Activation of the adrenergic nervous system appears to play a crucial role in the genesis of fatal arrhythmias associated with the very early stages of acute myocardial infarction. The second messenger of beta-adrenergic catecholamine stimulation, cyclic adenosine monophosphate (AMP), has established arrhythmogenic qualities, acting by an increase in cytosolic calcium, which potentially has three adverse electrophysiologic effects.

First, stimulation of the transient inward current by excess oscillations of cytosolic calcium can invoke delayed afterdepolarizations, so that triggered automaticity can develop in otherwise quiescent ventricular muscle. Second, cyclic AMP can evoke calcium-dependent slow responses in depolarized fibers, so that conditions for reentry are favored. Third, excess cytosolic calcium can cause intercellular uncoupling with conduction slowing.

Focal changes in cyclic AMP and cytosolic calcium promote the development of ventricular fibrillation. Beta-adrenergic blockade can limit the formation of cyclic AMP in ischemic tissue. Furthermore, by reducing sinus tachycardia it can lessen cytosolic calcium overload. Hence, beta-adrenergic blockade helps to prevent ventricular fibrillation in the early stages of acute myocardial infarction and protects from sudden death in the postinfarction phase.

In congestive heart failure, abnormalities of cytosolic calcium patterns exist with cytosolic calcium overload. It is proposed that the adverse effects of phosphodiesterase inhibitors on the mortality rate in patients with congestive heart failure can be explained by increased rates of formation of cyclic AMP and the development of calcium-dependent arrhythmias. Because calcium is the ultimate messenger of cyclic AMP-induced arrhythmias and because cytosolic calcium is increased in heart failure, it will be difficult to develop positive inotropic agents that are free of the risk of sudden death.

Ventricular arrhythmias can arise because of abnormal impulse formation and disordered conduction within the myocardium. The cellular events that underlie cardiac automaticity and conduction disturbances have been well characterized (1). These include partial depolarization of cells, leading to a decreased rest potential with consequent enhancement of automaticity in Purkinje fibers, inhibition of the rapid phase 0 depolarization (carried by the sodium current) with facilitation of the slow response (mediated by calcium ions), shortening of the action potential (with a decrease in the refractory period) and acceleration of phase 4 depolarization. When these changes are focal, they predispose to inhomogeneity of electrical activity, which has long been recognized as the "anatomic substrate" for ventricular fibrillation. Focal metabolic variations, probably reflecting localized deficits in the microcirculation, also contribute to inhomogeneity and thereby determine vulnerability to fibrillation. Thus, anatomic and metabolic substrates are mutually reinforcing rather than exclusive, thereby facilitating the precipitation of ventricular fibrillation by a triggering arrhythmia.

Several metabolic consequences of ischemia have already been shown to increase the vulnerability to fibrillation. Beck (2) proposed that gradients of oxygen in the heart with regional ischemia caused inhomogeneous metabolic and electrical activity. Harris et al. (3) suggested that ventricular
Figure 1. Proposed sequence whereby myocardial ischemia leads to catecholamine discharge, formation of cyclic adenosine monophosphate (AMP) and calcium (Ca²⁺)-mediated triggered tachycardia, reentry and automaticity. The resultant ventricular tachycardia can predispose to ventricular fibrillation, especially when there is electrical inhomogeneity. Note inhibition of this sequence by beta-adrenergic blockers and aggravation by phosphodiesterase (PDE) inhibitors. DADs = delayed afterdepolarizations; K⁺ = potassium; Na⁺ = sodium; SA = sinoatrial; SR = sarcoplasmic reticulum.

Evolution of the Calcium Arrhythmogenesis Concept

The concept that mechanisms involving the adrenergic nervous system are fundamental to the genesis of ventricular fibrillation was based both on the early activation of the adrenergic system in response to coronary artery occlusion (9) and the demonstration that catecholamine stimulation increases the vulnerability of the heart to fibrillation (10). Sympathetic nervous system activation occurs soon after coronary occlusion (11) when ventricular fibrillation commonly occurs. However, the mechanism or mechanisms whereby adrenergic neurotransmitters released during sympathetic activation might exert their influence on the vulnerability of the heart to fibrillation has been obscure. The cellular electrophysiologic responses to cyclic AMP were demonstrated in 1973 by Tsien (12); these resembled the electrophysiologic effects of epinephrine. Explanations for the involvement of cyclic AMP in pacemaker function (by enhancement of phase 4 depolarization), in triggered automaticity (by formation of delayed afterdepolarizations) and by facilitating reentry (stimulation of calcium-mediated slow responses) became available during the subsequent years (13, 14).

The cyclic AMP hypothesis. Observations in baboons (Fig. 2) and isolated rat heart models (Fig. 3) of acute regional myocardial ischemia led to the cyclic AMP hypothesis (8, 15, 16), whereby cyclic AMP, the second messenger of the adrenergic system, occupies a key role in the mediation of adrenergic effects on vulnerability to fibrillation. The effects of cyclic AMP on electrical function of cardiac cells, particularly when they are partially depolarized as in early ischemia, could explain several of the electrophysiologic phenomena encountered in arrhythmogenesis and ventricular fibrillation. The current concept is that calcium ions act as a third messenger for adrenergic influences.
Figure 3. The basic observations linking beta-adrenergic blockade, decreased tissue cyclic adenosine monophosphate (CAMP) and a decreased ventricular fibrillation threshold (VFT) with converse changes found during phosphodiesterase inhibition by theophylline. The response curve of ventricular fibrillation threshold to epinephrine (Adrenaline) coincides with an increase in tissue cyclic AMP, but not with changes in tissue phosphoereatine or tissue adenosine triphosphate. The curve was shifted to the left by theophylline (1 mM), with higher levels of tissue cyclic AMP achieved. Atenolol (30 µM) shifted the ventricular fibrillation threshold curve upward and to the right; an increase in tissue cyclic AMP was not seen until the reduction in ventricular fibrillation threshold occurred. Reprinted from Lubbe et al. (15), with permission of the Journal of Clinical Investigation.

Cyclic AMP and Arrhythmogenesis

The elevation of myocardial cyclic AMP levels after coronary artery occlusion has been linked to the development of ventricular fibrillation by Podzuweit et al. (25). In baboons, the onset of ventricular fibrillation was preceded by a progressive elevation of cyclic AMP in ischemic myocardium. Observations obtained in pigs supported this concept (16). In an isolated heart system, an increase in vulnerability to fibrillation could be induced by epinephrine (Fig. 3) as well as by dibutyl cyclic AMP, a form of cyclic AMP thought to penetrate the cell membrane (15).

The addition of theophylline causes greater reductions in ventricular fibrillation threshold values accompanied by higher levels of myocardial cyclic AMP. In dogs, toxic doses of aminophylline cause marked elevation of tissue cyclic AMP levels and the occurrence of spontaneous ventricular fibrillation (26).

Pharmacologic agents that decrease myocardial cyclic AMP levels protect against the occurrence of ventricular fibrillation. In the isolated rat heart, propranolol (27), amiodarone (28), labetalol (29) and adenosine (30) decrease myocardial cyclic AMP levels in ischemic zones and prevent a decrease in ventricular fibrillation threshold. Several of these agents also prevent spontaneous ventricular fibrillation after coronary artery ligation. In the pig, prostacyclin administration attenuates cyclic AMP levels after coronary artery ligation and protects against the development of arrhythmias (31). Choline esters prevent ventricular arrhythmias and cyclic AMP accumulation in pig myocardium by an action that can be blocked by atropine (32). Adenosine inhibits spontaneous arrhythmias in the isolated coronary artery-ligated rat heart by an action opposed by phosphodiesterase inhibitors (33).

An interesting series of experiments was reported by Podzuweit and coworkers (20,32,34,35) in which local stimulation of myocardial cyclic AMP was obtained. Intramyocardial infusion of norepinephrine, N⁶,O²²-dibutyl cyclic AMP (DBcAMP) or N⁶-monobutyryl cyclic AMP elicited arrhythmias, including ventricular tachycardia and fibrillation. Potent arrhythmogenic combinations involved infusions of norepinephrine or DBcAMP in combination with a phosphodiesterase inhibitor and calcium chloride. Infusion of the calcium chloride by itself did not cause arrhythmias. The arrhythmias induced by infusion of norepinephrine were blocked by coinfusion of propranolol. Biopsy specimens of myocardium obtained from the infusion site at the onset of ventricular tachycardia revealed elevated levels of cyclic AMP.

Adrenergic Activity and Ventricular Fibrillation

Although sympathetic activation (9) may represent a compensatory mechanism designed to maintain cardiac output by a damaged ventricle, it may also be causally related to the development of ventricular fibrillation. Aortic wall and carotid sinus stretch receptors have traditionally been thought to initiate the adrenergic activation. There is also activation of central noradrenergic centers in the hindbrain in response to vagal afferent traffic traveling from receptors within the ischemic myocardium (17).

Catecholamine stimulation causes an increase in vulnerability of the heart to ventricular fibrillation (10); stimulation of the left stellate ganglion is potent in the development of ventricular fibrillation in the cat with coronary artery occlusion (18). Administration of norepinephrine in the presence of ischemia will elicit ventricular tachycardia or fibrillation in a number of animal models: the isolated rat heart (15) or the dog (19) or pig (20). Conversely, when sympathetic activity is inhibited, there is protection against ventricular fibrillation. Surgical denervation (21), depletion of myocardial norepinephrine stores by reserpine or 6-hydroxydopamine (22) and blockade of the beta-receptors (23,24) all protect against the development of ventricular fibrillation in the presence of myocardial ischemia.
Evidence Against the Cyclic AMP Hypothesis

Nonetheless, evidence against a relation between tissue cyclic AMP levels and the occurrence of ventricular fibrillation has been provided by two sources. First, forskolin-induced increases in cyclic AMP levels in isolated rat hearts were not accompanied by ventricular fibrillation (36). Forskolin activates adenylate cyclase directly, bypassing the beta-receptors and membrane-based coupling proteins. However, our current data (37) suggest that compartmentalization of cyclic AMP may provide the answer. Our subsequent work has established that only the generation of very high levels of cyclic AMP by forskolin is accompanied by a decrease in the ventricular fibrillation threshold, suggesting an overflow phenomenon with some of the excess cyclic AMP reaching that compartment able to generate arrhythmias.

A second objection to the cyclic AMP hypothesis arose from the failure of the beta-adrenergic blocking agent metoprolol to decrease ischemic myocardial levels of cyclic AMP. Although ventricular fibrillation was prevented in pigs with coronary artery ligation (38). There are alternative explanations for this observation. Blood flow in the ischemic myocardium was considerably higher in the metoprolol-treated pigs than in pigs treated with propranolol or sotalol. Also, the relatively high dose of the beta-blocker might have had a negative inotropic effect, potentially annulling the antiarrhythmic effect, as may be the case for propranolol doses >0.1 mg/kg body weight (24).

Cellular and Electrophysiologic Effects of Cyclic AMP

Microiontophoresis of cyclic AMP into cardiac Purkinje fibers caused shortening of the action potential, elevation of the plateau level and enhancement of diastolic (phase 4) depolarization (12). In cells partially depolarized by elevated extracellular potassium, the magnitude and frequency of low voltage oscillations were increased by cyclic AMP. Automaticity followed after the induction of slow responses by cyclic AMP-induced inward calcium current (39). Watanabe and Besch (40) established the relation between cellular levels of cyclic AMP, the calcium-mediated inward current and electrical excitability in partially depolarized guinea pig hearts. The calcium channel antagonist D600 successfully blocked cyclic AMP-mediated effects on electrophysiologic function and contractile activity (41).

Links Between Cyclic AMP and Calcium: Mechanisms of Arrhythmias

Effect of calcium antagonists. Cyclic AMP, when injected into calcium-overloaded myocytes, can evoke large depolarizations that are calcium dependent (14). If cyclic AMP produced early ischemic arrhythmias by a mechanism involving calcium, it would be logical that calcium antagonists (calcium ion entry blockers) should inhibit such arrhythmias. Thus, verapamil given to dogs with coronary artery ligation protected against spontaneous ventricular arrhythmias (42) and prevented the lowering of ventricular fibrillation threshold (43). In such experiments, however, it was difficult to rule out a primary effect of the calcium antagonists on peripheral hemodynamic variables. Thandroyen (44) and Lubbe et al. (45) reported the protective action of calcium antagonists in isolated rat hearts. However, relatively high concentrations were required to protect against ventricular fibrillation. The active L(-) isomer of verapamil but not the inactive D(+) isomer prevented the decrease in the ventricular fibrillation threshold (Fig. 4) and in guinea pig papillary muscle also inhibited calcium-dependent slow responses. The antiarrhythmic effect could be found in the absence of changes in tissue cyclic AMP and supported the argument for a specific role of calcium channel activity in early ventricular fibrillation.
"Slow response" action potentials. These can be demonstrated by the addition of catecholamines or other agents that increase cyclic AMP in myocardial tissue (Fig. 5) in the presence of extracellular potassium concentrations sufficiently elevated to cause depolarization (46,47). Although the rate of microreentry in ventricular fibrillation and ventricular tachycardia is too fast to be dependent on slow responses (48,49), a slow response action potential could create an area of extremely slow conduction that, in turn, could predispose to reentrant circuits. Such a circuit could be relatively rapid. Slow responses are particularly likely to occur when high cyclic AMP levels are combined with high external potassium levels, as would occur in zones with severe ischemia.

"Flow of Injury" Current and Calcium

Jansc et al. (48,49) suggested that the origin of ischemia-related ventricular tachycardia and fibrillation was located at the "normal" side of the ischemic border, possibly caused by a "current of injury" that flowed from the ischemic to the normal zone. Such injury currents could flow as a result of differences in the electrical potential between these zones, as shown in a sucrose gap preparation (50). In ischemia, there is a gradient of extracellular potassium from the ischemic zone, where the level is high, to the nonischemic zone, where it is less elevated or normal. The current resulting from this potassium gradient can lead to a phenomenon known as depolarization-induced automaticity (51). Such automaticity occurring in depolarized myocardium is partially due to the calcium current (52) and is influenced by changes in the external calcium concentration (53). Therefore, inhibition of the calcium current by calcium antagonists should reduce depolarization-induced automaticity. In addition, calcium antagonists may lessen the release of potassium, decreasing the severity of depolarization and reducing the depolarization-induced current (54).

Jansc et al. (48) made another interesting prediction—namely, that the current of injury could induce afterdepolarizations in Purkinje fibers, especially in the presence of epinephrine stimulation. Hence, it became appropriate to examine the possible contribution of afterdepolarizations to ischemic ventricular arrhythmias.

Delayed Afterdepolarizations

Cyclic AMP, internal calcium and afterdepolarizations. The elevation of cyclic AMP in ischemic tissue may provoke delayed afterdepolarizations and, hence, ventricular automaticity (55). We found (56) that delayed afterdepolarizations were precipitated by dibutyryl cyclic AMP or isoproterenol under control conditions but not during ischemic perfusion of guinea pig papillary muscles; then, paradoxically, delayed afterdepolarizations could be precipitated during reperfusion. These findings could serve as an explanation for the observations that increased levels of cyclic AMP in ischemic myocardium predispose to reperfusion arrhythmias (32,57) and for the antiarrhythmic effect of severe myocardial ischemia on cyclic AMP-mediated arrhythmias (35). The proposed explanation for the lack of precipitation of delayed afterdepolarizations in severely ischemic preparations rests on the requirement for ATP in the cellular cycling of calcium.

Afterdepolarizations, transient inward current and energy requirements. Delayed afterdepolarizations are the electrophysiologic abnormalities associated with rhythmic internal calcium oscillations. Delayed afterdepolarizations can be evoked by a variety of conditions (Fig. 6) that induce intracellular calcium overload, including fast pacing, beta-adrenergic stimulation, the addition of dibutyryl cyclic AMP and intracellular injection of calcium. Because calcium overload may occur during ischemia and reperfusion, a reasonable hypothesis would be that delayed afterdepolarizations could play a role in ischemic and reperfusion arrhythmias (55). The factors capable of provoked and inhibiting delayed afterdepolarizations in guinea pig papillary muscles were studied (58); delayed afterdepolarizations were abolished by "simulated" ischemia consisting of the combined presence of increased extracellular potassium, high lactate, low pH and hypoxia. In contrast, reoxygenation after a hypoxic
glucose-free period led to an increased amplitude of delayed afterdepolarizations with associated extrasystoles (59). Similarly, Bhattacharya and Vassalle (60) found that digitalis-induced delayed afterdepolarizations were abolished by metabolic inhibition.

Mechanism underlying delayed afterdepolarizations. This mechanism is the calcium-induced transient inward current \( I_{T} \) or \( I_{a} \). It is proposed that rhythmic internal calcium oscillations cause rhythmic switching on and off of the transient inward current, thus predisposing to arrhythmias mediated by this current. The mechanism of abolition of the transient inward current by metabolic inhibition was investigated in guinea pig ventricular myocytes by the voltage clamp technique (61,62). The blocking effect of metabolic inhibition could not be explained solely by either an increased potassium current or changes in the inward calcium current \( I_{Ca} \). Internal dialysis of isolated myocytes showed that ATP depletion to <40% of control values blocked the transient inward current, probably by interfering with calcium uptake by the sarcoplasmic reticulum. Repletion of ATP by internal dialysis showed that levels of ATP of 2 to 5 mM were required for the transient inward current to be operative (61). The presumed mechanism of the effects of ATP was by restoration of energy-dependent internal calcium movements, probably at the level of the energy-dependent uptake of calcium by the sarcoplasmic reticulum.

Metabolic maps, cyclic AMP and ATP. The preceding data indicate that it is logical to expect that delayed afterdepolarizations can be induced by intracellular cytosolic calcium overload in conditions where there is a combination of an elevated tissue cyclic AMP level and tissue ATP levels that have not yet fallen to <2 mM (approximately 2 μmoles/g). In early regional ischemia, 20 min after coronary ligation, it is possible to find the combination of a localized increase in cyclic AMP with a relatively well maintained ATP level >2 μmoles/g (32). This combination is, however, highly focal, in keeping with the role of metabolic heterogeneity in precipitating ventricular arrhythmias. All these observations do not directly prove that delayed afterdepolarizations occur in ischemic myocardium, but they provide strong indirect evidence.

Other Calcium-Dependent Mechanisms Possibly Contributing to Early Ischemic Arrhythmias

1. Early afterdepolarizations. Although early afterdepolarizations are also calcium dependent (63) and arrhythmogenic, these abnormalities are precipitated under conditions associated with lengthening of the action potential duration, as may occur in ischemia (64). In contrast, delayed afterdepolarizations are provoked when calcium overload is accompanied by tachycardia. Early afterdepolarizations are more likely to cause torsade de pointes than the regular ventricular tachycardia precipitated by delayed afterdepolarizations. Among patients who died suddenly while wearing a Holter ECG monitor, 8% had torsade de pointes and 68% had some form of ventricular tachycardia (65).

2. Delayed intercellular conduction and altered cable properties. Both cyclic AMP (66) and calcium (67) augment the intercellular resistance, thereby decreasing conduction velocity and predisposing to reentry arrhythmias. Conduction velocity in myocardial ischemia may also be changed by altered cable properties. Thus, hypoxia increases the internal longitudinal resistance \( R_{L} \) (68,69). This effect is also seen with increased cyclic AMP (66), increased external calcium or intracellular acidosis (67). All these effects are probably mediated by elevated cytosolic calcium because the junctional conductance is much more dependent on the internal calcium ion concentration than on the internal proton concentration (70).

In addition, an increase in extracellular potassium concentration, as in ischemia, will depolarize the membrane potential, moving it into a range of potentials where the sodium current is partly inactivated. Within a certain range of ischemia-induced increases in the external potassium concentration, the upstroke of such a "depressed fast response" might actually consist of two phases, the first of which can be blocked by sodium channel blockers and the second of which is calcium dependent (47).
3. Direct evidence linking cytosolic calcium and ventricular tachycardia or fibrillation. More direct evidence for links between increased cytosolic calcium and ventricular arrhythmias is threefold. First, Lee et al. (71) measured local variations in cytosolic calcium among various sites in the ischemic zone. They proposed (72) that such local variations in cytosolic calcium may explain the alternans pattern in the T wave that precedes ventricular fibrillation in the dog.

Second, Merillat et al. (73) induced ventricular fibrillation in the rabbit heart by sodium pump inhibition. Decreasing external calcium to 80 μM or adding verapamil or nifedipine consistently prevented the initiation of such ventricular fibrillation. Ventricular fibrillation, once induced, may result in abnormalities of cytosolic calcium, including enhanced entry through the voltage-dependent calcium channel (74).

Third, Kihara and Morgan (75) showed that spontaneous ventricular fibrillation rapidly developed in an isolated ferret heart concomitant with large irregular oscillations in internal calcium. These oscillations probably represented calcium ions cycling in and out of the sarcoplasmic reticulum because the oscillations were reduced by caffeine, an inhibitor of calcium release from the sarcoplasmic reticulum. Pretreatment with ryanodine, a highly specific inhibitor of calcium release from the cytoplasmic reticulum, prevented the induction of ventricular fibrillation.

Fourth, Thandroyen et al. (76) found that spontaneous fibrillation in calcium-overloaded isolated myocytes was preceded by an increase in cytosolic calcium from nanomolar to micromolar levels. Furthermore, the tachyarrhythmia itself promoted severe calcium overload, which is thought to be important in the perpetuation and degeneration of the arrhythmias.

Nonetheless, it is clear that more data are required on cytosolic calcium levels in the whole heart preceding the induction of ventricular fibrillation by catecholamines, cyclic AMP and calcium.

Clinical Evidence Supporting the Hypothesis: Protection Against Sudden Cardiac Death by Beta-Adrenergic Blockade

Most instances of sudden cardiac death in developed countries are believed to be due to ventricular fibrillation, generally preceded by monomorphic ventricular tachycardia (65). In animal experiments, as we just reviewed, administration of some beta-blockers before coronary artery ligation lowers the ischemic myocardial cyclic AMP levels and reduces the incidence of ventricular fibrillation (24). There is now firm evidence that beta-blocker treatment offers protection against sudden cardiac death in victims of acute myocardial infarction (77), but this has no convincing evidence has been produced for a primary preventive action in hypertensive patients.

Primary prevention. The risk of all forms of coronary heart disease, including sudden cardiac death, is substantially increased in hypertensive patients. Propranolol in the Medical Research Council (MRC) trial, exprenolol in the International Prospective Primary Prevention Study in Hypertension (IPPSH) and atenolol or metoprolol in a third trial have been studied (78). No convincing primary preventive effect of beta-blocker treatment against sudden cardiac death could be demonstrated in these trials (78). Subsequently, in the Metoprolol Atherosclerosis Prevention in Hypertensive (MAPHY) trial (79), in which 3,234 hypertensive patients were randomized to metoprolol or diuretic therapy, a significant reduction in the incidence of sudden coronary death was suggested for subjects randomized to metoprolol. There were 99 deaths that were classified as due to cardiovascular causes and 78% of these were sudden (within 24 h of the onset of symptoms). The 32 sudden deaths in the metoprolol group were fewer than the 45 sudden deaths in the diuretic group (p < 0.02). However, there was no placebo control group and it is possible that the number of sudden deaths was increased in the diuretic-treated group rather than reduced in the metoprolol-treated cohort.

Secondary prevention. In secondary prevention trials, there is convincing evidence for a protective effect of beta-blockers against sudden cardiac death. Analysis of the pooled data (80) from trials in which beta-blocker treatment was started early after hospital admission and was maintained for ≥1 year suggests that beta-blocker treatment reduces the risk of sudden death by about 30%. In prolonged postinfarction follow-up therapy with metoprolol, the sudden death rate was reduced by 50% (81). At least some of these benefits may be explained by the combined effects of beta-blockade in preventing ischemic changes and the electrophysiologic changes mediated by ischemia.

Early intravenous beta-blockade for acute myocardial infarction. In 27 trials (77) in which beta-blockers were administered intravenously on admission to patients with myocardial infarction (before the thrombolytic era), a 15% reduction in the mortality rate was demonstrated in 27,600 subjects. Analysis of the pooled data for the 27 trials showed a 23 ± 8% reduction in the risk of dying in the first 24 h in patients with myocardial infarction treated with beta-blockers versus 11 ± 11% in the second 48 h and a 1 ± 11% reduction in the period between days 4 and 7. The importance of very early administration of beta-blockers for obtaining the protective effect of beta-blockade against sudden death is well illustrated by comparing the results of the First International Study of Infarct Survival (ISIS-1) (82) and the trial reported by Norris et al. (83). When atenolol was administered within 8 h of symptom onset in the ISIS-1 (82) to 81% of 8,037 subjects, the incidence rate of ventricular fibrillation was 2.4% versus 2.5% in control subjects. Administration of intravenous propranolol within 4 h of the onset of symptoms of myocardial infarction decreased the incidence of ventricular fibrillation from 5.7% to 0.8% (p < 0.01). The maximal early benefit of beta-blockers in the
prevention of ventricular fibrillation in acute myocardial infarction supports observations in animal experiments (25) that show a distinct time phase when ischemic myocardial cyclic AMP levels are elevated.

Factors enhancing the protective effect of beta-blockers. Other factors based on experimental data may also be relevant for the clinically important protective effect of beta-blockers to become manifest. First, exercise training for 10 weeks in rats (84) previously subjected to coronary artery ligation resulted in a blunted increase in myocardial cyclic AMP levels (at 10 s) after a second coronary artery ligation. Second, the dosage of the beta-blocker administered intravenously may also be a determining factor. In pigs (24), 0.1 mg/kg of propranolol administered 30 min before and 10 min after coronary artery ligation prevented ventricular fibrillation, whereas perhaps unexpectedly, doses of 0.5 and 3 mg/kg did not. It was proposed that the protective effect shown at the lower dose was offset by the negative inotropic effect encountered with the higher doses. Third, hypokalemia associated with acute adrenergic overactivity may be of paramount importance. The reduction in serum potassium is mediated by beta-adrenoceptors, and beta-blockers with beta-antagonist activity may attenuate the severity of hypokalemia (85). Reduced extracellular levels of potassium are associated with greater elevation of myocardial cyclic AMP levels after coronary artery ligation (86).

Fourth, ancillary properties of beta-blockers may also be important (87). Propranolol, which is fat soluble, is concentrated in cardiac cells and some actions may not strictly reflect plasma levels. In the isolated rat heart (27), propranolol (d- and l-isomers) prevented the early increase in cyclic AMP after coronary artery ligation, whereas atenolol did not. However, controlled clinical trials will be required to establish whether propranolol has a more powerful protective effect than other beta-blockers against ischemia-related ventricular fibrillation.

Stress and Ventricular Fibrillation

Although postinfarction death is not linked to a type A personality (88), the most common triggers of acute myocardial infarction are emotional upset (18%) and physical activity (14%) (89), both associated with catecholamine discharge. Of interest is the experimental finding (90) that intracerebral administration of propranolol acts to reduce the incidence of ventricular fibrillation in stressed pigs with regional ischemia. It remains possible that beta-blockade may act in part against sudden death by a centrally mediated reduction of stress-stimulated pathways. In the Beta-Blockade Heart Attack Trial (BHAT) study (91), propranolol reduced the incidence of early morning sudden cardiac death, which is thought to be mediated by increased sympathetic activity. In patients with spontaneous ventricular tachycardia or fibrillation, there is evidence for selective cardiac sympathetic activation (92).

Heart Failure, Cyclic AMP-Calciun, Phosphodiesterase Inhibitors and Sudden Cardiac Death

Systolic and diastolic dysfunction in heart failure. Disruptions in cellular levels of cyclic AMP and cytosolic calcium are pivotal to the disordered systolic and diastolic function in heart failure (93,94). The overactivity of the adrenergic nervous system, with enhanced neurotransmitter release and circulating catecholamines, is paradoxically associated with reduced intracellular levels of cyclic AMP, chiefly because of downregulation of myocardial beta-adrenergic receptors or increased expression of the inhibitory G-protein (Fig. 7 and 8), or both (95). Subcellularly, there are abnormalities in patterns of rise and fall of cytosolic calcium levels. The systolic calcium transients are reduced (as a consequence of inadequate cyclic AMP-mediated calcium channel activation), resulting in reduced force generation and lower stroke output. Impaired interaction of calcium with troponin-actomyosin also contributes to the systolic dysfunction. Uptake of cytosolic calcium by the sarcoplasmic reticulum is impaired with consequent prolonged diastolic calcium transients, which may account for the diastolic dysfunction in heart failure.

Arrhythmias in congestive heart failure (Table 1). Patients with congestive heart failure have a poor prognosis, and about 50% of the deaths are sudden and probably arrhythmic in origin (96). In patients with severe heart failure (functional classes III and IV), Maskin et al. (97) found a high prevalence of arrhythmias: 92% of the patients in their study had multifocal premature ventricular complexes and 71% had nonsustained runs of ventricular tachycardia. Treatment of heart failure with inotropic agents with proarrhythmic potential may therefore improve hemodynamic function but increase mortality.

Arrhythmias due to inotropic therapy. The time-honored approach to inotropic therapy of heart failure involves increasing intracellular levels of calcium by digitalis glycosides, which act by a cyclic AMP-independent mechanism. The proarrhythmic potential of toxic doses of glycosides is established, with the role of calcium in such ventricular tachyarrhythmias well supported by laboratory observations. Alternative approaches whereby systolic function can be boosted involve increasing intracellular levels of cyclic AMP either by stimulation of available beta-receptors or reducing cyclic AMP breakdown by inhibition of the phosphodiesterase responsible for cyclic AMP breakdown. All positively inotropic agents ultimately acting through an increase in cytosolic calcium are likely to be proarrhythmic (Fig. 7).

Treatment with beta,-agonists: pirenalere and dobutamine. The results of long-term treatment of heart failure with the use of beta,-agonists (pirenalere, dobutamine) have been disappointing. The initial improvement seen in cardiac function is not maintained, suggesting further downregulation of beta-receptors. A meta-analysis (98) of nine trials involving the use of beta-receptor agonists shows a distressing
increase by 2.07 in the relative risk of dying during such therapy. It is possible that intracellular calcium overload, related to persistent beta-receptor stimulation and fluctuations in intracellular cyclic AMP levels determined by variable degrees of phosphodiesterase inhibition by ischemia and cellular acidosis, may be responsible for fatal arrhythmias (Fig. 8).

Treatment with phosphodiesterase inhibitors: amrinone, milrinone and enoximone. A substantial improvement in hemodynamic function can be obtained in heart failure with the short-term use of inhibitors of phosphodiesterase type III, such as amrinone, milrinone and enoximone. These agents selectively increase cellular levels of cyclic AMP and have the potentially beneficial additional action of vasodilation. Their use as therapeutic agents in heart failure is therefore based on rational principles. However, according to the cyclic AMP hypothesis, phosphodiesterase type III inhibition have the potential to cause ventricular tachycardia and fibrillation. Analysis of 12 trials (98) in which phosphodiesterase inhibitors were used has indicated an increased relative risk (1.58) of dying during treatment with such agents. The Prospective Randomized Milrinone Survival Evaluation (PROMIS) study, in which milrinone was used in patients refractory to conventional therapy of heart failure, was terminated because of the increased cardiovascular mortality in treated patients (99). Earlier uncontrolled studies (100) with milrinone revealed an increase in complex ventricular ectopic activity and instances of sudden death despite hemodynamic improvements.

Caffeine and arrhythmias. Caffeine, a phosphodiesterase inhibitor, will elevate myocardial cyclic AMP (101), yet no clear links have emerged between heavy coffee drinking and Table 1. Factors Influencing Development of Potentially Lethal Arrhythmias in Congestive Heart Failure

<table>
<thead>
<tr>
<th>Proarrhythmic factors</th>
<th>Antiarrhythmic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Cardiac cellular factors</td>
</tr>
<tr>
<td></td>
<td>Decreased rates of formation of cAMP (beta-receptor</td>
</tr>
<tr>
<td></td>
<td>downgrading, adenylate cyclase inhibition, excess G, protein)</td>
</tr>
<tr>
<td></td>
<td>Beta-adrenergic blockade</td>
</tr>
<tr>
<td></td>
<td>Angiotensin-converting enzyme inhibition</td>
</tr>
</tbody>
</table>

Figure 7. Calcium (Ca$^{2+}$), inotropes and arrhythmias. Three positively inotropic principles include the use of digitalis, beta-adrenergic agents or phosphodiesterase (PDE) inhibitors. In each case, the ultimate effect is an increase in cytosolic calcium with risk of arrhythmias. AC = adenylate cyclase. G, = stimulatory G-protein; I, = transient inward current; other abbreviations as in Figures 1 and 6.
sudden cardiac death. Probably in contrast to the other phosphodiesterase inhibitors, caffeine has extremely complex additional effects on calcium uptake and release by the sarcoplasmic reticulum. These latter effects probably explain why caffeine decreases the incidence of ischemic and ventricular arrhythmias in the rat heart (101). Caffeine acts on the calcium release channel of the sarcoplasmic reticulum to increase the open probability of this channel and therefore to discharge calcium from the sarcoplasmic reticulum (102), leading to decreased calcium availability for calcium-induced calcium release (103) and consequent inhibition of calcium recycling in and out of the sarcoplasmic reticulum. The latter effect is antiarrhythmic in contrast to the early initial proarrhythmic discharge of calcium from the sarcoplasmic reticulum (104).

Conclusions: Cyclic AMP, Calcium and Ventricular Arrhythmias

Although there are considerable indirect evidence suggesting a role for cytosolic calcium excess in mediating the effects of an increased cellular cyclic AMP level, cytosolic calcium concentrations can increase as part of the metabolic changes in ischemia through mechanisms that are not necessarily directly linked to an increased tissue level of cyclic AMP. In general, catecholamine stimulation will increase the severity of ischemia and the rate of accumulation of cyclic AMP and cytosolic calcium. Crucial experiments linking beta-receptor stimulation with levels of cyclic AMP and levels of cytosolic calcium must still be undertaken before it can be stated with confidence that cytosolic calcium is the ultimate mediator of catecholamine activity in causing early ischemic ventricular arrhythmias.

However, the cyclic AMP hypothesis provides a rational scientific basis for the effect of beta-blockade in decreasing the incidence of ventricular fibrillation after the onset of myocardial infarction and reducing sudden death in the postinfarction period, as well as explaining why phosphodiesterase inhibitors can increase the mortality rate in patients with congestive heart failure. Nonetheless, it must not be supposed that cyclic AMP itself is the "prime mover"; rather, the ultimate messenger seems to be elevation of cytosolic calcium. Because cytosolic calcium is increased in heart failure (106), it will be difficult to develop positive inotropic agents that are free of the risk of sudden death.

References


7. Russell DC, Oliver MF. The effect of intravenous glucose on ventricular vulnerability following acute coronary artery occlusion in the dog. J Mol Cell Cardiol 1979;11:31-44.


25. Podzuweit T, Dalby AJ, Cherry GW, Opie LH. Cyclic AMP levels in...


44. Thadepally PT. Protective action of calcium channel antagonist agents against ventricular fibrillation in isolated perfused rat heart. J Mol Cell Cardiol 1982;14:21-32.


Cyclic AMP, Calcium and Arrhythmias


