Toxic Mechanisms of the Heart: A Review

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ABSTRACT
Toxic injury is one of the many ways by which the functional integrity of the heart may become compromised. Any of the subcellular elements may be the target of toxic injury, including all of the various membranes and organelles. Understanding the mechanisms underlying cardiotoxicity may lead to treatment of the toxicity or to its prevention. Doxorubicin and its analogs are very important cancer chemotherapeutic agents that can cause cardiotoxicity. Other agents which are cardiotoxic and which have profound public health implications include the alkaloid emetine in ipecac syrup, cocaine, and ethyl alcohol. The most important cardiotoxic mechanisms proposed for doxorubicin include oxidative stress with its resultant damage to myocardial elements, changes in calcium homeostasis, decreased ability to produce ATP, and systemic release of cardiotoxic humoral mediators from tissue mast cells. Each of the first 3 mechanisms can lead to each of the other 2, and the causal relationships between all of these mechanisms are not clear. New evidence suggests that doxorubicinol, one of the metabolites of doxorubicin may be the moiety responsible for cardiotoxicity. Several other potential mechanisms also have been proposed for doxorubicin. Emetine in ipecac syrup is the first aid treatment of choice for many acute toxic oral ingestions and the alkaloid, itself, is used to treat amebiasis. Cardiotoxicity occurs following chronic exposure, such as occurs therapeutically in amebiasis and with ipecac abuse by bulimics. A number of mechanisms are proposed for emetine cardiotoxicity, but the current mechanistic literature is quite scarce. Cocaine abuse recently has caught the public interest, in particular because of the drug-related sudden deaths of certain athletes. Cocaine can cause hypertension, arrhythmias, and reduced coronary blood flow, each of which can contribute to its lethality. However, it may be possible that cocaine sudden death episodes are more related to hyperthermia and convulsive seizures, rather than to cardiovascular toxicity. Chronic alcohol use leads to dilated cardiomyopathy and failure as part of the general physical degeneration that occurs with alcoholism. Several mechanisms are proposed for the cardiomyopathy, but only 2 things seem clear. The cardiotoxicity is due to an intrinsic effect of alcohol, rather than to malnutrition or co-toxicity, and abstinence is the only effective treatment for the cardiomyopathy. Recent articles indicate that very moderate use of alcohol may be beneficial and protect against cardiovascular-related morbidity. One explanation for these findings seems to be that the non-drinking groups, against whom the moderate drinking comparisons were made, were enriched in former drinkers with significant alcohol-related cardiovascular pathology.

Keywords. Cardiotoxicity; doxorubicin; anthracyclines; ipecac; emetine; cocaine; alcohol

INTRODUCTION
The heart is an organ that pumps blood through the vascular system, thereby, providing necessary perfusion for the tissues. This organ must remain active and effective, providing uninterrupted service throughout life. Thus, there is great current societal interest in the maintenance of cardiovascular health. Toxic injury is one way the functional integrity of the heart may become impaired. The degree of impairment may be small or great, reversible or irreversible, depending on the particular cardiac poison and its intensity and duration of exposure. Because the heart is so acutely necessary for continued survival, the advent of cardiac toxicity may appear to be sudden and critical, and in severe cases it is all too frequently fatal.

Any of the myocardial cellular components can be targets of toxic injury. The contractile elements, themselves, may become damaged by certain poisons, causing the heart to lose efficiency as a pump. Injury to organelle membranes can lead to structural and functional difficulties which are specific to the particular organelle involved. For example, the ion-
ic regulatory functions of the sarcolemma may become impaired following a toxic insult. In the most severe cases, the sarcolemma may become leaky, leading to loss of cellular contents and fatal calcium influx. Disturbances of the sarcoplasmic reticulum may result in disturbances of protein synthesis and in inappropriate intracellular calcium handling. Harm to mitochondrial membranes may lead to ATP depletion, an effect that will have profound adverse consequences throughout the cell. Lyosomal membrane leakage may lead to destruction of intracellular enzymes and other cellular constituents. Injury to nuclear membranes may perturb protein synthesis and regulation of cellular processes. Finally, damage may occur to intracellular protective mechanisms such as those that protect against oxidative stress and those responsible for intracellular repair.

This review will be very mechanistic in its approach. The therapeutic hope behind mechanistic research is that the knowledge gained may allow cardiotoxicity to be treated or avoided and, in the case of therapeutic agents, may allow higher doses and more effective therapy in patients. If any proposed mechanism for the cardiac toxicity is to be useful in these regards, it must satisfy two requirements. It must satisfactorily explain the cardiac toxicity shown by the poison, and it should provide the reason behind any cardiac specificity that may exist; however seldom are these requirements met.

The greater portion of this review will deal with the anthracycline anticancer agents. By any measure one might propose—time, intellectual effort, manuscripts generated, or resources—much more has been expended working with these compounds than has been spent studying any other cardiac poison. Part of the reason for this is the unique utility of these compounds in cancer chemotherapy, and part may be an attraction for the deep, challenging nature of the problem. The anthracycline literature encompasses several thousands of articles. As described, if the mechanisms causing the cardiotoxicity were well enough understood to be avoided or treated, higher and more therapeutically effective doses could be used in patients. Indeed, there have been significant advances in this direction in the case of the anthracyclines. In addition, mechanistic principles learned from studies on the anthracyclines are generalizable to many other cardiotoxic compounds.

As well as the anthracyclines, three other compounds will be discussed. These are emetine, cocaine, and ethanol. Each is associated with conspicuous cardiotoxicity. In addition, each of these entities represents a significant public health concern. Chronic abuse of emetine in the form of ipecac syrup, the highly publicized sudden deaths with cocaine, and alcoholic cardiomyopathy will be described.

**The Anthracyclines**

The anthracycline antibiotics have been among our most effective anticancer therapeutic agents for over 2 decades. Doxorubicin, also known as Adriamycin®, is currently the most clinically useful anthracycline, and it serves as the prototype for the group. It is active against solid tumors as well as many disseminated ones (179). The usefulness of this drug is limited, however, because of the insidious, dose-related, irreversible cardiotoxicity that it can cause (97, 176). The amount of drug that can be used in therapy is usually restricted to less than 550 mg/m² (10). Damage to the heart is characterized by interstitial edema, vacuolization, destruction of muscle cells, loss of contractile elements in the remaining cells, and ventricular dilation, though the clinical symptomology does not always correlate with the degree of histopathological damage (26, 75).

Currently there are 4 major mechanisms and several minor ones proposed for anthracycline cardiotoxicity. The major mechanisms include oxidative stress, disturbances in intracellular calcium homeostasis, disturbances in myocardial energetics, and the release of cardiotoxic humoral mediators. These possibilities will be discussed in greater depth because of their mechanistic prominence. Other mechanisms include formation of the cardiotoxic metabolite doxorubicinol, inhibition of synthesis of cardiac cyclic nucleotides, inhibition of nucleic acid synthesis in various locations, destruction of contractile components, lysosomal alterations, changes in protein synthesis, decreased fatty acid utilization, decreased adrenergic support for the heart, and others.

**Oxidative Stress Leading to Membrane Peroxidation**

Myers et al (122), first reported that the cardiac toxicity of doxorubicin in mice was associated with lipid peroxidation. Since then, many investigators have studied anthracycline-induced peroxidative injury (8, 37, 111, 131, 132, 165). Because the antioxidant defense capacities of the heart are inherently low in comparison to other tissues (27, 37), and because tocopherol and other antioxidants were shown to be useful in animal models in protecting against its experimental toxicity (52, 104, 121, 132), the oxidative stress concept of doxorubicin cardiotoxicity was proposed (131). In this model, doxorubicin undergoes activation by a one electron reduction to its semiquinone. This reduction is followed by redox cycle (69) which leads to the production
of free radicals and various reactive oxygen species (111, 165).

*In vitro* models by which anthracyclines can produce active oxygen species abound. The first models involved microsomal cytochrome P450 (7, 8, 131). Oxygen free radicals can also be generated by cardiac mitochondrial systems (30, 36), and by xanthine/xanthine oxidase systems (152). Recently, Nohl has reported that microsomal activation of doxorubicin may actually be caused by contamination with mitochondrial fragments containing NADH-oxidoreductase (125). This enzyme is very specific for the heart, and its activity may help to explain the cardiac specificity of doxorubicin toxicity.

Very recently, the involvement of iron as a necessary component for anthracycline-induced lipid damage, perhaps, without the involvement of the usually implicated oxygen radicals, has been proposed (62, 114, 120). This mechanism may be relevant to the therapeutic action of ICRF-187 as discussed below.

The *in vivo* evidence for oxidative stress is considerably more indirect than is the *in vitro* evidence. The first report implicating oxidative stress was by Myers et al in 1977 (122). Other investigations also have indicated the possible involvement of oxidative stress with anthracycline toxicity (70, 113, 149, 167). Another line of evidence was provided by workers who found that various antioxidant treatments help to reduce the toxicity of anthracyclines in diverse animal models. Such antioxidants include α-tocopherol (121, 161), N-acetylcysteine (172), cysteamine (104), reduced glutathione (104, 183), and ubiquinone (49, 180).

An *in vivo* contradiction to the oxidative stress concept was provided when simultaneous administration of doxorubicin and BCNU (carmustine) resulted in little more than additive toxicity in mice (136). According to the literature, doxorubicin would be expected to produce active oxygen species. In addition, carmustine is a potent inhibitor of glutathione reductase (82). Administration of the 2 drugs together would be expected to cause highly synergistic toxicity, but that did not happen. Other animals studies also argue that oxidative stress may not be a significant factor in doxorubicin cardiomyopathy (78).

Antioxidants have been used in various attempts to prevent anthracycline-induced cardiotoxicity. Two conclusions are apparent with respect to these efforts. First, the protection is not complete and is greatly subject to species and other experimental variations (68, 112, 154, 170, 174). Second, the lack of efficacy of all antioxidants to protect the heart significantly in clinical trials has been nearly universal (99, 119). It seems likely that oxidative stress as it is usually conceived, although very well established *in vitro*, may have been a blind alley in its relevance to *in vivo* causation of anthracycline cardiotoxicity. Moreover, many of the animal models in which protection was shown were acute in nature, and those in which no protection was found were chronic studies (99). The human clinical cardiotoxicity resulting from anthracyclines usually presents as a chronic problem, though acute cardiac changes have been documented (26) and endomyocardial biopsies have shown that very acute human cardiac damage can occur following single doses of doxorubicin (171).

Although the traditional picture of oxygen radical-mediated doxorubicin cardiotoxicity may be in question, the observations about iron-mediated doxorubicin oxidative damage help to maintain some vitality to the oxidative stress hypothesis. Further support for the concept that iron-mediated oxidative stress may be involved with doxorubicin cardiotoxicity is provided by the successful therapeutic application of the iron-chelating agent, ICRF-187. This compound decreases doxorubicin toxicity in many animal models (66, 67). Protection is also afforded against the newer anthracycline, epirubicin (29). Finally, in contrast to the disappointing results of antioxidant clinical trials, ICRF-187 appears to provide protection against doxorubicin cardiotoxicity in human patients (163). If confirmed, this observation signals a significant therapeutic advance.

**Disturbances in Calcium Homeostasis**

Fleckenstein et al articulated the calcium overload hypothesis as an explanation for the cardiac toxicity associated with catecholamines (48). This hypothesis has been generalized into the concept that deregulation of intracellular free calcium is a critical step in the progression from reversible to irreversible cellular injury (169). Concurrent to the development of the oxidative stress hypothesis, evidence linking anthracycline cardiotoxicity to disturbances in intracellular calcium homeostasis also began to accumulate. Olson et al reported that increases in ventricular calcium content might be involved in doxorubicin-induced cardiotoxicity in rabbits (130) and rats (129). Revis and Marusic (144) confirmed that doxorubicin decreases cardiac mitochondrial calcium accumulation in the rabbit. Similar data were obtained with rat heart mitochondria (6), and with mouse hearts (25). The doxorubicin aglycone triggered calcium release in calcium-loaded rat heart mitochondria *in vitro*, an effect which may be caused by alterations in mitochondrial sulfhydryl groups (159). Recently, Eckenhoff and Somlyo used electron probe microanalysis to measure mitochondrial calcium content *in situ* in quickly-frozen cardiac
sections following doxorubicin administration to rats (42). They concluded that the previously reported mitochondrial calcium changes are secondary to cellular damage from other causes. An example of this may be provided in the report of Singal et al in which doxorubicin caused mitochondrial accumulation in rabbit hearts rendered hypertrophic by aortic stenosis (156).

Other, more subtle effects on calcium function have been reported. Villiani et al reported that small doses of doxorubicin caused a reduction in calcium exchangeability in isolated guinea pig atria, while leaving the cardiac calcium content unchanged (175). A structure-activity study indicated a correlation between anthracycline toxicity and the ability to inhibit rapid calcium exchange (117). The specific cause for this effect may be anthracycline inhibition of the plasma membrane Na⁺/Ca²⁺ exchange mechanism (19).

In addition to causing perturbations in calcium exchange, doxorubicin can change the calcium conductance in rat papillary muscle (94). Other investigators have reported that doxorubicin may enhance slow channel calcium influx (5, 24).

Early in the 1980s, it seemed very rational to test the effect of calcium channel blocking agents on anthracycline toxicity in vivo. First, these blocking agents would be expected to decrease the elevated myocardial calcium associated with anthracycline toxicity. In addition, there is a large volume of literature concerning the observation that verapamil enhances doxorubicin cytotoxicity in many different anthracycline-resistant tumor cell lines in vitro. The mechanism for this reversal of resistance appears to be associated with inhibition of a carrier-mediated, active anthracycline efflux from within the cells, rather than to any change in calcium status (72, 83). It might be hoped, therefore, that verapamil would have a similar effect in clinically dangerous tumors. Protection against doxorubicin-induced cardiotoxicity in mice was reported in a study using the calcium antagonist prenylamine (108). Prenylamine also may have provided minor protection as shown in a recent clinical study (109). Another favorable response was reported in a clinical study using a combination of α-tocopherol and nifidipine to protect against doxorubicin cardiotoxicity (103). Nevertheless, the great preponderance of in vivo animal evidence indicates that the addition of calcium channel blockers to a doxorubicin regimen either has no benefit, or results in substantially enhanced toxicity (58, 90, 160, 164). Moreover, Rabkin reported that both intracellular cardiac calcium content and survival decreased in rabbits given verapamil and doxorubicin (141). It seems clear that with the possible exception of prenylamine, calcium channel blockers should not be used clinically with the anthracyclines. The reason for this interaction may be that doxorubicin and verapamil both cause negative inotropic effects which could lead to synergistic lethality. An alternative, pharmacokinetic explanation is that verapamil may change anthracycline pharmacokinetics, resulting in decreased excretion (126).

Another area of anthracycline interaction with calcium function is that doxorubicin and other anthracyclines appear to cause release of calcium sequestered within the sarcoplasmic reticulum of skeletal muscle in vitro, an effect which is blocked by ruthenium red (123). Skeletal muscle and, in particular, the diaphragm, appear to be vulnerable to doxorubicin. The induced lesions are very similar, under electron microscopy, to those seen in the heart (38). Hence, it seems very likely that the skeletal muscle observations about doxorubicin-induced release of calcium from the sarcoplasmic reticulum also may be relevant to cardiac muscle. The difference in selectivity of toxicity between cardiac and skeletal muscle may be pharmacokinetic in nature. When doxorubicin is given in an intravenous bolus, the heart, in contrast to other organs, is exposed transiently to concentrations many times higher than those that occur after mixing throughout the blood compartment (168, 178). In fact, administration of doxorubicin by continuous infusion, rather than by the usual bolus, is an effective clinical strategy to protect the myocardium against doxorubicin-induced injury (71, 98). The utilization of pharmacokinetic principles in doxorubicin dosing is a significant advance in the effort to prevent anthracycline cardiotoxicity.

**Disturbances in Energy Production**

Doxorubicin can produce profound alterations in myocardial energy production. This led to the concept that these changes might be responsible for anthracycline cardiotoxicity. Decreased mitochondrial respiratory control reflecting a decrease in the maximum oxidative capacity was reported by Ferrero and coworkers (46). Folkers et al showed that doxorubicin inhibits the succinate dehydrogenase-coenzyme Q reductase and the NADH oxidase-coenzyme Q reductase systems of beef heart mitochondria (85, 86). More recently, Goormaghtigh and his coworkers, and others have shown that doxorubicin inhibits cytochrome c oxidase by binding with and removing the mitochondrial membrane cardiolipin necessary for mitochondrial enzyme function (59, 60, 124). By these actions, doxorubicin could decrease the ability of the heart to perform oxidative metabolism, thereby leading to cardiac injury, especially under conditions of increased ox-
ygen demand. Additional evidence for mitochondrial involvement in doxorubicin cardiotoxicity is provided by studies showing that the glycolysis substrate fructose-1,6-diphosphate can decrease cardiac damage \textit{in vitro} (11) and \textit{in vivo} (95). On the other hand, studies with mitochondria from perfused rat hearts provide evidence against mitochondrial injury being causal in doxorubicin cardiotoxicity (137).

\textit{Causal Relationships Between the Previous Factors}

The hope of isolating and proving the mechanism(s) ultimately responsible for doxorubicin cardiotoxicity has provoked intense investigation. Nevertheless, the cause and effect relationships between the three most prominent of the proposed mechanisms, oxidative stress, calcium changes, and mitochondrial injury are unclear. This is because each lesion has the capability of directly or indirectly causing the other 2.

Oxidative stress can lead to decreased energy production in that injury to cellular membranes can lead to loss of their functional capacity. Damage can occur to membranes of the sarcoplasmic reticulum, nucleus, mitochondria, peroxisomes, and the sarcoplemma (18, 51). Mitochondrial oxidative phosphorylation depends upon membrane integrity, and mitochondrial membrane destruction can lead to decreased energy production. More subtle processes of oxidative injury may also be involved. For example, hydrogen peroxide decreases both mitochondrial and glycolytic production of ATP in P388 cells \textit{in vitro} (73).

Intracellular free calcium concentrations are controlled by the activity of membrane-related sequestration and release mechanisms (2, 45). Disturbances in calcium homeostasis would be expected to occur following peroxidative injury to these membranes. For example, Lebedev et al recently reported that products of lipid peroxidation increase the permeability of membranes to calcium and other ions (96). Harris and Doroshow showed that manipulations that prevent oxidative stress \textit{in vitro} also decrease doxorubicin block of calcium transport into the cardiac sarcoplasmic reticulum (65). Orrenius and Moldéus described how oxidative stress caused by hydroperoxide metabolism can cause the early loss of calcium homeostasis in mitochondria and sarcoplasmic reticulum (134). Richter and Frei proposed that substances which cause oxidative stress result in loss of the ability of mitochondria to retain their calcium content (145). Individual oxygen free radicals can cause very specific changes in the activity of the sarcolemmal calcium pump (79).

A recent hypothesis proposed for the cardiotoxic action of the anthracyclines is that they cause the release of humoral mediators such as histamine, and that it is the humoral mediator that causes the cardiotoxicity. Though difficult to reconcile with other mechanisms, this hypothesis represents a novel approach to the problem of anthracycline cardiotoxicity. Doxorubicin and other anthracyclines are very powerful in causing release of histamine from mast cells. They are comparable in action to the standard mast cell-degranulating agent, 48/80 (32, 146). This histamine-releasing action is probably responsible for the acute cutaneous reactions (162), and possibly for the acute arrhythmias that sometimes occur following clinical doxorubicin administration (176).
Bristow et al proposed that doxorubicin cardiotoxicity may be mediated by released histamine (16, 17). Agents such as theophylline, cromolyn sodium and high doses of N-acetylcysteine, all of which act to prevent histamine release, appear to protect against the cardiotoxicity of doxorubicin and epirubicin in certain experimental systems (16, 88, 89). The mouse does not appear to be a good model to demonstrate this effect, however (53). The anthracycline-associated histamine release does not appear to be mediated by free radicals (33). Fructose-1,6-diphosphate inhibits doxorubicin-induced mast cell release of histamine (151). This may provide an alternative explanation for the previously described protective effects of fructose-1,6-diphosphate.

If this hypothesis is to become established in explaining anthracycline cardiotoxicity, several things will have to be demonstrated. The doxorubicin metabolite “doxorubicinol” which may be responsible for the doxorubicin cardiotoxicity (see below) should be a more active degranulator of mast cells than is doxorubicin. In addition, it must be shown that histamine infusion can produce the various cardiac effects ascribed to the anthracyclines. Some progress has been made in this direction—very recently, Kantrowitz et al provided evidence that histamine administration causes specific, H1-mediated cardiotoxic effects that are independent of changes in coronary blood flow (80). It will be of interest to determine whether parallel findings of oxidative stress, calcium dislocations, and disturbances in ATP production similar to those caused by anthracyclines will also occur following histamine administration.

Miscellaneous Mechanisms Proposed for Anthracycline Cardiotoxicity

As well as the previously described mechanisms, doxorubicin has the capability to affect many different biological processes in the heart. Some of these may be relevant to cardiac injury and others may be secondary in nature. Determining which is which is one of the continuing challenges within the field.

Evidence is accumulating that doxorubicinol, a metabolite of doxorubicin, may contribute to the cardiac toxicity when doxorubicin is given. With repeated dosing in rats, the development of cardiac toxicity more closely follows the course of doxorubicinol pharmacokinetics than it does the course of the parent compound (34). *In vitro* studies with isolated muscle and cellular organelles from rabbit hearts led Olson et al to conclude that doxorubicinol is more cardiotoxic and less cytotoxic than doxorubicin, and that cardiotoxicity may be caused by doxorubicinol (133). Alternatively, Danesi et al found that doxorubicinol was less toxic than doxorubicin *in vivo* in rats (28).

The anthracyclines are inhibitors of cardiac guanylate cyclase. A structure-activity study with many different analogs showed a correlation between cyclase inhibition and cardiotoxic potency (101). The inhibition may be secondary to production of oxidative stress (100). In addition, it seems reasonable that changes in cyclic-GMP levels may cause changes in intracellular calcium regulation.

Many other actions of doxorubicin are candidates for cardiotoxic mechanisms. Destruction of cardiac contractile elements is an example. Doxorubicin binds to actin (105) and it prevents actin polymerization (23). Damage to the intracellular microtubules appears to occur (140). Changes in lysosomal morphology and enzyme function, perhaps secondary to lipid peroxidation, comprise another potential cardiotoxic mechanism (54, 157). Doxorubicin causes decreased cardiac m-RNA and decreased protein synthesis, which may result from doxorubicin’s cytotoxic action on DNA (184). A decrease in the ability to use fatty acids has been reported (102). Chronic doxorubicin treatment appears to decrease adrenergic support in the rat heart (77), and impaired response of catecholamine receptors has been reported (147). Anthracyclines can disturb plasma membrane redox function by inhibiting NADH dehydrogenase (166). The cardiac collagen matrix can be changed by doxorubicin (20). It does seem likely that many of these changes may be secondary to other processes such as oxidative stress.

**Emetine**

An interface between cardiovascular toxicology and tragically conflicting public health concerns is provided by the case of ipecac syrup. With a few well defined exceptions, oral administration of ipecac syrup is the emergency treatment of choice in acute toxic oral ingestions, particularly in children (84, 118). Ipecac syrup is as effective as apomorphine and it produces less central nervous system depression (106). If used with care, it is safe in infants (91). It is very effective in preventing absorption of drugs as measured by their plasma concentrations (3). In 1984, more than 68,000 preschool children were treated with ipecac syrup for poisoning (3). For this primary indication, ipecac syrup is a very useful drug.

The active ingredient of ipecac syrup is the alkaloid emetine. In addition, emetine, itself, is highly useful in treating amebiasis. Emetine is a well-known cardiotoxicin. In animal models, it can cause both acute and chronic cardiotoxicity (13, 14, 57). Human cardiotoxicity usually results from chronic administration. This cardiotoxicity is dose-limiting in the treatment of amebiasis (110). The societal problem is that cardiotoxicity occurs with chronic abuse
in people afflicted with bulimia nervosa (1, 135). The problem of ipecac abuse and its resulting cardiomyopathy may be more common than previously thought. Pope et al estimate that as many as one-million American women may be involved in bingeing—emesis/laxation cycles (139). An even more poignant potential for ipecac-induced lethality is indicated in a recent report describing an abused child who had fatal cardiomyopathy secondary to chronically administered ipecac syrup (31).

The injurious effects of emetine on the heart are many. Disturbances in the EKG and histopathological changes occur, and the damage appears to be cumulative (110, 181). Much of the early literature indicated that emetine accumulation results in disturbances of mitochondrial function and energy production (181). Studies with pair-fed controls indicate that the reported mitochondrial changes may be non-specific effects of food deprivation (39, 40). A quinidine-like action on sodium channels and consequent reduction in membrane excitatory activity also has been suggested (181). An alternative mechanism proposed for emetine cardiotoxicity is a decrease in protein synthesis (9). In addition, there is evidence that emetine may be working through β-adrenergic mechanisms (110, 115).

The current literature on the mechanisms for emetine cardiotoxicity is very scarce and, perhaps, interest in this area may be stimulated because of the present misuse of ipecac syrup by people suffering from bulimia nervosa. For the sake of its ready availability as a treatment for toxic ingestions, it will be a great misfortune if ipecac abuse causes it to become available only on prescription.

**Cocaine**

The emerging problem of cocaine abuse (76), and the highly publicized deaths of certain athletes have recently brought cocaine cardiotoxicity to public attention. Nevertheless, cocaine’s cardiovascular effects and toxicity have been known for many decades. Cocaine causes dose-related increases in heart rate and blood pressure in humans (47). Warnings against the potential to cause fatal arrhythmias are well-documented in the medical literature. Nevertheless, well-known cases are hard to find (61). In fact, animal studies indicate that hyperthermia and seizures are the primary causes of death after cocaine overdose (61). It may be certain cardiovascular changes, resulting from cocaine administration, are secondary to these effects.

The currently most accepted mechanism for the toxicity is cocaine’s ability to block reuptake of norepinephrine back into adrenergic nerve endings following its release (12). This would be expected to cause prolongation of norepinephrine’s action, leading to hypertension, an increased probability of arrhythmias, and fatal ventricular fibrillation. Another mechanism proposed for cocaine cardiotoxicity is reduced coronary blood flow (64), perhaps caused by coronary vasospasm (74, 93), and leading to histopathological evidence of microinfarcts (61). These mechanisms are consistent with reports that ischemic damage is characteristic of hearts from patients with cocaine-induced sudden death (81).

One of the occasional cardiac compensations associated with athletic training is an increased response to catecholamines (150). Cocaine sudden death, though certainly in the public eye, is not common in comparison to other causes of cardiac death. Thus, it ironic to speculate that physical training may render the athlete more susceptible to cocaine lethality.

**Alcohol (Ethanol)**

Worldwide, the most common and costly drug problem is alcohol misuse. Injuries and deaths related to driving while intoxicated, acute overdose fatalities, drug interactions, alcohol dependency and withdrawal, teratology, psychological disorders, physical and psychological abuse of family members, and toxic effects to many different body systems are an incomplete listing of the spectrum of problems associated with alcohol.

Among alcohol’s adverse biomedical effects is cardiotoxicity. Although acute cardiac toxicity can occur, the most troublesome cardiac problem is alcohol cardiomyopathy, a condition which has been known for over a century. It is chronic in nature, it usually occurs in alcoholics of 10 or more years duration, and it may be one of the most frequent forms of cardiomyopathy (177). Manifestations include hypertrophy, cardiac dilation, and fibrotic changes. Corresponding changes are displayed on the cellular and ultrastructural levels (87). The symptoms displayed by the patient are nonspecific and generally are consistent with slowly developing congestive heart failure. The patient may exhibit elevated diastolic pressure, exertional dyspnea, chest pain, and cardiomegaly (41). Cardiac damage is found in up to one-third and skeletal muscle changes in as many as one-half of chronic alcoholics. The amount of damage incurred generally is proportional to the lifetime amount of alcohol consumed (173). Current therapy consists of symptomatic treatment of the failure and total, unrelenting abstinence from alcohol (116, 153), difficult though this may be to achieve.

It is clear that alcohol-induced cardiac injury, as are liver and skeletal muscle damage, is a specific toxic action of alcohol, itself. The toxicity is not related to nutritional deficiencies, nor to the pres-
ence of adulterants, though thiamine deficiency and certain previously used beverage additives such as cobalt were shown to enhance the production of cardiomyopathy (177). Much effort has been expended in trying to understand the mechanisms behind alcohol cardiomyopathy, and many reviews of the literature are available. In many respects, these cardiotoxic mechanisms are quite similar to those proposed for doxorubicin, e.g., oxidative stress, calcium dislocations, and mitochondrial changes. A fundamental problem hindering mechanistic studies is that there is no completely satisfactory animal model for human alcohol cardiomyopathy (177).

Myocardial lipid peroxidation occurs in the rat after chronic ethanol treatment. Antioxidants protect against this effect in murine models (44, 142). Xanthine oxidase-mediated oxidative stress has been suggested as a possibility for alcohol toxicity to the rat heart (127, 128). However, the applicability to clinical cardiomyopathy is minimal because xanthine oxidase is not present in human heart tissue (43, 63). Instead of oxygen-based free radicals, the production of carbon-centered free radicals is another possibility for alcohol toxicity (143).

Whether mediated by oxidative stress or by other processes, damage to membranes may lead to leakage and, in the case of the sarcolemma, to harmful calcium influx (138, 148). Another calcium-related change is that chronic alcohol exposure appears to increase the numbers of voltage-dependent calcium channels in the heart. Verapamil appears to protect against this aspect of alcohol cardiotoxicity in animal models (35).

Changes in cellular ATP levels (56) and in the lipid composition of mitochondria (50) have been reported. Because the heart is so highly dependent on ATP production for beat-by-beat maintenance of the cardiac output, chronic mitochondrial injury might be expected to lead to cardiac damage. Other proposed mechanisms for alcohol cardiomyopathy include decreased protein synthesis (177), decreases in the number of β-receptors (92), and accumulation of toxic metabolites (35). None of these mechanistic models has led, as yet, to clinically useful treatment.

A final consideration in the story of alcohol cardiotoxicity concerns putative beneficial effects of alcohol upon the heart. Recent articles have indicated that cardiovascular death rates are lower in moderate alcohol drinkers than they are in either heavy drinkers, or nondrinkers. This result continues to be found, even after the studies have been controlled for age, sex, smoking, and diet (22, 158). Other studies indicated that moderate drinking may provide protection against stroke (55). The implication of such studies is that moderate consumption of alcohol is advantageous and protective to the heart and vascular system. These results were greeted with glee by some and with disbelief by others. The topic continues to be highly controversial because of the social, political, moral, economic, and scientific issues it raises. One possible resolution of the controversy is indicated by a recent British prospective study with over 7,000 men (4, 155). As was found with many other studies, there was increased mortality in the nondrinking group in comparison to the moderate drinkers. Analysis of the nondrinking groups showed that they were not a homogeneous group. Rather, the group contained many former drinkers whose cardiovascular status was worse than that of the moderate drinkers against whom the survival comparisons were made. These former drinkers were the people who were dying, which explained the greater mortality in the nondrinking group. If such a confounding factor turns out to have been operating in the other studies reporting protection with moderate alcohol drinking, then it seems likely that moderate alcohol use does not protect the cardiovascular system. The question then becomes, is there any measurable adverse effect of moderate drinking?

ACKNOWLEDGMENTS

Dr. Combs is a Bergen Centennial Fellow in Pharmacy. Dr. Acosta is a Burroughs Welcome Scholar in Toxicology.

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