients with known CAD had fourfold the incidence of sudden death. However, 55% of those dying suddenly had no prior evidence of CAD.
3. **Blood Pressure** (see Fig. 1): In general, incidence rose with blood pressure. Men with systolic BP greater than 160 mm Hg had 3 times the incidence of sudden death as those with systolic pressures less than 140 mm Hg.

4. **Cigarette Smoking** (see Fig. 1): In the entire cohort, smokers had 3 times the incidence of sudden death as compared to nonsmokers. Further, smokers of greater than one pack per day had higher rates than smokers of 1 to 20 cigarettes per day.

5. **Cholesterol** (see Fig. 1): No stepwise trend proportional to serum cholesterol was noted.

6. **Overweight** (see Fig. 1): There was a progressive increase in sudden death with increased weight. Those 120% of greater than ideal weight had more than double the risk of those less than 110% of ideal weight.

7. **Left Ventricular Hypertrophy (LVH) by ECG**: These patients had a fivefold increased incidence of sudden death.

From the above data a coronary risk profile can be obtained using: systolic blood pressure, body weight, serum cholesterol, cigarette habit and evidence of LVH by ECG [39]. One third of all sudden deaths occurred in patients in the top decile of risk. However, it was impossible to predict from this risk profile whether death from CAD would be sudden or more protracted. As can be seen, risk factors for sudden death are the same as those for CAD in general.

**The Role of Premature Ventricular Contractions (PVC's)**

Chiang et al [49] showed in the Tecumseh study that patients with PVC's had a sixfold incidence of SD. Further, the incidence of CAD was higher in the population with PVC's, and 5 of 10 sudden death patients with PVC's had known CAD. The Coronary Drug Project [46] showed that among survivors of MI those with PVC's seen on 12 lead ECG had approximately double the incidence of both overall deaths and SD when compared to patients without ectopy.

Recently, Vismara et al [42] examined survivors of MI with 10 hour Holter monitoring an average of 11 days after discharge from the CCU. The patients were then followed for an average of 25.8 months. Of the 12 patients who died suddenly, all had ventricular ectopy seen on Holter. These patients were similar to survivors in terms of extent and location of infarct, and other known risk factors. Furthermore,
the occurrence of acute arrhythmias in the CCU did not correlate with eventual sudden death. These authors have also found that routine ECG will miss a great percentage of patients with ectopy [43].

Schultze et al have further clarified the group at high risk for sudden death after MI [50]. In their series, 81 patients had both 24 hour Holter monitoring and gated cardiac blood pool scans prior to discharge. There were 8 patients who died suddenly during a mean 7 month follow-up period. All of these patients come from a group of 26 who had both complicated ventricular arrhythmias on Holter, and an ejection fraction of less than 40%. Thus, the combination of poor ventricular function and significant ventricular ectopy selected out the post-infarction patient at highest risk of sudden death.

In summary, in the general population, the risk of sudden death (SD) appears to be associated with the same risk factors which predispose to coronary artery disease. At present, there is no means of predicting whether the first manifestation of coronary artery disease will be SD or other events (angina, MI). The post-infarct patient is at higher risk for SD than the general population. Within this post-infarct group, there appears to be a strong relationship between PVC's seen on Holter monitor after the acute phase of MI and subsequent SD.

In addition, a particularly high risk of sudden death is seen in survivors of MI who show both depressed ventricular function and significant ventricular ectopy before discharge from the hospital.

B. Prodrome and Terminal Events

In two large series [40,51] over two-thirds of deaths due to CAD occurred outside the hospital. The majority of these were within one hour of the onset of symptoms. In Framingham [40], 42 of 120 deaths occurred suddenly in patients with no prior history of CAD. Similar percentages (20–25%) of SD as the first manifestation of CAD have been obtained in other studies [4,8]. Even in patients with known CAD, nearly one half of deaths occurred outside of the hospital in the Framingham study [40].

In view of the suddenness of death it would be desirable to isolate a clinical prodrome of SD. In an excellent review of this topic, Feinleib et al [52] point out that from 20–80% of victims have prodromal symptoms. Fatigue is most common, followed by dyspnea and chest pain. Chest pain accounts for only 11–33% of symptoms. This prodrome is similar to that before MI, except that chest pain is more common in the infarct group (25–70%). As many as 20–40% of patients see a physician during the month before SD or MI. However, these visits are often for noncardiac symptoms [4,52].

An added problem is the delay from the onset of symptoms to the entrance of a medical facility. Simon et al [53] found that the mean hospital arrival time after the onset of acute symptoms in MI victims was 2 hours 45 minutes. When one considers the high rate of VF in the early stages of MI, it is clear how crucial such a delay can be. Interestingly, patients with a known history of coronary artery disease took slightly longer to reach medical care as compared to patients without such a history. In a summary of prehospital care of acute MI, Yu [54] noted that several factors contribute to delay of hospitalization. These include: lack of patient information about symptoms, fear and denial, reluctance to seek aid at an inconvenient time, and lack of encouragement from lay individuals consulted. While much of the delay is at the patient level, physician associated delay, travel time and receiving area delay all can contribute.
To summarize, two-thirds of deaths due to CAD occur outside the hospital. Sudden death accounts for nearly half of all deaths of patients with known CAD. Prodromal symptoms are often not present, and even when present are often nonspecific. Finally, a variety of factors contribute to delay of patients in seeking and receiving medical care after acute symptoms begin.

**Therapy and Prevention**

**A. Emergency Care outside the Hospital**

It can be seen that victims of SD may or may not have known CAD, may or may not have a prodrome, and may or may not have an acute MI associated with their attack. Therapy and prevention may differ for these subgroups. One need all potential victims share, however, is that for emergency care at the time of the attack.

Mobile coronary care units were started in Belfast, Ireland, in 1967 [24]. The system has probably been refined best in the U.S. by the Seattle system, Medic 1 [14,16]. This system allows trained paramedical personnel to reach the victim within 2 to 5 minutes in most instances. Recent reports [16,29] show that 43% of all patients initially in VF are resuscitated. Further, 23% of the total population live to be discharged from the hospital. Thus with rapid, skilled care up to one fourth of all potential SD victims can be saved.

Schaffer et al [29] followed 234 of these long-term survivors of VF. There were 89 episodes of fatal or near-fatal events noted during the follow-up period. The mean follow-up period was 71 weeks and median time for a recurrence was 20 weeks. Of these 89 episodes, 71% were VF or sudden death. The authors also noted that long-term prognosis was significantly poorer in patients without acute transmural MI associated with their initial episode.

As noted earlier, data from the Belfast group [24,28] show that the risk of VF with acute MI is highest during the first two hours after onset of acute symptoms. It is tempting to speculate that VF may be prevented in a group of acute MI patients with early administration of antiarrhythmic medication. Ideally, this would be even before the patient reaches medical care. Cohen et al [55] have shown that therapeutic blood levels of lidocaine can be obtained within 10 minutes via IM deltoid injection. Valentine et al [56] showed a significant decrease in mortality in acute MI patients in a two-hour period after IM lidocaine administration. Thus, early use of lidocaine may reduce SD associated with acute MI. The injection could be self-administered or given by a family member soon after the onset of symptoms.

The final aspect of prehospital care is the delay that symptomatic patients take in seeking medical attention. As noted above, prior studies have indicated that this delay is often significant [53,54]. The bulk of this time consists of patient delay and lack of action by consulted lay persons. The Seattle group's success is in part due to a high level of awareness of the general population as to the symptoms of CAD [16].

In summary, prehospital care involves the rapid adminsitration of medical care to potential victims, the possible early use of antiarrhythmics, and the diminution of time symptomatic patients take in seeking medical attention.

**B. CCU Management**

Recent work has clarified several aspects of primary VF in patients with acute MI. Primary VF often occurs without warning arrhythmia in the early stages of MI [18,20,21]. Lie et al [57] showed that prophylactic lidocaine was highly effective in preventing primary VF in infarct patients. This result must be tempered by noting
that high doses of the drug were used and there was a 15% incidence of side effects (mainly neurologic). Thus, particularly in the early hours of MI, it seems reasonable to use lidocaine prophylactically.

Short term studies of prophylaxis of MI patients with propranolol, quinidine and procainamide have been reviewed elsewhere [8,58]. Koch-Weser et al showed that procainamide was effective in suppressing ventricular arrhythmias in the CCU. Wyman and Hammersmith [59] using lidocaine first, then procainamide if PVC's persisted, had an incidence of primary VF of only 0.3%. However, variable metabolism and potential toxic side effects made the safe use of procainamide difficult without frequent monitoring of serum levels.

Acute trials of quinidine and propranolol have not shown an effective reduction of VF or sudden death [8,58].

The work of Vismara et al [42,60] focused on the importance of ventricular ectopy late in hospitalization of acute MI. As mentioned above, they showed that the risk of subsequent SD was related to ventricular ectopy seen on Holter monitoring days after CCU discharge. Schultze et al [61] have shown that post-infarct patients with ectopy have more proximal CAD and poorer LV function when compared to a similar group without ectopy. Thus, the ectopy seen in these patients may be a manifestation of greater CAD. Of interest is a recent study of long-term survivors of VF [62]. As might be expected, 94% had significant disease of one or more coronary vessels. The same study examined 14 patients who sustained a second attack of VF. These patients showed a greater degree of 3 vessel disease and poorer LV function than those with only a single attack of VF. Thus, patients with the most severe CAD seem more prone to sudden death.

C. Post-Hospital Care

To review, it appears that among survivors of VF, those who had their episode without MI have a poorer prognosis than infarct-associated VF [16,29]. There is evidence that those who do have recurrent VF have more extensive CAD and poorer LV function [62]. Post-infarct patients with late-hospital ventricular ectopy have a significantly higher incidence of SD [42]. Other studies have shown that patients with CAD and ventricular ectopy on routine electrocardiography are also more prone to SD [46,49]. Finally, there are two well documented cases of patients with VPC's developing VF and then dying suddenly [6,37].

The above suggest that patients with CAD who manifest ventricular ectopy have an increased risk of sudden death. Unfortunately, to date no ideal study of the use of antiarrhythmics and the effect on SD has been done. However, some data do exist. In a study of procainamide in post-infarct patients [63], a 54% incidence of significant adverse effects within three months was seen. This high percentage precluded meaningful analysis of the drug's effect. Lovell [64] has recently reviewed experience with phenytoin and concludes it is ineffective for long term prophylaxis. Quinidine will probably never receive an adequate trial in view of its toxic side effects and its reported association with sudden death.

Recently, two large trials with beta-blocking drugs have been reported. In a double-blind study of post-infarct patients alprrenol was compared with placebo [65]. There was a significant reduction in both sudden death and non-fatal infarction in the alprenolol group. No analysis of pre- or post-treatment arrhythmia was done. An multicenter study of long-term prophylaxis of post-MI patients with practolol was also reported [66]. The practolol group had significantly less sudden death.
Interestingly, this protection was limited to those with anterior wall infarcts. Again, no specific mention of ectopy was made.

In view of the extent of CAD seen in SD victims, the role of bypass surgery as a preventative measure has been examined. Surgery has been shown to reduce life-threatening ventricular arrhythmias in small groups of patients [67]. However, in many of these bypass procedures, ventricular aneurysmectomy has also been performed. Thus, the beneficial effect may not be entirely secondary to bypass alone. One recent study [60] showed a reduction of SD in bypassed patients as compared to a medically treated group. Although the groups were well matched, it should be noted that the study was not randomized.

Finally, it would seem most prudent to attempt to eliminate any known predisposing factors to SD in patients with CAD. Thus, control of blood pressure, cholesterol and weight should be attempted. Cessation of cigarette smoking should be strongly advised. Indeed, control of these factors in the general population would hopefully reduce all forms of coronary artery disease, including sudden cardiac death.

At present, an overall attack on the problem of sudden cardiac death would include:

1. Establishment of effective mobile care units for administration of immediate care and transport to the hospital. Lidocaine should ideally be given as early as possible to all victims.

2. Patients with symptoms compatible with acute MI should be given parenteral lidocaine as early as possible and admitted to a coronary care unit.

3. Education of the population as to the symptoms of coronary artery disease and in CPR should be optimized.

4. In the CCU, prophylactic lidocaine should be administered to all infarct and potential infarct patients within the first twelve hours after the onset of acute symptoms.

5. If ventricular ectopy persists in the CCU, parenteral procainamide should be given with monitoring of serum levels, if possible.

6. Ambulatory monitoring of post-infarct and post-VF patients should be done before discharge. At present it would be reasonable to treat those with ventricular ectopy with long-term prophylaxis. Although no drug is ideal, a beta-blocking agent may prove to be the best form of therapy. At present, in the U.S., a randomized trial with propranolol is underway.

7. Survivors of myocardial infarction or VF should be strongly urged to eliminate cigarette smoking. Blood pressure, cholesterol and body weight should be optimized in these patients. They should be educated as to the prodromal symptoms of sudden death and infarction and encouraged to seek medical attention as soon as possible should these symptoms occur.

8. Some survivors may continue to demonstrate significant ventricular ectopy despite medical treatment. In these cases coronary bypass surgery may be beneficial.

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