Review Article

Sudden cardiac death and the potential role of beta-adrenoceptor-blocking drugs

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Summary: Sudden cardiac death is a major health problem in the industrially developed countries. The risk of sudden cardiac death may be reduced by early detection of coronary heart disease, elimination of the risk factors, treatment of the ischaemia in patients known to have coronary heart disease and suppression of ventricular arrhythmias. Of all the therapeutic measures currently available to reduce the risk of sudden cardiac death, beta-adrenoceptor-blocking drugs (beta blockers) appear to be the most effective. In this paper their actions are reviewed and evidence for their efficacy is presented.

Introduction

Sudden cardiac death is defined as unexpected death that occurs within one hour of the onset of symptoms.^{1–3} Most victims die while sedentary or participating in mild exertional activities. However, a substantial minority die during or just after performing vigorous physical activity.⁴ Nearly 75% of all sudden deaths occur at home; 8–12% occur at work.⁵

There are many possible causes of sudden cardiac death, but most (90%) are caused by coronary heart disease and potential candidates have sub-clinical coronary heart disease. Cardiomyopathy, ventricular hypertrophy, valvular heart disease or congenital heart disease are less common but well-known causes of sudden cardiac death⁶ (Table I).

Arrhythmias are the usual cause of sudden cardiac death and they may be divided into three categories: (1) primary ventricular tachycardia or ventricular fibrillation; (2) primary supraventricular tachycardia with a very rapid ventricular response rate; and (3) bradycardia/asystole. Ventricular fibrillation is the most common cause of sudden cardiac death (80–90% of cases), although it is only the agonal event.^{7,8} Bradycardia and asystole are usually seen in patients with end-stage heart failure.^{9,10}

The Framingham study, and many others, suggested that few sudden death victims had reported prodromata that could have been construed as symptoms of coronary heart disease.¹¹

Incidence and importance of sudden cardiac death

Sudden cardiac death is responsible for more than 350,000 deaths per year in the USA.^{12–15} Approximately one half of cardiac deaths occur suddenly.¹⁶ In patients not known to have coronary heart disease, the first presentation of their disease may be sudden death.¹⁷ In fact, in almost 20% of men who die from coronary artery disease, sudden death is the first and only manifestation of the disease. Furthermore, approximately one in six adults who die before the age of 65 die suddenly.^{18–20}

In the Multiple Risk Factors Intervention Trial (MRFIT), cardiovascular mortality among men entering the study at 35–57 years old was 9.7 per 1,000 men per 6 years or about 1.6 deaths per 1,000 men per year.²¹ Many victims are young and middle-aged men. Coronary heart disease is common, highly lethal, and frequently attacks without warning. The high mortality rate from coronary heart disease can only be substantially reduced, therefore, if sudden, unexpected cardiac deaths can be prevented.

Table I Causes of sudden cardiac death

Coronary heart disease
Cardiomyopathy
Ventricular hypertrophy
Valvular heart disease (mitral valve prolapse, aortic stenosis)
Congenital heart disease
Prolonged QT syndrome, WPW syndrome

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Accepted: 23 July 1993

Anatomic substrate of the sudden cardiac death and trigger factors

Severe coronary atherosclerosis is the most frequent cause of sudden cardiac death.² In 40–70% of victims of sudden cardiac death, evidence of healed myocardial infarction has been found at autopsy⁹ even in those with no history of coronary heart disease.^{1,22} Acute coronary thrombosis with recent acute myocardial infarction is observed in a minority (30%).²³

At autopsy, narrowing of two or more coronary vessels is common in those who die suddenly. In a study of 239 cases of sudden cardiac death without previous infarction, 20%, 32% and 48% had single-, double- and triple-vessel disease. In 118 cases of sudden cardiac death with previous infarction, the corresponding figures were 12%, 26% and 62%, respectively.²⁴ A substantial proportion of sudden deaths are provoked by transient ischaemia without the development of myocardial infarction.^{2,25}

Frequently, the anatomic substrate for sudden cardiac death is chronically abnormal myocardium with various degrees of fibrosis.²² When no fibrosis is found, other abnormalities such as ventricular hypertrophy, infiltration or inflammation are often present.²⁶ Patients with a substantial increase in left ventricular mass ('giant heart') are at particular risk of dying suddenly. Prolonged action potential, characteristic of hypertrophic heart muscle cells, develop more easily early after depolarization and cause ventricular tachycardias.^{3,27}

If at autopsy, the ventricular myocardium appeared to be normal by conventional criteria, this should be interpreted with caution since many autopsies do not include a sufficiently careful examination of the heart with ultrastructural analyses.¹ Ventricular tachycardia may be associated with an unrecognized localized pathological abnormality or biochemical lesion.²⁵

Trigger factors for arrhythmias

Malignant arrhythmia may be caused by various triggers in a vulnerable myocardium. Some of the most important are: (a) myocardial ischaemia;^{23,24,28} (b) autonomic influence;²⁹ (c) electrolyte abnormalities;^{30,31} (d) pharmacological effects; and (e) physical or emotional stress.^{32,33}

(a) *Myocardial ischaemia* Garan *et al.*³⁴ showed that spontaneous ventricular arrhythmias in post-infarction dogs were the result of ischaemia. Reports from the Framingham study demonstrated a circadian variation in the incidence of sudden cardiac death that coincides with the morning increase in platelet aggregability and non-fatal

myocardial infarction.³⁵ The decrease in sudden cardiac death in patients with documented myocardial ischaemia undergoing surgical revascularization confirms the importance of myocardial ischaemia.²³

(b) *Autonomic influences* During the last two decades, compelling evidence for a close relationship between the autonomic nervous system, specifically high sympathetic and low parasympathetic tone, and sudden cardiac death has been obtained.³⁶ Vagal activation exerts a protective and antifibrillatory effect whereas myocardial infarction which reduces baroreflex sensitivity, a marker of vagal activity, increases the risk of sudden cardiac death. Beat to beat variation (sinus respiratory arrhythmia) in heart rate may also be used to assess vagal tone.³⁶ Kleiger *et al.*³⁷ found in a large population of postmyocardial infarction patients that depressed heart rate variability over the 24 hours (expressed as the standard duration of the RR interval) was significantly correlated with mortality. The relative risk was five times higher in patients with a heart rate variability lower than 50 milliseconds than in those with values greater than 100 milliseconds.

(c) *Electrolyte abnormalities* Alteration in extracellular potassium and magnesium, and intracellular calcium induce electrophysiological changes and cause arrhythmias.³⁸ Hypokalaemia is a well-recognized cause of lethal or potentially lethal arrhythmias^{39,40} and, in hypokalaemic patients with acute myocardial infarction, the incidence of ventricular tachycardia and fibrillation is increased.^{41,42} There are also some reports to suggest an association between out of hospital sudden cardiac death and hypokalaemia.^{43,44}

The role of abnormal magnesium concentrations is less clearly established but there is a possible relation between hypomagnesaemia and arrhythmias in the setting of acute myocardial infarction.^{45,46} Recent reports suggest that prophylactic therapy with magnesium salts reduces the incidence of ventricular arrhythmias and deaths in the first 24 hours after an infarction.^{47,48}

(d) *Pharmacological events* Some antiarrhythmic drugs can aggravate or even cause arrhythmias.⁴⁹ Flecainide and encainide may promote arrhythmias as shown in the Cardiac Arrhythmia Suppression Trial.⁵⁰ Agents that prolong myocardial conduction may produce ventricular tachycardia and drugs that prolong ventricular muscle recovery can cause arrhythmias leading to ventricular fibrillation.^{51,52}

Reducing the risk of sudden cardiac death

The correctable risk factors for coronary artery disease are: hypertension, cigarette smoking and hypercholesterolaemia. Males have a four-fold higher risk. Other risk factors include: diabetes, obesity and stress.^{53–55} Physical activity may protect against coronary attacks and even coronary deaths, but those who take vigorous exercise may die suddenly whilst they are physically active.² Overall, regular sensible exercise is beneficial.

(a) Subjects not known to have coronary heart disease

To reduce the risk of sudden cardiac death in those unaware of their coronary heart disease, the first steps would be: (a) the identification of the risk factors; and (b) the search for the latent disease. It has been suggested that the most helpful test for mass screening would be a symptom-limited electrocardiogram (ECG) stress test. Exercise-induced ST-segment depression, which occurred in 12% of men in the MRFIT Trial (Multiple Risk Factor Intervention Trial) was associated with a nearly four-fold increase in 7-year mortality from coronary heart disease compared with the men who had no exercise-induced ST-segment depression.⁵⁶ The most predictive information would be from coronary arteriography but this is only possible in small numbers of selected subjects.

(b) Subjects with known coronary heart disease

Subjects known to have coronary heart disease are a non-homogeneous population whose coronary lesions and ventricular function are extremely variable. An electrically inducible ventricular tachycardia test is the best predictor of serious arrhythmias, though a low ventricular ejection fraction, the presence of high grade of ventricular ectopic activity and changes on exercise testing may suggest increased risk.⁵⁷ Inducibility of ventricular tachycardia by programmed ventricular stimulation is a good predictor of sudden cardiac death in infarct survivors, but it is an invasive procedure and it is therefore restricted to patients with poor left ventricular function in whom it is possible to identify those most at risk.^{58–60} Richards⁵⁹ reported positive and negative predictive accuracies of 30% and 90%, respectively, for inducibility of ventricular tachycardia in predicting arrhythmic events.

Farrell *et al.*⁶¹ found that the best predictor of inducible ventricular tachycardia after myocardial infarction was evidence of reduced vagal activity. Depressed baroreceptor sensitivity and beat to beat variations (sinus respiratory arrhythmia) in heart rate which reflect vagal tone are simple methods of identifying patients at increased risk of arrhyth-

mias.^{62,63} Reduced vagal tone may increase susceptibility by shortening ventricular refractoriness.⁶⁴

Patients known to have coronary heart disease but whose left ventricular ejection fraction is greater than 45% are usually reasonably active but often have asymptomatic or mildly symptomatic ventricular arrhythmias.¹⁶ However, there is no evidence that simple ventricular premature complexes progress to fatal ventricular tachyarrhythmia and antiarrhythmic drugs do not reduce the incidence of sudden cardiac death in these patients.

In patients with a left ventricular ejection fraction of less than 30%, the incidence of cardiac deaths is 40% per year and half of these are sudden.⁶⁵ The main cause of death is ventricular tachycardia which leads to ventricular fibrillation. Those patients with markedly reduced ventricular systolic and diastolic function are particularly vulnerable. They may not be able to tolerate even brief episodes of ventricular tachyarrhythmias which cause inadequate diastolic filling time. In such patients, reduction of sudden coronary death has been achieved using implantable defibrillators and in one study about 50% of patients received at least one appropriate life-saving discharge over a 6 year period.⁶⁶

Documentation of severe coronary artery disease, especially left main or advanced multivessel disease, generally warrants surgical revascularization which is often effective when used alone in survivors without inducible ventricular tachycardia.

Surawicz¹⁶ suggests three lines of attack on the problem of sudden cardiac death:

1. Early detection of coronary heart disease and elimination of the risk factors.
2. Detection and treatment of the ischaemia in patients with known coronary heart disease.
3. Suppression of the ventricular tachyarrhythmias.

A number of different approaches for each of the above have been suggested; however, beta-adrenoceptor-blocking drugs (beta blockers) could have beneficial effects on all three levels.

Mechanism of action of beta blockers in preventing sudden cardiac death

Anti-ischaemic effects of beta blockers

Beta blockers may reduce myocardial oxygen demand by decreasing the heart rate, blood pressure and myocardial contractility. These effects might help to prevent ischaemia (Table II). Beta blockers also increase myocardial oxygen supply by increasing diastolic perfusion time. Other possible anti-ischaemic mechanisms include altering myocardial metabolism, decreasing microvascular

Table II Effects of beta blockers in prevention of sudden cardiac death

1. Anti-ischaemic effects
Reduce myocardial oxygen demand
Increase myocardial oxygen supply
Effects on myocardial metabolism, subendocardial blood flow and microvascular injury
Effects on platelet aggregation
Reduce infarct size
2. Antiarrhythmic effects
Peripheral beta adrenergic blockade – ventricular fibrillation threshold increased
Parasympathetic cardiac inhibition – augmented
Blockade of the CNS receptors (central blockade)

injury during ischaemia^{67,68} and redistributing blood flow in favour of the ischaemia subendocardium.^{69,70} In those with ischaemic heart disease beta blockers may modify the role of platelets and platelet embolism in inducing sudden cardiac death.⁷¹

Infarct size, assessed by ECG, enzyme measurement and scintigraphic methods are of vital importance.^{72,73} Beta blockers given intravenously within 4 hours of coronary occlusion reduce infarct size.^{74,75} There are data for propranolol,⁷⁶ atenolol,⁷⁷ metoprolol,⁷⁸ sotalol and timolol.⁷⁹ Norris *et al.*^{76,80} also showed that intravenous propranolol given early to patients with symptoms of myocardial ischaemia but without diagnostic ECG changes, may prevent the development of a myocardial infarct.

Antiarrhythmic effects of beta blockers

Beta blockers have a positive impact on arrhythmias in vulnerable postmyocardial infarct patients.^{77,81–83} During prolonged ambulatory monitoring, nearly 85% of patients with coronary heart disease exhibit ectopic activity. However, ventricular premature complexes (VPC) need to be graded according to frequency, persistence, multi-formity, repetitive pattern and degree of prematurity. Only frequent advanced grades or complex forms of VPC, those with couplets and runs and possibly those with early cycle ectopic complexes increase the risk of sudden cardiac death in patients with coronary heart disease.^{19,84}

Beta blockers are often considered less effective in suppressing chronic ventricular arrhythmias than the classic antiarrhythmic drugs.⁸⁵ In a double-blind postinfarction trial, metoprolol showed no significant effect on less serious arrhythmias such as VPC but the major ventricular tachyarrhythmias were suppressed: ventricular fibrillation occurred in 0.9% patients on metoprolol compared with 2.4% on placebo.⁸¹ These observations sug-

gest that the cause of VPC and ventricular fibrillation are not necessarily the same.

Beta blockers and sympathetic drive

Catecholamine levels are highest early after myocardial infarction and may play a role in causing ventricular arrhythmias.⁸² Therefore, the antiarrhythmic effect of beta blockers would be expected to be most pronounced at that time. However, a reduction in serious ventricular arrhythmias is most evident later, that is, after the first post-infarction day.^{75,81}

Animal experiments confirm that beta blockers significantly increase the ventricular fibrillation threshold suggesting that this is a potential mechanism for their antiarrhythmic action.⁸⁶ Anderson and colleagues investigated five beta blockers (timolol, pindolol, propranolol, metoprolol and labetalol) and all of them raised the ventricular fibrillation threshold in anaesthetized open chest dogs.⁸⁶ Repetitive ventricular response thresholds, another index of antifibrillatory effect,⁸⁷ were increased in parallel with ventricular fibrillation threshold. Gang *et al.*⁸⁸ obtained similar results with timolol and propranolol in closed chest dogs. In this study moderate and high doses of propranolol significantly prolonged the effective ventricular refractory period of pentobarbital anaesthetized dogs possibly by slowing reactivation of the inward sodium current without significantly altering action potential duration. High doses of some beta blockers prolong the effective ventricular refractory period by a direct membrane effect.⁸⁸

Sympathetic stimulation decreases and bilateral stellate ganglionectomy increases fibrillation threshold. The latter may be further increased by timolol which suggests combined blockade of circulating catecholamines and cardiac sympathetic innervation.⁸⁹ In animal studies various beta blockers show a 'class' effect on ventricular fibrillation threshold related primarily to blocking effects on the cardiac beta-1 adrenergic receptors. They all have this action unlike membrane stabilizing (propranolol), cardioselectivity (metoprolol), alpha blockade (labetalol) and beta-blocking potency.^{90–92} The effects of beta blockers on the experimental ventricular fibrillation threshold is only one of many ways used to define antiarrhythmic potential of beta blockers. The open chest anaesthetized dog model is characterized by high sympathetic stimulation that may be particularly responsive to beta blockers.⁸⁶

Beta blockers and vagal tone

Susceptibility to arrhythmias is also dependent on diminished vagal reflex activity. There is good evidence that beta blockers augment the level of

vagal cardiac inhibition as shown by increases in the R–R interval variability.⁹³ This may contribute to the antiarrhythmic actions of beta blockers by electrically stabilizing ventricular myocardium.⁹⁴ Increased vagal tone produced by edrophonium or phenylephrine also protects against ventricular fibrillation or may terminate ventricular tachycardia in man.⁹⁴ Further, increased vagal tone is associated with good prognosis and patients who have sinus arrhythmia after myocardial infarction are more likely to survive than those who do not.^{95,96} By contrast, Eckberg *et al.*⁹⁷ suggest that one of the reasons why patients with congestive heart failure, coronary heart disease and prior myocardial infarction are prone to die suddenly is because of their reduced vagal tone.

Thus beta blockers have the potential to improve survival of patients with coronary artery disease by simultaneously counteracting beta adrenergic stimulation and augmenting parasympathetic inhibition.

Psychological stress enhances susceptibility to ventricular fibrillation and animal experiments indicate that it lowers the ventricular fibrillation threshold.^{33,98–100} Some authors suggest therefore that the focus should be shifted from the heart as a target to the brain as a trigger.^{29,33,100} The stimulation of the specific loci in the posterior hypothalamus and frontocortical brainstem locus can provoke many diverse arrhythmias and lower the ventricular fibrillation threshold.^{100–102}

In animal experiments in pigs, propranolol was administered by an intracerebral injection in a dose too low to have an impact in the systemic circulation and produce peripheral beta blockade. Nevertheless, it protected from ventricular fibrillation.^{33,100} In experiments in rabbits, Ablad *et al.*¹⁰³ reduced the incidence of ventricular fibrillation following acute coronary occlusion in the group of animals pretreated for 3 weeks with metoprolol though not with atenolol. This was explained by lipophilic character of metoprolol which achieved comparable concentrations in cerebrospinal fluid and plasma whereas the cerebrospinal fluid concentrations of hydrophilic atenolol was only 10% that of plasma. These data suggest an important role for the blockade of beta-1 receptors located in the brain. Elevation of central vagal tone (R–R interval variation) was significantly increased with metoprolol but not with atenolol. These results suggest that lipophilicity may be an important property of beta blocking drugs in preventing sudden cardiac death.

The role of beta blockers in the primary prevention of coronary heart disease

There is evidence that beta blockers have a primary preventive role especially in men with severe hyper-

tension. Hypertension is one of the major risk factors for coronary heart disease and sudden cardiac death. Beta blockers control hypertension and may reduce coronary morbidity, mortality and sudden death.

In the MAPHY study (Metoprolol Atherosclerosis Prevention in Hypertensives), hypertensive patients (diastolic pressure in the sitting position 100–129 mmHg) were treated with either metoprolol or thiazide diuretics. Patients with previous myocardial infarction, angina pectoris or stroke were not included. The mean duration of the follow-up was 5 years. Sudden deaths constituted 78% of total cardiovascular mortality and therapy with metoprolol was associated with a significantly lower incidence of sudden deaths than diuretic treatment (32 of 1,609 on metoprolol, 45 of 1,625 on diuretics).¹⁰⁴

The UK Department of Health and Social Security Hypertension Care Computing Project (DHCCP) included three groups: patients on beta blockers, on methyldopa and on other treatment (70% only diuretics). Subjects who received beta blockers had the lowest rate for total mortality (no data for sudden cardiac death were available).¹⁰⁵

In the IPPPSH trial (International Prospective Primary Prevention Study in Hypertension) and MRC trial (Medical Research Council) the differences in mortality rates between the beta blocker treatment and bendrofluazide or placebo was not significant.^{106,107} However, half the patients were middle-aged females with mild hypertension, a low-risk group in whom it would have been difficult to demonstrate a benefit from beta blockade. When silent infarcts from the MRC trial were included, propranolol did significantly reduce coronary event rates.¹⁰⁸

The Swedish Trial in Old Patients with Hypertension (STOP hypertension trial) compared the effects of active antihypertensive therapy (atenolol, metoprolol or pindolol and diuretic) in old patients aged 70–84 years. Patients on active therapy had significantly lower total mortality. On active treatment there were four (0.23%) sudden deaths compared with 12 (0.68%) in the placebo group.¹⁰⁹

Secondary prevention

Acute studies

Snow in 1965 was the first to report that propranolol reduced mortality when it was administered after acute myocardial infarction.¹¹⁰ Since then a number of trials in which beta blockers were given soon after the onset of myocardial infarction have been performed. Yusuf *et al.*¹¹¹ reviewed 26 smaller randomized studies and two large studies. Both large studies: First International Study of

Infarct Survival (ISIS 1 – with atenolol) and Metoprolol in Acute Myocardial Infarction (MIAMI) showed reduced mortality most effectively in patients at greatest risk (no data for sudden death rate).^{112,113}

Pooling the results of all available acute beta-blocker trials Yusuf *et al.* calculated that treatment with beta blockers reduces mortality by 13% in the first 2 days,¹¹¹ mainly due to prevention of ventricular fibrillation or cardiac rupture.

Long-term studies

Pooled results of seven long-term beta-blocker trials (including only those with more than 100 patients) showed a 28% reduction in all cause mortality. The sudden cardiac death rates were lower in the beta blocker group for all seven trials (4.2% of 5,728 patients on beta blockers and 6.3% in 5,454 patients on placebo), a reduction of 33%.¹¹⁴

Two key studies are the Norwegian Timolol Study and Beta Blocker Heart Attack Trial (BHAT) (Figure 1). In the first study, timolol

Figure 1 Sudden cardiac death rate in chronic beta blocker trials.

reduced mortality in patients who had had myocardial infarction, during a follow-up period of 12–33 months. The most pronounced effects were on sudden cardiac death rate (7.7% patients died suddenly in the timolol group compared with 13.9% in the placebo group).¹¹⁵

In the large study of propranolol (BHAT), total mortality was reduced by propranolol and sudden cardiac death rate was 3.3% in propranolol group

compared with 4.6% in the placebo group.¹¹⁶

Olsson *et al.* (1992) analysed pooled data from the five different metoprolol trials and found a significant reduction in total mortality mainly due to significant reduction in sudden cardiac deaths (33% of deaths were sudden on metoprolol, 47% on placebo).¹¹⁷

With the exception of aspirin and aspirin-like drugs and perhaps amiodarone,²⁷ beta blockers are the only agents that reduce the incidence of sudden cardiac death in controlled trials.¹¹⁸ The data for beta blockers are far more extensive. Beta blockers may be particularly helpful in high-risk postinfarction patients, for example, those with hypertension, with a major ST-segment depression during convalescence, patients with 4 and 5 grade VPC in the first 6 months after the infarction,¹¹⁹ and in patients with angina with accelerating salvos of ventricular tachycardia or ventricular arrhythmias during exercise. In patients with definite infarction it is important to start beta blockers as soon as possible. They can be used in addition to thrombolytic therapy and aspirin.^{19,119}

Conclusions

The incidence of sudden cardiac death may be reduced by optimizing health care on three levels: early detection of coronary heart disease and elimination of the risk factors, detection and treatment of ischaemia in patients with known coronary heart disease, and suppression of the ventricular tachyarrhythmias. It has been shown that beta blockers have beneficial effects on all three. There is much evidence to show that beta blockers reduce the incidence of total cardiac as well as sudden cardiac deaths.

The relevance of the lipophilicity and hydrophilicity of beta blockers is contentious. Animal data suggest that lipophilic beta blockers penetrate the brain and reduce the risk of ventricular fibrillation when myocardial ischaemia is produced acutely.^{33,103} The clinical evidence on primary prevention is based largely on trials in which lipophilic beta blockers were used.^{104,106,107} Sudden death reduction postinfarction was demonstrated with timolol,¹¹⁵ metoprolol¹¹⁷ and propranolol,¹¹⁶ all lipophilic beta-blockers. Comparable data for hydrophilic beta-blockers do not exist. Atenolol did not reduce cardiac mortality in the HAPPY trial¹²⁰ or in the MRC trial in the elderly,¹²¹ and sotalol reduced reinfarction rates but not sudden deaths in post-infarct patients.¹²²

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