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Sudden cardiac death

Report of a WHO
Scientific Group

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WHO SCIENTIFIC GROUP ON SUDDEN CARDIAC DEATH

Geneva, 24-27 October 1984

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SUDDEN CARDIAC DEATH

Report of a WHO Scientific Group

1. INTRODUCTION

A WHO Scientific Group on Sudden Cardiac Death met in Geneva from 24 to 27 October 1984. Dr V.J. Grabauskas, Director, Division of Noncommunicable Diseases, opened the meeting on behalf of the Director-General.

This Scientific Group was held in the context of the WHO long-term programme on cardiovascular diseases initiated on the basis of resolution WHA29.49, adopted by the Twenty-ninth World Health Assembly in 1976, and further promoted by resolution WHA36.32, adopted by the Thirty-sixth World Health Assembly in 1983. Both these resolutions identified cardiovascular diseases as the main cause of morbidity and mortality in virtually all industrialized countries and as of increasing significance as a cause of ill health and death in many developing countries.

Many people die suddenly from heart disease and the task of this Scientific Group was to review the available scientific knowledge related to sudden cardiac death and identify areas of research that might improve understanding of this problem and finally lead to its prevention and control.

2. DEFINING SUDDEN CARDIAC DEATH

Numerous definitions of sudden cardiac death have been proposed over the past twenty-five years. However, such deaths can be caused by many mechanisms and no all-purpose definition can be applied to every situation.

It is therefore more meaningful to define the specific characteristics surrounding cardiac arrest, and register and collect data in a standardized way, than to try to define the word "sudden" in the context of death. Irrespective of how the terminal event is defined, some important data that should be collected include: occurrence of prior pain or myocardial infarction; presence of underlying cardiac disease; time of onset of, or absence of, prior

symptoms; place of death (e.g., at home or in hospital); whether death was expected, witnessed, or medically attended; and cause of death. Such an approach would contribute to a better understanding of the pathogenic mechanisms involved.

3. EPIDEMIOLOGY

The incidence of sudden cardiac death within the first hour after onset of symptoms in industrialized areas is around 19–159 per 100 000 per annum for men aged 20–64 years and 2–35 for women of the same age group. For males, these first-hour death rates rank among the five major causes of death (1). In other words, there are about 30 sudden cardiac deaths per week per million population in industrialized countries. The position is, however, very different in non-industrialized countries, where the frequency of sudden cardiac death is much lower. A study in China has revealed that in Beijing, for example, it is less than 1.5 per week per million population, the majority of such deaths being associated with coronary heart disease (2). In the Central Asian republics of the USSR, the incidence of sudden cardiac death is five times lower than in the European Soviet republics (3). There is little information on the incidence of sudden cardiac death in black African populations, but it is probably uncommon, and most cases are not due to coronary heart disease (4).

Data collected in many industrialized countries indicate that 25–28% of patients who suffer a heart attack die suddenly. Of those who die during the first two weeks after the event, approximately 40% die within one hour of the onset of symptoms and the vast majority of those die before they reach hospital (5). In about 55% of all cardiac deaths mortality occurs within the first hour. A study of patients who died suddenly and of resuscitated patients indicated that 75–80% had some prior manifestation of cardiac disease (6), and that in more than half of the remaining 20–25% cardiac arrest was due to acute myocardial infarction. These findings, however, apply to groups of patients whose mean age was 60 years, and the percentage dying suddenly without prior symptoms may be higher in younger age groups.

The question whether, and to what extent, it is possible to predict sudden death is important, because identification of the potential

victims would permit the application of preventive measures. Nevertheless, epidemiological studies have indicated that, unlike myocardial infarction with survival, there are no sets of risk factors that are specific to sudden cardiac death. Although specific risk factors for sudden cardiac death have not been identified, it should be noted that in many studies sudden cardiac death was not rigorously defined as this was often not the main object of the investigations. While the relative importance of risk factors in predicting coronary heart disease is recognized, the ability to predict sudden cardiac death is low and is no better than for any other clinical manifestations of coronary heart disease.

It therefore follows that effective action in preventing sudden cardiac death requires much more than just control of the classical risk factors of coronary heart disease. Thus, far more needs to be learned about the factors that are specific to sudden cardiac death, their predictive power, and the likelihood of controlling them. Valuable information could perhaps be obtained by studying whether there is any difference in the secular trends of sudden cardiac death in comparison with other manifestations of coronary heart disease.

The chance of prediction is better for patients with clinically identified heart disease, since the risk of sudden death is 8–10 times greater in the presence of extensive myocardial damage such as cardiomegaly, impaired left ventricular function, electrocardiographic evidence of left ventricular hypertrophy, and conduction disturbances.

4. PATHOLOGY AND PATHOGENESIS

Severe coronary atherosclerosis, often accompanied by stenosis, is the most common characteristic found in cases of sudden cardiac death (3). But this does not necessarily imply a cause-and-effect relationship, and demonstration at autopsy of severe coronary atherosclerosis does not mean that this was the cause of death, sudden or otherwise. In fact, only a small percentage of individuals with such severe coronary disease actually die suddenly, and there is an ill-defined fraction of sudden cardiac deaths, perhaps as large as 15–20%, that occurs in individuals exhibiting little or no coronary

atherosclerosis. From the point of view of its prevention, sudden cardiac death should not, therefore, be equated with coronary atherosclerosis, although this may be the most frequently identified feature of the transitory or functional events that trigger the fatal episode.

One of the most pressing problems is to identify the causes of sudden cardiac death in young and middle-aged adults. This is more important than attempting to establish a relation between sudden cardiac death and the occurrence of progressive atherosclerotic occlusion with advancing age.

More immediate impact on the control of sudden cardiac death is likely to be made by identifying the many triggering factors, although the mechanisms whereby these lead to the final fatal episode are not necessarily the same. Such factors include platelet-thrombus formation, sudden increases in myocardial oxygen demand, alteration of autonomic neural control, coronary spasm, changes in the cardiac conduction system, increased sensitivity of the myocardium to ischaemia, and other factors known and unknown.

A particular problem, still incompletely resolved, is the role of platelet-thrombus formation in precipitating ventricular fibrillation. A wide variation in the frequency of occlusive thrombi is reported in the literature, even in cases in which an autopsy was carried out soon after death (7), but it increases with the interval between the onset of symptoms and sudden cardiac death. It has been found that 90–95% of occlusive thrombi are associated with visible structural changes in the atheromatous plaque (cracks and haemorrhages). It is also not clear whether thrombi can dissolve and recur after myocardial infarction, although it is now well established that thrombolytic regimens permit reperfusion of large arteries.

While it is likely that older people are susceptible to any of the known trigger mechanisms of sudden cardiac death, in the young who die suddenly particular emphasis should be given to the occurrence of these triggers and also to the possible existence of cardioneuropathies, or malformation or pathological transformation of the cardiac conducting system.

Since it is widely believed that the ultimate common cause of sudden cardiac death is electrical instability of the heart, post-mortem studies are essential in every case of sudden cardiac death. In this respect, particular emphasis should be given to the structures normally responsible for the origin and conduction of cardiac rhythm (8–10). The small coronary arteries and the nerves and

ganglia of the heart should also be more carefully assessed, particularly in relation to the cardiac conduction system.

Cardiac enlargement, particularly left ventricular hypertrophy, is a frequent finding in cases of sudden cardiac death, but very little effort has been directed at determining whether the collagen in such enlarged left ventricles is abnormal. Studies should examine both the amount and pattern of distribution of the fibrous tissue and collagen. More precise autopsies of sudden cardiac death cases are also required to assess the adequacy of arteriolar and capillary formation in such patients.

Sudden cardiac death arising from alcoholic cardiomyopathy represents a special case. Such deaths occur in regular drinkers some hours after drinking rather than during acute alcoholic intoxication. Post-mortem findings indicate, *inter alia*, atrophy of cardiac myocytes, loss of myofibrils, hyperplasia of the small mitochondria, and dilatation of the sarcoplasmic reticulum. Numerous foci of fatty replacement in the left ventricular myocardium are also found. The exact cause of these changes is unclear, but both ethanol and its metabolites (e.g., acetaldehyde) are suspected. Accompanying myocardial metabolic changes, including impairment of electrolyte transfer, alteration of the calcium pump, hypomagnesaemia, and enzyme dysfunction, occur either as primary sensitizing factors or as a consequence of alcoholism. Coronary disease of the usual type is not a factor, although microcirculatory changes may occur (11). Alcohol-related sudden cardiac death merits more investigation, both as a specific problem itself and as a factor in other forms of sudden cardiac death. Analogous considerations apply to all other forms of cardiomyopathy, such as those associated with viral disease, malnutrition, or idiopathic hypertrophy, details of which will not be discussed here. Post-mortem evaluation of such causes of sudden death should include not only the histological characteristics of the hypertrophy, but also those of the cardiac conduction system, the small coronary vessels, and the neural system.

There is a need for improved and more precise description of two aspects of coronary stenosis:

- systematic grading of stenosis should become routine, for example, 22–49%, 50–74%, 75–84%, and 85% to complete occlusion; and
- the histological character of the stenosis should be explicitly described.

In addition, the extent of stenosis found at autopsy should be compared more carefully with that estimated from coronary arteriograms.

In general, post-mortem examination remains underutilized as a means of providing more information on the pathogenesis of sudden cardiac death and for planning additional research projects or programmes of prevention.

5. MECHANISMS OF THE TERMINAL EVENT

Ventricular fibrillation is generally considered to be the most frequent arrhythmia responsible for sudden cardiac death (12). Bradycardiac and asystolic cardiac arrests are uncommon as the sole terminal event (13). However, these and similar arrhythmias may precede and play a role in precipitating ventricular fibrillation, and some sudden cardiac deaths (e.g., those caused by ventricular rupture) may be nonarrhythmic in nature.

When ventricular fibrillation develops:

- it may be the result of acute ischaemia (acute myocardial infarction, acute reversible ischaemia, cardiac spasm, formation of platelet aggregates, or mechanical factors impairing flow); or
- it may occur in the absence of acute ischaemia, for example, in patients with severe coronary heart disease and scars of myocardial infarction, or with ventricular aneurysm.

Ventricular fibrillation may also develop in patients with either severe bradycardia, electrolyte imbalance, drug intoxication, or congenital abnormalities (e.g., long QT syndrome or patients with overt or concealed accessory pathways). Drug-induced bradycardiac death may occasionally be observed in patients with or without coronary heart disease.

Better identification of the various clinical markers associated with each pathogenic mechanism is needed to assess the prevalence of the various causes of sudden cardiac death, especially in apparently normal individuals.

5.1 Arrhythmias associated with acute ischaemic events

Ventricular fibrillation is generally considered to result from sustained, rapid, and irregular excitation of the heart caused by

multiple re-entrant wavelets. Onset of fibrillation requires the fractionation and desynchronization of local activation wave-fronts, slowed conduction, and reduced ventricular refractoriness. These conditions occur in cases of acute ischaemia, however they arise.

Several studies have investigated the effects of coronary artery occlusion on the local bipolar electrogram of the myocardium when it becomes ischaemic (14, 15, 16). Within minutes, the electrogram becomes fragmented into multiple low-amplitude deflections that continue for a longer time than the period of the T wave. The electrical activity associated with these deflections may reactivate surrounding tissue and create re-entry. At this stage, ventricular fibrillation may also arise from ventricular premature beats resulting from the electrical stimulation by the injury current of myocardial Purkinje fibres in the vicinity of the ischaemic zone.

Investigations with animal models indicate that when acute myocardial infarction develops, a delayed phase of ventricular arrhythmias (6–24 hours) arises caused by the development of intrinsic automatic rhythm in surviving Purkinje fibres on the endocardial surface of the infarct. Although there is no definite proof, studies suggest that the same mechanism might also operate in man.

5.2 Reperfusion arrhythmias

In animals, experimentally-induced ischaemia and reperfusion of the myocardium both cause malignant ventricular arrhythmias. The importance of reperfusion in producing arrhythmias in man is, however, still controversial. Nevertheless, the observation that, in man, approximately 50% of the arrhythmic episodes associated with coronary spasm occur during reperfusion points to the importance of reperfusion-induced arrhythmias. It has also been indicated that recanalization by thrombolysis during episodes of acute myocardial infarction is associated with ventricular arrhythmias of varying incidence and severity. In spite of a relatively low incidence of severe arrhythmias in patients following successful thrombolysis, it is clear that in this form of therapy the presence of ventricular arrhythmias is often considered to be an indication of the success of recanalization. It is therefore reasonable to suppose that arrhythmias associated with reperfusion of the ischaemic myocardium occur in man.

Arrhythmias associated with abrupt reperfusion are known to result from abnormal conduction and refractoriness (17, 22). However, the precise changes in these properties responsible for reperfusion ventricular fibrillation are not yet clear, and several factors (changes in ventricular fibrillation threshold, local intracellular or extracellular ionic changes, increase in α -adrenergic responsiveness or in the number of α -adrenergic receptors) may all play an important role.

5.3 Arrhythmias not associated with an acute ischaemic event

Ventricular fibrillation can develop in patients with myocardial scars or ventricular aneurysm. In such cases, the electrophysiological conditions required for the development of the fibrillation are usually induced by repetitive ventricular extrastimuli or acceleration of a sustained ventricular tachycardia. Such arrhythmias may sometimes be facilitated by antiarrhythmic agents which, if they have a different effect on normal and abnormal tissues, might enhance the spread of refractoriness and conduction within the heart.

5.4 Coronary spasm

The development of ventricular fibrillation in some patients with coronary heart disease but no acute myocardial infarction is considered to be caused by coronary spasm (18). In man, sudden massive ischaemia and reperfusion can result from coronary spasm, and sudden death frequently results.

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are the most common, potentially fatal arrhythmias that arise during transient ischaemic episodes and can occur either at the onset of sinus tachycardia or during the reperfusion phase. Approximately 30% of VT-VF episodes develop during silent, painless ischaemia. Furthermore, VT-VF episodes and syncope tend to be frequent and recurrent in about 25% of patients with coronary spasm, but only develop in approximately 3% of spontaneous ischaemic episodes. Interestingly, the occurrence of VT-VF and syncope does not appear to depend on the duration or severity of the ischaemia.

Patients with coronary spasm and recurrent VT-VF do not usually exhibit more severe coronary artery disease than those with coronary spasm but no arrhythmias. However, the incidence of

sudden death is higher in patients with VT-VF, especially if they also have severe coronary artery disease or scars from previous myocardial infarction. Coronary spasm complicated by VT-VF can also occur in patients with angiographically normal coronary arteries as well as in those with triple vessel disease.

6. THE AUTONOMIC NERVOUS SYSTEM AND SUDDEN CARDIAC DEATH

There is evidence that certain types of autonomic neural activity can lead to the onset of lethal arrhythmias. For example, experimental stimulation of cardiac sympathetic nerves may lower the electrical threshold for ventricular fibrillation; in contrast, this threshold may be raised by bilateral stellectomy, unilateral left stellectomy, and vagal stimulation (19).

6.1 Autonomic influences on ischaemia-related arrhythmias

Ventricular fibrillation can be induced in cats by combining transient myocardial ischaemia with brief left stellate stimulation, and this has been used as a model system for testing antiarrhythmic drugs (20). In free-running dogs, ventricular fibrillation can also be induced by strenuous exercise in conjunction with a transient coronary occlusion, with or without a previous episode of myocardial infarction; in this model system, fibrillation is prevented by left stellate ablation (20). Interestingly, susceptibility to ventricular fibrillation and to sudden death in these dogs is inversely related to baroreflex sensitivity, and it has been suggested that reflex vagal excitability may be a protective factor (21).

The arrhythmogenic adrenergic influence is mediated by both β - and α -receptors (19, 20), the latter being particularly important in reperfusion arrhythmias (22). The possibility that this α -mediated influence may operate via vasoconstriction of the coronary bed has recently been raised (20, 23).

It has also been demonstrated that coronary occlusion stimulates cardiac receptors connected to sympathetic fibres, and that this situation involves a reflex increase in cardiac sympathetic activity (24); abolition of this reflex by dorsal root section reduces the frequency of ischaemic-induced arrhythmias (19). Other events associated with myocardial ischaemia can generate additional cardiogenic reflexes (25).

Also, there is experimental evidence of depressor reflexes mediated by the vagus nerve; however, the relation between these potentially dangerous reflexes and the protective action of vagal activity requires clarification.

6.2 Autonomic influences on arrhythmias unrelated to ischaemia

(a) *Psychological stress.* Evidence relating acute psychological stress to the development of sudden cardiac death in man is only circumstantial, and a convincing explanation of the mechanisms involved is still lacking (19); however, increased catecholamine activity is thought to be a likely mediator. Experiments using dogs indicate that a stressful environment can, through sympathetic stimulation, raise the incidence of repetitive ventricular extrasystoles (26).

(b) *Sleep.* The effect of sleep on cardiac arrhythmias is controversial, with conflicting reports of improvement and deterioration of arrhythmias during sleep (19).

(c) *The long QT syndrome.* The unique characteristic of this syndrome is the frequent occurrence of syncopal episodes (and possibly sudden death) due to ventricular fibrillation associated with sympathetic discharges. It has been proposed that the underlying mechanism is a congenital imbalance between right and left cardiac sympathetic nerves, the latter being predominant (27). The association of syncopal episodes with emotional events has prompted a therapeutic approach based on administration of a beta-blocker, supplemented by left stellectomy if syncopal episodes persist. The results of an ongoing prospective study using this approach appear promising (28).

Prolongation of the QT interval can also be an acquired characteristic and is encountered in a variety of clinical situations, for example after therapy involving antiarrhythmic agents or antidepressants, and in cases of hypokalaemia, hypomagnesaemia, acute damage to the central nervous system, or severe bradycardia. The condition may be complicated by *torsade de pointes*, which occasionally degenerates into ventricular fibrillation.

It has been shown that those who survive a myocardial infarction have, on the whole, a longer QT interval than controls. Furthermore, patients with a significantly longer QT interval have an increased risk of sudden cardiac death (29). This aspect, however, should be investigated further.

7. DISORDERS OF THE MYOCARDIUM

Surprisingly, disorders of the myocardium have received much less attention as causes of sudden cardiac death than have coronary artery disease and ventricular arrhythmias. Nevertheless, the vulnerability or the resistance of the myocardium to acute ischaemia may be a crucial factor in determining whether or not lethal ventricular arrhythmias occur; trigger factors such as coronary spasm, autonomic influences, and intravascular thrombosis may be of greater or less importance, depending upon the sensitivity of the myocardium to abrupt reduction of myocardial blood flow. There are several related mechanisms to consider, including local release of catecholamines by the myocardium, substrate availability, alterations in normal ionic gradients, and prostaglandin and leukotriene activation.

The sympatho-noradrenaline-adrenaline activation (30), which occurs as part of a broad stress-response at the time of acute ischaemia, is responsible not only for the complex modulation of autonomic outflow to the heart, but also for multiple changes in carbohydrate and lipid metabolism, as well as various endocrine responses.

A critical factor in the onset of early malignant ventricular arrhythmias appears to be localized inhomogeneity in cardiac electrophysiological activity, being particularly marked in regions of lipid accumulation and reduced glucose availability (31). The net intramyocardial and peripheral metabolic responses to acute ischaemia following central and peripheral catecholamine activation lead to mobilization of free fatty acids and glucose at tissue concentrations that, while appropriate for the greater energy requirements of the normal heart in response to increased demands, may be inappropriate for continued metabolism and survival of ischaemic myocardial cells. An energy crisis may therefore develop (32, 33). Thus, the combination of myocardial glycogen depletion, impaired glycolysis, and reduced plasma glucose uptake, together with increased myocardial lipid storage and lipolysis may, in the presence of ischaemia, lead to extremely rapid depletion of high-energy phosphate reserves and uncoupling of oxidative phosphorylation. Ischaemic regions also exhibit inhomogeneity in cardiac electrophysiological activity as a result of different concentration gradients of ions such as potassium and calcium and of different pH gradients (34). Hypokalaemia and hypercalcaemia

have both been associated with sudden cardiac death, and some studies have indicated that some patients have an excess of myocardial magnesium. This can arise for many reasons, and greater attention should be given to identifying factors that alter membrane permeability during ischaemia; for example, very rapid changes in fatty acid concentration can affect the esterification pattern of individual phospholipids in mitochondrial and sarcolemmal membranes, leading to physical changes in the lipid bilayer.

The possibility that various fatty acids are metabolized differently and that some might have an adverse effect on myocardial function and the development of arrhythmias requires further examination. The importance during acute myocardial ischaemia of local membrane detergency, lysophosphatide release, lipid peroxide formation in the absence of adequate concentrations of antioxidant, and the possibility that unopposed free radical formation may perpetuate tissue damage should be studied in detail because all these factors are, at least in theory, preventable.

These and other cellular effects together with those resulting from adrenergic stimulation of the cyclic AMP cascade may alter the action potential and favour re-entry and diastolic depolarization of specialized conduction tissue, accelerate repolarization, and shorten refractoriness.

Catecholamines also activate membrane phospholipases, stimulating production of prostaglandins and leukotrienes (35). The prostaglandin pathway may be associated with imbalance of prostacyclin-thromboxane interaction, and the possibility of platelet aggregation. Local increases in the concentration of leukotrienes may lead to accumulation of leukocytes, possibly resulting in release of free radicals and self-perpetuating tissue damage.

The metabolic and ionic changes that occur in the myocardium during ischaemia are profound and interdependent and, hence, it is likely that no individual metabolic or ionic influence can contribute more than another to ventricular fibrillation. There is a rapidly changing milieu in areas of myocardial ischaemia, and it is probable that the dynamic and heterogeneous changes in the availability of substrates and ions determine whether or not ventricular arrhythmias occur during acute ischaemic episodes.

Even if it is not possible to control factors such as coronary spasm and autonomic imbalance that might trigger serious ventricular arrhythmias, it is possible that provision of the myocardium with an optimum balance of substrates and electrolytes might obviate some

of the serious consequences of these trigger effects and reduce the vulnerability of the myocardium to ischaemia.

It follows that more research is needed to identify individuals who are likely to be particularly vulnerable to an ischaemic crisis. Studies should be made of the feasibility of conditioning the myocardium with the appropriate substrate and ionic balance to protect it against the consequences of an ischaemic energy crisis. Also a more vigorous attempt should be made to modulate the metabolic crisis when ischaemia actually develops and to assess the preventive potential of this approach.

8. PREDICTION OF SUDDEN CARDIAC DEATH

Current methods for identifying patients who have a high risk of sudden cardiac death leave much to be desired. One of the striking characteristics of the population at risk of sudden cardiac death is the number of mechanisms that may lead to the development of ventricular fibrillation and to derangement of ventricular function, and the variation in the degree of coronary atherosclerosis and even in age. At present there is a limited ability to identify individual patients who will develop sudden cardiac death within 1–3 years.

Also, there is currently no known means of identifying the 20% of patients who will undergo sudden cardiac death without pre-existing symptoms or signs of cardiovascular disease.

For patients with recognized coronary heart disease, the most sensitive and specific indicator of risk is probably the severity of left ventricular dysfunction. This is not an approach that has high predictive power, but it does make it possible to identify statistically those patients at relatively high risk of sudden cardiac death. Furthermore, a number of other markers have been recognized, including histories of prior myocardial infarction or congestive heart failure, complex forms of ventricular ectopia, responses to exercise, and certain electrocardiographic abnormalities related to conduction and repolarization (30). Hence, there are a number of individual, statistically significant predictors that facilitate identification of groups of patients at relatively high risk. For a given patient, however, none of these markers appears to have sufficient predictive value to be useful in formulating plans for intervention—unless the intervention adopted is effective, free of complications, and relatively inexpensive.

9. PREVENTION OF SUDDEN CARDIAC DEATH

A number of interventions have been proposed as possible means of preventing sudden cardiac death. These include antiarrhythmic drugs, beta-blockers, antiplatelet drugs, coronary artery bypass grafting, myocardial surgery, and psychophysiological intervention.

In view of the involvement of arrhythmias in sudden cardiac death, it was presumed that antiarrhythmic drugs might provide effective prophylaxis. However, there is little evidence that prolonged administration of currently available antiarrhythmic drugs influences the incidence of sudden cardiac death in patients with chronic heart disease. The controlled clinical trials of antiarrhythmic drugs undertaken so far have been small, but several studies indicate that the administration of such drugs to survivors of acute myocardial infarction produces no change in mortality rate, and may even lead to deterioration of survival.

Three means of prevention have been identified:

- the administration of beta-blockers over the 2-year period following acute myocardial infarction;
- on-the-spot resuscitation from cardiac arrest due to ventricular fibrillation; and
- coronary artery bypass surgery in selected groups of patients with angina pectoris.

However, for any of these and related approaches to prevention of sudden cardiac death, the number of lives saved is small.

9.1 Administration of beta-blockers following acute myocardial infarction

A number of studies have demonstrated that sudden cardiac death as well as overall cardiac mortality can be reduced by the administration of beta-blockers during the first 1–2 years after acute myocardial infarction (36). Although these findings are important, it seems unlikely that such interventions will have a major impact on reducing the incidence of sudden cardiac death. In fact, the number of sudden cardiac deaths in patients who survive acute myocardial infarction represents only a small fraction of all sudden cardiac deaths. It is not yet known whether a similar reduction in

mortality would be achieved by long-term administration of beta-blockers to patients with other clinical signs of coronary heart disease, in whom the majority of sudden deaths occur.

The mechanisms whereby beta-blockers afford protection during the first years following myocardial infarction are not known, but they include reducing myocardial oxygen requirements and antiarrhythmic effects. However, since beta-blockers also lead to a reduction in the incidence of recurrent non-fatal myocardial infarctions which cause some sudden cardiac deaths, these drugs could provide protection against sudden death by lowering the incidence of reinfarction.

9.2 Emergency medical services

On-the-spot treatment of patients who undergo cardiac arrest represents one means of averting sudden cardiac death (37, 38). The outcome for patients who suffer cardiac arrest with ventricular fibrillation, which most often occurs at home, is primarily related to the delays in providing emergency care. Very high resuscitation rates have been reported if a defibrillatory shock is applied within a few minutes of cardiac arrest. In one series of studies involving 27 cases, a 100% survival rate was reported after treatment for exertion-related cardiac arrest. The participation of the general public in initiating cardiopulmonary resuscitation has been useful, as has the increased deployment of defibrillators. The concept of making inexpensive, automated, external defibrillators widely available needs further development.

9.3 Coronary artery bypass grafting

An obvious strategy in preventing sudden coronary death is to improve myocardial perfusion by means of coronary artery bypass grafting, since there is increasing evidence that this operation prevents such death.

In the European coronary surgery study (39), patients with stable angina pectoris and relatively well-preserved left ventricular function were subjected to surgical or medical treatment on a random basis. Significant reductions in overall and sudden death were recorded for patients with triple vessel coronary artery disease who had undergone surgical treatment. On the other hand, such benefit was not demonstrated in the US Coronary Artery Surgery

Study (40). In the latter study, however, patients exhibited only mild symptoms of angina pectoris or were asymptomatic after myocardial infarction; mortality in the controls was also low. Hence, any identification of therapy that led to a prolongation of life, regardless of its magnitude, would have been difficult.

It is also generally agreed that patients with symptoms of obstruction of the left main coronary artery have a substantially improved chance of survival after coronary artery bypass graft surgery.

10. CONCLUSIONS AND RECOMMENDATIONS

The Scientific Group recognizes that, although a considerable amount of valuable information has been obtained in recent years about the problem of sudden cardiac death, much remains to be elucidated.

The association of sudden cardiac death with coronary heart disease is well established, but the precise mechanisms, whereby some patients die suddenly while the majority of others with similar arterial lesions and ventricular function do not, remain almost completely unknown.

The Group agreed that very few recommendations for prevention of sudden cardiac death can be made at present. The frequently-held hypothesis that the prevention of coronary artery disease, even if it were feasible, might reduce the incidence of sudden cardiac death was not fully endorsed and needs to be examined more carefully. Overall, the preventive measures currently available affect only a relatively small number of patients. Although beta-blockers and coronary artery bypass grafting produce beneficial effects in a few specific groups of patients, even here the increase in survival rate is limited, and these kinds of therapy will not be able to solve the general problem of sudden death in the community.

Of the preventive measures considered by the Scientific Group, the development of emergency community medical services is likely to make an impact on sudden cardiac death and should be encouraged. These services, which also make provision for emergency treatment of other complaints, have the added advantages of involving the participation of the population at large and increasing their health awareness.

The Group concluded, therefore, that prevention of sudden cardiac death at present cannot be based on any population strategy, and that the initiation of effective preventive measures is impeded by the low sensitivity and specificity of methods of predicting the terminal event.

The Scientific Group therefore recommends that further research be carried out, especially on the mechanisms leading to sudden cardiac death. In this respect, the following areas were identified:

1. All investigators involved in epidemiological surveys or clinical studies should be encouraged to record sudden cardiac death as a separate category. The definition of sudden cardiac death employed should be clearly stated, and a distinction made between coronary and non-coronary etiologies. This policy should facilitate the collection of data about the circumstances surrounding such deaths. In addition, careful examination of data about patients who die suddenly without recognizable cardiovascular disease may shed some light on the mechanisms triggering sudden death in patients with coronary heart disease.

2. The secular trends in coronary heart disease and sudden cardiac death should be studied simultaneously. The MONICA Project (monitoring of trends and determinants in cardiovascular diseases) may provide information on this aspect (41).

3. There is an urgent need to identify the various predisposing and precipitating factors that, in the presence or absence of coronary heart disease and ischaemia, may lead to lethal arrhythmias. The vulnerability of some but not of other patients who seemingly have the same factors is a major enigma.

4. It is essential to study sudden cardiac deaths connected with alcoholic cardiomyopathy caused by chronic alcohol use.

5. The contribution made by the nervous system to sudden cardiac death deserves further attention. The responses of the sympathetic and parasympathetic systems in the presence of ischaemia or myocardial infarction are important. Techniques should be developed to assess vagal and sympathetic tones and the reflex response to various interventions. Investigations are required into how the nervous system influences the heart and coronary circulation.

6. Post-mortem examinations are generally an underutilized source of information on sudden cardiac death. Better

standardization of post-mortem methods should be developed (such as a systematic grading of stenoses to facilitate *in vivo* comparison and precise histological description of arterial lesions). More detailed post-mortem examinations, including the use of electron microscopy, should be made of the cardiac conducting system and its blood supply, the cardiac nerves and ganglia, and the micro-circulation of the myocardium. The adverse prognostic importance of left ventricular enlargement is well recognized, but needs further pathological investigation.

7. There is a need to determine the temporal relation between thrombosis and ventricular fibrillation, using clinical and experimental observations, autopsy studies and, if possible, *in vivo* markers of intravascular thrombosis.

8. More studies are required to identify whether there is a relation between a systemic or local tendency to thrombogenesis and sudden cardiac death.

9. Biochemical analyses of the human myocardium are needed to identify whether there are differences in the concentrations or types of metabolic substrates or ions in cases of sudden cardiac death compared with controls who died from sudden accidental death. For these purposes, and those in paragraph 4 above, autopsies should be performed as soon as possible after death.

10. The relation should be determined between changes in the membrane permeability of cardiac myocytes during episodes of ischaemia and the onset of ventricular fibrillation. In this connection, studies of extracardiac tissue, such as erythrocytes, blood platelets, and adipocytes could be useful.

11. The identification of clinical markers to indicate the likelihood of patients developing potentially lethal arrhythmias following ischaemia induced by cardiac spasm, and of cardiac spasm developing in high-risk patients would make it possible to undertake limited, relatively inexpensive clinical trials of antispasmodic or antifibrillatory drugs.

12. Limited and inexpensive clinical trials of the effectiveness of protecting the myocardium against ventricular fibrillation need to be carried out on regimens, including drugs, designed to optimize energy requirements during ischaemia.

13. The development and deployment of inexpensive, automated, defibrillators for external use should be encouraged.

14. The potential benefits and hazards of vigorous exercise in relation to sudden cardiac death should be further studied; changes

in the autonomic neural system induced by physical training are of particular interest in this respect.

15. The probability that sudden cardiac death may be induced by various forms of cardiovascular or noncardiovascular therapies should be further investigated.

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