Catecholamine Cardiomyopathy: Review and Analysis of Pathogenetic Mechanisms

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Catecholamines given in high concentrations produce myocardial damage in several mammalian species. The histological changes are similar to those found in patients given large amounts of pressor agents and in those who develop pheochromocytomas. They include myofiber necrosis, myofibrillar degeneration, and mononuclear leukocytic infiltration. Cardiac function is significantly impaired. Endogenous release of catecholamines can also induce myocardial injury in rabbits infused with tyramine. Anatomic and functional abnormalities described in various models of catecholamine cardiomyopathy are summarized. The several major theories regarding pathogenesis are reviewed. Recent data suggesting that O2-derived free radical generation is involved are discussed.

It has been recognized for several decades that sympathetic agonists can cause significant myocardial damage in experimental models and in human hearts. Morphological changes include myofiber necrosis and a predominantly mononuclear leukocytic infiltrate. The lesions are similar to those found in patients given large amounts of pressor agents to treat shock states, and in those who develop pheochromocytomas. Mechanical function is substantially impaired.

A range of mechanisms has been proposed to explain the morphological and functional damage. Early workers suggested that elevated concentrations of free fatty acids induced by catecholamines were toxic to myocytes. A second hypothesis involved platelet aggregation with microvascular obstruction. Neither possibility has withstood subsequent analysis. While calcium overload has been repeatedly demonstrated in dead or dying cells, evidence would suggest that this condition is a secondary event. Alpha receptor blockade has been shown to inhibit both coronary vasoconstriction and myocyte injury by norepinephrine, suggesting an ischemic mechanism. Allopurinol is also effective, but preservation of purine pools may not be a critical consideration. Recent studies suggest a common denominator involving the generation of O2-derived free radicals as the primary mechanism leading to membrane damage and myocyte death.

The purpose of this review is to describe the anatomic and functional abnormalities encountered in various models of catecholamine injury and to discuss evidence supporting the several mechanisms proposed to explain the pathogenesis of this process.

Abbreviations: ALLO: allopurinol FFA: free fatty acids NE: norepinephrine SOD: superoxide dismutase

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PATHOLOGY OF CATECHOLAMINE CARDIOMYOPATHY

The histological and ultrastructural changes of catecholamine cardiomyopathy have been well characterized [1–10]. Shortly after large doses are given, focal and diffuse subendocardial hemorrhages are visible on gross examination [4,9,11–13]. Hemorrhage has also been noted in the myocardium and epicardium [4]. Within 48 hours, well-demarcated lesions appear, involving particularly the apical portion of the heart. The tricuspid, mitral, and aortic valves often become edematous and distorted, and commonly are hemorrhagic [11,12]. Fibrosis begins to appear at about the fourth or fifth day, with formation of indistinct linear scars. Aneurysms also occasionally occur in the fibrotic area [14].

Early histological findings include interstitial edema, subendocardial congestion, and hemorrhages [9]. Myofibrillar degeneration has been demonstrated as early as two to three minutes following a bolus injection of the agonist [2]. An interstitial inflammatory response composed primarily of mononuclear cells appears within six to ten hours and is most intense in the subendocardium [1,9,13,15]. Lymphocytes, granulocytes, and perivascular Anitschkoff myocytes are also present in the inflammatory infiltrate [1,5,7,9]. Numerous contraction bands may occur as well [16,17]. These represent irregular, acidophilic condensations of the contractile proteins, in combination with hypercontracted sarcomeres.

After 72 hours, thin bands of collagenous connective tissue appear, and numerous fibroblasts can be identified [7,9]. Resorption of necrotic muscle fibers and granulation tissue becomes prominent by the sixth day [18]. Sheets of histiocytes and fibroblasts appear, suggesting a granulomatous reaction [8,9]. These reactive areas are progressively replaced by fibrous tissue [5]. By two weeks, only scar remains.

Yunge et al. [19] studied isoproterenol-induced myocyte injury by using freeze-fracture electron microscopy and the extracellular diffusion tracer, horseradish peroxidase. They found myocytes exhibited significant loss of integral proteins of the sarcolemmal membrane as early as ten minutes after injection. Small irregular tears were prominent. These findings, together with the decrease in intramembrane particle densities, suggested that cell leakage was likely.

MECHANICAL DYSFUNCTION IN NOREPINEPHRINE-INJURED HEARTS

In vivo functional abnormalities have been shown to correlate with histopathological changes. Werner et al. [20] studied the capacity of the cardiomyopathic left ventricle to respond to afterload stresses. They demonstrated that in norepinephrine-(NE-) injured hearts, pressure function curves were significantly lower than in control animals, consistent with depressed left ventricular performance. Fripp et al. [21] studied a measure of contractile element velocity (dP/dt) in similar preparations. They found that the resting dP/dt max did not differ from control hearts, suggesting no difference in the resting contractile state. Inotropic responsiveness to NE and calcium stimulation were, however, markedly reduced in the injured hearts. This condition was manifested by a lesser proportional increase in dP/dt max during NE or calcium administration. Since the responses to both agents were diminished, it is unlikely that the abnormality is limited to the adrenergic receptor system, but probably includes other mechanisms, such as excitation-contraction coupling [21].
We have also studied left ventricular pump function in these preparations, using standard ventricular function curves [17]. Mean stroke volume at left ventricular end diastolic pressure of 10 cm H₂O (SV₁₀) was 20 percent lower in the injured hearts than in the controls. The ability to augment global pump function with inotropic stimulation was, however, similar to that of control animals. These studies confirmed that in catecholamine cardiomyopathy there is a dissociation of velocity (dP/dt_max) and force (SV₁₀) responses. A similar dissociation has been identified in other circumstances, including myocardial infarction and circulatory shock [17].

PATHOGENESIS OF CATECHOLAMINE CARDIOMYOPATHY

Over the years, a number of mechanisms have been proposed to explain the pathogenesis of catecholamine cardiomyopathy. Some of the more prominent concepts will be reviewed. Although a definitive conclusion cannot be reached at this time, present evidence indicates that several of the previously proposed mechanisms are untenable. A common pathway involving free radical generation is the most likely candidate to explain the injury process.

Fatty Acid Toxicity

Maling and Highman (1958) first noted that fatty degeneration is a typical feature of myocardial lesions resulting from infusion of levarterenol. They hypothesized that the appearance of fat droplets in the myocardial fibers reflected altered lipid metabolism which injured the myocytes [11]. This theory was supported by the findings of Norkin et al. [22], who demonstrated that long-chain fatty acids are cytotoxic to cells in tissue culture and can induce acute myocardial failure in dogs when injected intravenously in the unbound state [23]. Hoak et al. [13] suggested that elevated free fatty acids (FFA) in myocytes may cause uncoupling of oxidative phosphorylation and direct myocardial tissue damage. Increased FFA may also modify the lipid bilayer of the sarcolemmal membrane and indirectly alter membrane protein function [24].

Quantitative relationships between elevated FFA levels and degrees of ischemic injury have been identified. Plasma FFA concentrations are significantly increased in patients with acute myocardial infarction and cerebral vascular occlusion [25]. Those with serum FFA concentrations above 1,200 mEq/liter following an acute myocardial infarction are more likely to suffer serious arrhythmias or death [26]. In a necropsy study, patients who died following acute myocardial infarction had the highest serum FFA concentration of any group [27].

Catecholamines increase plasma FFA by stimulating the mobilization of lipids from adipose tissues [13]. Hence, the foregoing observations provide a potential mechanism for myocyte injury. Others have found, however, that FFA, phospholipases, and lysophosphatidies have little effect on dog myocardium, even during severe ischemia [28]. Moreover, the very high levels of FFA necessary to induce myocardial injury have never been found in experimental or naturally occurring catecholamine cardiomyopathy. Dogs were used in most of the studies mentioned. Schenk and Moss [9] showed that rabbits develop identical myocardial lesions after administration of levarterenol. Unlike dogs, there is little increase in the plasma FFA concentration in this species. Hence, fatty acids probably contribute little or nothing to the pathogenesis of myocyte injury.
Platelet Aggregation

In the early 1970s, Haft and colleagues proposed that intravascular platelet aggregation is the primary pathogenetic mechanism responsible for myocyte injury by the catecholamines [29-31]. Cannon and Gray [32] demonstrated in 1914 that sympathetic hormones enhance coagulation of blood. In vitro experiments have subsequently shown that epinephrine and norepinephrine promote platelet aggregation [33-35]. Studies by Haft et al. [29] found that the extent of injury was reduced when dogs were pre-treated with platelet inhibitors such as aspirin and dipyridamole prior to epinephrine infusion. Using electron microscopy, this group found platelet aggregates in small vessels immediately following four hours of norepinephrine infusion [30]. All stages of aggregation were identified, ranging from a few adherent platelets to platelet plugs completely occluding the vessel. In most, the endothelial surface appeared intact, suggesting that the platelet aggregation was not secondary to endothelial damage.

To determine experimentally if endogenous catecholamine release can cause platelet aggregation, rats were exposed to various environmental stresses, including cold water [36], hot water [37], and hemorrhage [37]. Overall, 87 to 100 percent of the animals had coronary intravascular platelet aggregation, but they were identified in only 7 percent of controls.

Kammermeier and Ober [38] have reported that animals pre-treated with antithrombocyte serum or a prostacycline analog suffer less injury from isoproterenol. Other investigators were, however, unable to confirm the appearance of platelet aggregates after catecholamine administration [8]. It is known that alpha agonists may induce platelet aggregation via the alpha-2 receptors, but beta receptor stimulation has never been shown to promote platelet activation. Thus, a different mechanism must be invoked to explain injury by isoproterenol, a pure beta agonist. Fibrinogen or other local factors which activate the coagulation cascade could be involved, as may vasoconstriction by initiating microvascular platelet aggregation. This process could also be a secondary event following initial myocyte damage, as occurs in ischemic cardiac injury. Nevertheless, most recent studies have failed to identify the presence of microthrombi sufficient to explain the myocyte injury [3,10,16,19].

Hypercontraction Hypothesis

Fleisher and Loeb suggested many years ago that myocardial injury caused by adrenaline is the result of violent muscle contractions [39]. Csavo et al. [40] studied the early electron microscopic changes from isoproterenol administration. They found that injured myocytes demonstrated characteristic changes of hypercontraction of myofilaments with formation of contraction bands, and disorganization and fragmentation of myofibrils. It has been shown that insulin substantially reduces contractility responses to norepinephrine (NE) in isolated cardiac muscle preparations and in the intact swine heart [41,42]. Insulin also reduces myofiber injury in rabbits given NE. This fact suggested a linkage between inotropic stimulation and catecholamine cardiomyopathy [3].

Subsequent studies [10,43,44] failed to support a causal relationship between inotropic activity and cardiac injury. Beta-blocking drugs, such as propranolol and practolol, which abolish inotropic responses, have no significant effect on NE-induced damage in the rabbit model. Rather, the alpha-antagonist phentolamine largely prevents lesion formation. The alpha agonist methoxamine, which has little or no
inotropic action, causes lesions identical to those produced with NE. The severity of injury is dose-dependent. The demonstration that prazosin, but not yohimbine, reduces the extent of injury indicates that the alpha<sub>1</sub> receptor system is involved [45]. These studies demonstrate a clear dissociation between excess mechanical activity following beta adrenergic stimulation and myofiber necrosis.

**Calcium Overload**

Catecholamines cause increased calcium transport into myocytes [46]. Some have suggested that this effect may result in ATP hydrolysis leading to myocardial injury. Opie et al. [47] showed that lowering the calcium concentration in the perfusate and the use of calcium antagonists both reduce the extent of injury by catecholamine. No alterations in myocardial high-energy phosphate stores were identified. These experiments suggested that changes in myofiber calcium translocation, uptake, and binding through alpha<sub>1</sub> receptor activation may be factors contributing to membrane damage [43].

Increased cytosolic calcium concentrations could have detrimental effects in several different ways. Calcium-dependent phospholipases may be activated and lead to increased production of FFA and lysophospholipids. Many important intracellular enzymes, such as proteases, nucleases, adenylate cyclases, Na-K-ATPases, and glycerol phosphorylases could be altered and lead to cellular injury. If, however, calcium overload is to be implicated as the primary mechanism, it must be shown that increased cytosolic calcium appears prior to the irreversible phase of cell injury. This hypothesis has been very difficult to prove, primarily because of uncertainties in defining the transition from reversible to irreversible cell injury. The finding of increased intracellular calcium does not by itself prove the calcium overload theory. The possibility remains that influx of calcium takes place after the plasma membrane and cell are irreversibly damaged.

**Coronary Vasoconstriction**

Ischemia has been suggested as a potentially important factor in the pathogenesis of catecholamine cardiomyopathy. Handforth [48] infused India ink into the coronary arteries of hamsters sacrificed shortly after isoproterenol administration; he found that flow to the subendocardium was markedly reduced. This result suggested that the cardiac injury was due either to localized vasoconstriction or shunting of blood away from the subendocardial layer, causing ischemic necrosis. NE has also been shown to cause a reduction in absolute subendocardial flow, and in the subendocardial-to-epicardial flow ratio in isolated canine heart preparations [49]. Histological changes in catecholamine damage are most prominent in the subendocardium. A significant rise in coronary artery resistance occurs minutes after starting the infusion of NE in conscious dogs, and phentolamine blocks this response [50]. In these animals, there was a 92 percent increase in coronary resistance after giving methoxamine, indicating substantial alpha receptor-mediated coronary vasoactivity.

More recent studies in a rabbit model support the hypothesis that norepinephrine injury may involve ischemia and alpha adrenergic pathways [44]. Coronary flow rates measured with radioactive microspheres fell by nearly 45 percent within 40 minutes of NE infusion (3 μg/minute/kg). Pre-treatment with phentolamine abolished this response. In related studies [3,17], however, no evidence for a supply-demand mismatch which might cause ischemic injury was found. It is also noteworthy that the
pathology of catecholamine injury is inconsistent with acute ischemic damage to heart muscle. Lesions 48 hours after NE show a primarily mononuclear infiltrate, in contrast with the predominantly polymorphonuclear infiltrate found following ischemic injury [10,21]. This finding does not rule out the possibility that reperfusion after relative ischemia may contribute to the injury and possibly modify the usual histological features of ischemic necrosis.

**Free Radical Hypothesis**

Several reports using rats suggest that highly cytotoxic free radicals from catecholamine autoxidation are involved in the genesis of myocyte damage [51–53]. Peroxidation of membrane phospholipids resulting in permeability changes is presumed to form the basis for intracellular calcium overload. The latter is probably responsible for inducing arrhythmias, abnormal metabolism, structural damage, and contractile failure. Some [51] have proposed that oxidation products of the catecholamines, such as the free radical adrenochrome, play a major role. When fresh isoproterenol or epinephrine is given, it does not induce injury in isolated rat heart preparations. Lesions do appear when the hearts are perfused with isoproterenol that has undergone oxidation, however. Administration of adrenochromes induces similar lesions and significant contractile dysfunction [51].

Hydrogen peroxide and hydroxyl radicals can also be generated by catecholamine metabolism through the monoamine oxidase system because an oxidation reaction is involved. Singal et al. [54,55] showed that rats, pre-treated with either vitamin E or zinc, developed significantly less injury from isoproterenol. They suggested that vitamin E, an antioxidant, protected the myocardium by directly scavenging free radicals. Zinc, on the other hand, has a membrane-stabilizing effect which presumably diminished radical-induced damage. The mechanism of radical generation by catecholamines remains unproven, however, and could involve more than one pathway.

**Role of Reperfusion and Oxygen Free Radical Generation**

Because severe coronary vasoconstriction is associated with exposure to catecholamines [44,48–50], reperfusion injury may be an important pathway. Reperfusion of ischemic myocardium provides a potential means of preventing cell death. During the reversible phase, however, it can also accelerate the process of cell death and elicit potentially lethal ventricular arrhythmias [56–58]. Although the precise pathogenetic mechanisms remain controversial, attention has focused recently on the contribution of oxygen-derived free radicals [60–64]. Shlafer et al. [65] studied isolated cat hearts with global ischemia. They found that ventricular pressure development, dP/dt_{max}, and coronary blood flow were significantly improved following reperfusion when superoxide dismutase (SOD) and catalase were added to the cardioplegia solution. Effectiveness of these scavengers in this and other studies [66,67] suggests that oxygen free radicals contribute to reperfusion injury.

Otani et al. [68] showed that when mitochondria isolated from globally ischemic rabbit hearts are incubated with SOD and catalase, ATP production is enhanced during aerobic respiration. Using electron spin resonance spectroscopy, they also demonstrated that signals detected from hydroxyl radicals are markedly suppressed in the presence of these scavengers. There is evidence at the tissue level that oxygen radicals induce irreversible myocardial damage. Studies in canine models [69,70] have shown a significant reduction in infarct size in animals treated with SOD and catalase.
It is important to note that the myocardial protection is not temporally related to the duration of treatment during ischemia. Rather, damage by oxygen radicals occurs primarily during the initial phase of reperfusion [71].

Oxygen free radicals may arise from a number of different sources during ischemia and reperfusion. The major sources presently recognized include: (a) catecholamine degradation, (b) mitochondrial dysfunction, (c) leukocyte activation, and (d) xanthine oxidase. Each of these shares a common oxidation step where oxygen can serve as an electron acceptor. Hence, reperfusion with reintroduction of large amounts of oxygen would potentially initiate and accelerate the process of cell injury.

**Allopurinol and Cardiomyocyte Preservation**

Allopurinol (ALLO) has been extensively studied because of its ability to reduce ischemia-reperfusion damage to myocardium [72–76]. We recently demonstrated substantial protection following norepinephrine infusion in the rabbit [88]. Mechanical function in animals not given ALLO was significantly impaired, and this condition was accompanied by reduced concentrations of ATP and glycogen, and sharply elevated creatine phosphokinase and lactic dehydrogenase release. There was extensive myocyte injury assessed by histological analysis. These abnormalities were reduced or absent in the treated animals. Protection may involve scavenging of free radicals, suppression of free radical production, or preservation of the adenine nucleotide pool [63,77,78]. Since both ischemia and free radical generation have been implicated in the generation of catecholamine injury [44,79], the findings are consistent with known properties of allopurinol.

During ischemia, xanthine dehydrogenase in endothelial cells is converted in many species to xanthine oxidase, while the extracellular fluid hypoxanthine concentration is markedly increased. Hypoxanthine serves as substrate for xanthine oxidase. With reperfusion, oxygen free radicals are produced, thereby accelerating the process of cell death [63,80,81]. Grum et al. [82], however, measured coronary effluent purine concentrations following myocardial ischemia in rabbits. They found a total absence of xanthine and uric acid, but an elevated level of hypoxanthine. This efflux profile strongly suggested the absence of myocardial xanthine oxidase or dehydrogenase in this species. Hence, other pathways must be implicated to explain the action of ALLO in the rabbit model.

Free radicals are also produced by activated leukocytes (NADPH oxidase activity) and, at the mitochondrial level, “superoxide leak” [60,63,81,83]. Ischemia is accompanied by a regional release of NE from sympathetic nerve endings [63]. This process raises the potential for free radical production through oxidation in the monamine oxidase system. Hence, the protective action of ALLO in our system could involve direct scavenging of free radicals. Moorhouse et al. [78] have shown that ALLO and its metabolites, which are aromatic compounds, function as free radical scavengers in heart muscle. Its scavenging potential is equal to that of mannitol. Oxypurinol, a major degradative product of ALLO, has even higher scavenging capabilities.

Several studies [77,84,85] have suggested that preservation of ATP is an important additional mechanism whereby ALLO reduces ischemic injury in myocardium. DeWall et al. [84] demonstrated, in allopurinol-treated myocardium, enhancement of labeled hypoxanthine uptake and incorporation into the adenine nucleotide pool [86]. This hypothesis has been revived recently by Lasley et al. [77], who also found that ALLO protects ischemic rat myocardium by preserving adenine nucleotide pools. Moreover,
the administration of hypoxanthine enhanced recovery of function without being arrhythmogenic. These findings appear contrary to the idea that free radical production through the xanthine oxidase system is a significant cause of ischemic injury. Preservation of ATP may be important in the outcome of some ischemic insults, but this condition does not appear to be true for hearts subjected to catecholamine injury. Recent data from our laboratory have shown that the mechanical performance of hearts isolated immediately following 90 minutes of norepinephrine infusion was impaired, while energy-rich phosphate concentrations remained unchanged [87]. This dissociation suggests that preservation of ATP does not explain the protective action of allopurinol in these circumstances.

SUMMARY

Present evidence indicates that two quite disparate mechanisms are involved in the pathogenesis of catecholamine cardiomyopathy. Alpha adrenergic blockade with phentolamine or prazosin sharply reduces myocyte injury, suggesting that ischemia secondary to coronary vasoconstriction could be involved; however, allopurinol is equally effective. This drug has never been shown to alter adrenergic receptors or effector pathways. As has been discussed, the available data favor a free radical scavenging action as the most likely basis for the protective action of allopurinol. Linkages to a common mechanism are possible, though speculative. Various aromatic compounds, including ALLO, possess free radical scavenging properties. Because phentolamine has two aromatic rings, it might be an effective scavenger, though this fact has not been demonstrated. A second possibility is that, by preventing significant coronary vasoconstriction, phentolamine prevents ischemia-induced free radical generation. Direct evidence regarding these hypotheses must await future investigations.

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