Cardiac Metabolism: Its Contributions to Alcoholic Heart Disease and Myocardial Failure

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SUMMARY Changes in cardiac metabolism in myocardial failure and after alcohol ingestion are discussed. The main effect of alcohol ingestion is loss of cardiac contractility. Since heart muscle does not contain alcohol dehydrogenase, its toxicity is probably the result of a direct toxic effect of ethanol and acetaldehyde on the myocardial cell, possibly involving various membrane systems. Alcohol inhibits mitochondrial respiration and the activity of enzymes in the tricarboxylic acid cycle, and it interferes with both mitochondrial calcium uptake and binding. Ethanol profoundly affects myocardial lipid metabolism. Acetaldehyde diminishes myocardial protein synthesis and inhibits Ca\(^{2+}\)-activated myofibrillar ATPase. In myocardial failure, a series of possibilities may be responsible for the loss of contractility. Excitation-contraction coupling could be disturbed at the level of the sarcotubular, at the sarcoplasmic reticulum, at the mitochondria, and between calcium and the regulatory proteins. Deficiencies in Ca\(^{2+}\) delivery systems of excitation-contraction coupling on the myosin ATPase activity could be responsible for the diminution in cardiac contractility. Mitochondrial function may also be involved, since mitochondria from failing human hearts are defective with respect to respiratory control and calcium accumulation. Under certain conditions, the relationship of mitochondria to calcium sequestration is very important in influencing contractility. The involvement of contractile and regulatory proteins in myocardial failure cannot be excluded.

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Supported by grants from the US Public Health Service (#5 ROI AA 00304-05) and the Margaret W. and Herbert Hoover, Jr. Foundation.

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ETHANOL AFFECTS MANY ORGANS, including the liver,\(^1\) the heart,\(^2\),\(^5\) the bone marrow,\(^4\),\(^5\) the central nervous system\(^6\) and the reticulo-endothelial system.\(^7\) The liver is the primary organ for the breakdown of alcohol by virtue of its high concentration of alcohol dehydrogenase, the most important enzyme in hepatic ethanol metabolism.\(^1\) Therefore, oxidation of ethanol in the liver results in an increase in the NADH/NAD\(^+\) ratio, as shown by Lieber and Davidson.\(^8\) In this organ, the excess of NADH, resulting from the activity of alcohol dehydrogenase, shifts redox pairs to their reduced substrates.

The heart contains no alcohol dehydrogenase; yet alcoholic cardiomyopathy is a definite clinical entity, belonging to the group characterized by Goodwin as congestive cardiomyopathy.\(^9\) Prolonged intake of ethanol results in chronic myocardial toxicity with electronmicroscopic changes, arrhythmias and even sudden death.\(^10\)-\(^21\) The reversal of the disease on alcohol withdrawal is definitive evidence that alcohol is involved in the etiology of this condition.\(^17\),\(^22\),\(^23\)

Although one of the primary effects of alcohol ingestion is loss of cardiac contractility,\(^10\),\(^24\)-\(^26\) the actions of alcohol are equally pronounced at the metabolic level. These include disturbances in mitochondrial respiration, mitochondrial enzymes, calcium uptake and binding by mitochondria and by the sarcoplasmic reticulum (SR), and myocardial lipid metabolism.\(^22\),\(^25\)-\(^30\) If acetaldehyde is included with alcohol, we can add to this myofibrillar ATPase\(^41\) and myocardial protein synthesis.\(^32\)

Effect of Alcohol on Mitochondrial Function

Wendt and coworkers found release of enzymes by the heart muscle into coronary sinus blood in patients with chronic alcoholism.\(^29\) This was interpreted as an indicator of changes in mitochondrial membrane permeability. Changes in mitochondrial function were later demonstrated by Pachinger,\(^27\) who studied mitochondrial respiration as well as the activity of the intra-mitochondrial isocitrate dehydrogenase from dogs maintained on alcohol for several months. In the group exposed to alcohol, diminution in respiratory function of mitochondria occurred. Mitochondrial \(\text{O}_2\) and respiratory control indices were markedly diminished. A significant decline in the intramitochondrial NAD-ICDH also was observed. Segal and coworkers obtained similar results in their experiments with rats.\(^29\) In this study ethanol consumption had no apparent effect on mitochondrial respiration until the animals were given 25% ethanol.\(^32\) Mitochondria exhibited significantly lower respiratory control and \(\text{O}_2\). As in the experiments of Pachinger, no effect was seen on the ADP/O ratio. The changes observed in mitochondrial respiration are not surprising in the light of the destruction wrought by ethanol on their ultrastructure.\(^18\),\(^34\)

Effect of Ethanol on the Calcium Binding and Uptake of Mitochondria and SR

Subsequent discussion of the alterations in excitation-contraction coupling in myocardial failure
deals more extensively with the fundamental aspects of the role of calcium in the process of excitation-contraction coupling. The administration of ethanol for a period of six months caused marked depression of calcium binding and uptake in the mitochondria and SR. In mitochondria, calcium uptake is respiration-linked because of the addition of succinate and phosphate. Calcium transport by fragmented SR is increased in the presence of calcium precipitating anions such as oxalate and phosphate. This anion-dependent transport in SR is referred to as calcium binding and occurs as a result of the ability of these anions to precipitate calcium when the internal Ca++ concentration rises. In the absence of oxalate, calcium transport, referred to as calcium binding, is quickly inhibited by the inhibitory action of the high Ca++ concentration within the vesicles. Ebashi showed the binding process in the absence of oxalate is probably of primary significance.

Bing and coworkers showed that ethanol inhibits both calcium binding and uptake by SR of dogs exposed to ethanol for several weeks. This may be partially responsible for the diminution in contractility resulting from ethanol intake.

**Myocardial Lipid Metabolism**

Regan found that after acute ingestion of alcohol by dogs, the heart muscle accumulates triglycerides and myocardial extraction of fatty acids diminishes. Marciniak and coworkers studied the effect of chronic alcohol administration on glyceride content of heart muscle in dogs. A significant increase in glyceride content of heart muscle was observed. Lochner and coworkers, in studying the effect of ethanol on the metabolism and function of perfused rat hearts, discovered that ethanol increased incorporation of tC-labeled palmitate uptake into tissue lipids, while tCO₂ formation decreased. Since long-chain fatty acids are a major fuel for the heart, a decrease in their rate of oxidation was thought to suggest some other endogenous substrate which might have become a major source of energy. Kikuchi and Kako also found that ethanol diminished oxidation of fatty acids and enhanced fatty acid esterification of triglycerides. They linked the accumulation of triglycerides after ethanol administration to decreased fatty acid oxidation rather than increased triglyceride uptake or increased fatty acid synthesis. It is therefore possible that lipids may accumulate in the heart after alcohol ingestion because of difficulty in transporting long-chain fatty acyl-CoA into the mitochondria for β-oxidation or through damage to mitochondrial membrane or mitochondrial enzymes.

Williams and Li have tested these hypotheses by examining selected portions of the oxidative pathway of fatty acids. They concluded from their experiments that the ability to transport and to oxidize incorporated fatty acids was normal. They considered other reasons for the decline in myocardial fatty acid oxidation, such as competition of metabolic byproducts of alcohol with fatty acids for a common oxidative pathway in the mitochondria, or possibly increased tryglyceride synthesis from fatty acids and α-glycerophosphate. They, as well as Pachinger and coworkers, found marked impairment of mitochondrial pyruvate oxidation. Since the rates of acetylarcarnitine oxidation were normal, the defect might involve pyruvate dehydrogenase or the transport of pyruvate into mitochondria.

The causes of triglyceride accumulation, the inhibition of fatty acid oxidation, and the deficiency in calcium transport in mitochondria and SR are not fully understood. It is possible, however, that these changes are the result of a direct toxic effect of alcohol on the myocardial cell, possibly involving various membrane systems.

**The Role of Acetaldehyde**

The cardiac toxicity of ethanol is augmented and supplemented by that of acetaldehyde. The inotropic and chronotropic effects resulting from acetaldehyde induced release of catecholamines may explain the occurrence of cardiac arrhythmias observed after ingestion of ethanol. Acetaldehyde also results in vitro in a marked decrease in myocardial protein synthesis. This finding is significant in light of the observation by Zühlke and coworkers that inhibition of myocardial protein synthesis leads to the development of myocardial failure in hearts with increased afterload. Additional damaging effects of acetaldehyde may be due to the inhibition of Ca++-activated myofibrillar ATPase, as shown by Nayler. This could be partially responsible for the diminished cardiac contractility observed after the ingestion of ethanol. Further reduction in myocardial contractility could arise from diminished Ca++ uptake and binding by sarcoplasmic reticulum induced by ethanol.

**Myocardial Failure and Myocardial Metabolism**

Intubation of the coronary sinus has demonstrated unchanged myocardial usage of carbohydrates, fatty acids, amino acids or ketones, while there was impairment of myocardial lactate extraction in heart failure, suggesting that glycolysis may occur in the failing heart when energy demands are increased. In 1960 it was recognized that cardiac metabolism in heart failure in patients with coronary arteriosclerosis, hypertension or valvular heart disease may differ from heart failure due to anemia, hemorrhagic shock, hyperthyroidism and thiamine deficiency. In the first group, normal utilization of substrate and oxygen by the failing heart suggested that the underlying defect may be located in "energy conservation or utilization." It was felt that, by exclusion, the evidence points to energy utilization as the site of derangement. In 1966, the division into these groups was maintained; however, the relationship between cardiac hypertrophy, abnormal protein synthesis and myocardial failure was stressed. Later came the recognition that an abnormality of the process of excitation-contraction coupling has profound effects on tension produced by the heart muscle.

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Additional notes:

- The original text is from a scientific journal article discussing the effects of alcohol and related compounds on myocardial function.
- The text delves into various physiological processes and metabolic pathways impacted by alcohol intake.
- The author references several studies and researchers, including Bing, Marciniak, and Williams, among others.
- The document is from CIRCULATION, Volume 58, No 6, December 1978.
Calcium ions are the link between excitation and contraction. Events leading from excitation to contraction begin at the cardiac sarcolemma. A series of calcium links are called into play when the need arises. These include particularly the SR and mitochondria. The principal discoveries of the interaction of calcium with the contractile apparatus were made by Ebashi, who found that the regulatory protein-binding calcium was distinguished from myosin; Bailey, who discovered tropomyosin; and by Ebashi, who defined troponin as the calcium-binding protein responsible for the calcium sensitivity of the myofibril. The role of the SR in its relation to calcium was first demonstrated by Hasselbach and Makinose, who showed that the granules, later identified by Ebashi as part of the endoplasmic reticulum, contained an ATP-dependent calcium pump which concentrated cytoplasmic calcium 500 times and, in the presence of oxalate, 6000 times. During diastole, in the absence of calcium, the regulatory proteins may inhibit the actin-myosin interaction, while during systole, calcium abolishes the inhibition of the actin-myosin interaction by the tropomyosin-troponin complex.

There are multiple possibilities in which myocardial failure could interfere with the excitation-contraction coupling: 1) at the level of the sarcolemma, between extracellular and intracellular calcium and sodium-calcium exchange, 2) at the SR and mitochondria (calcium binding, uptake and release), and 3) between calcium and the regulatory proteins. Each of these structures is composed of a series of elements which may be affected in myocardial failure. The sarcolemma has various substructures, and is much more complicated than the simple "plasma membrane" first described. A specialized surface code composed of fibrillar material is bound to the plasma membrane; adjacent to the internal aspect of the membrane is the fibrillar cytoplasm, which in cardiac muscle is prominent in regions of cell adhesions, and the surface code identified by Langer as site of lanthanum binding. These substructures may have different functions. The T System, composed of large invaginations of the membrane, is particularly important. This spreads the excitory process to the SR. It is a tubular network which is formed by invagination of the sarcolemma and carries the extracellular space deep into the interior of the cell. It represents about 20% of the total plasma membrane in some species. The spatial sarcolemma-SR relationship is close. Huxley and Taylor have first shown that activation of SR occurs via the T System, suggesting that calcium is released from terminal cisternae. Calcium release from the SR is initiated by trigger calcium, as first shown by Bianchi. The uptake of calcium must follow the transfer of calcium through the sarcolemma. In heart muscle, calcium-induced calcium release is more easily evoked than in skeletal muscle, with a lower level of free calcium. Calcium may move through the sarcoplasm by two routes: 1) a small pore or channel, and 2) a larger amount via electroneutral carriers. This is consistent with the proposal that the immediate source of calcium responsible for contraction is derived from sites external to the sarcolemma and T-tubular membranes. It also correlates with the finding that calcium antagonists leave the action potential unaffected while interfering with contractility.

The complexities of the calcium binding and release mechanism of the SR, which may play a role in myocardial failure, have already been discussed. A general principle in biological systems is that accumulation and release processes are usually operated by entirely different systems. Thus, mechanisms concerned with calcium accumulation and release by the SR are different. Because of its intimate ultrastructural relationship of the sarcolemma to the SR, one can expect an interdependence of these structures in calcium uptake. Schwartz has suggested a variety of interchanges between sarcolemma and SR, all affecting the role of the trigger or activator calcium. The Ca++ transport of SR (Ca++ uptake of Ca++ pump) is energized by ATP through a Mg++ activated ATPase. Tada et al. have reviewed the mechanism by which Ca++ is actively transported across the membrane of the SR, with particular reference to the function of ATPase within its membrane. He described evidence that the energy-transmitting mechanism in this membrane system is associated with calcium-induced phosphorylase of the ATPase enzyme.

It is not surprising, considering the role of calcium ion as a transmitter of superficial excitation to mechanical reaction, that inhibitors of this transmission result in interruption of excitation-contraction coupling, thus resulting in diminished myocardial contractility. A series of potent calcium antagonists have been developed which appear to block special calcium channels in the mammalian cardiac muscle fiber membranes. Although the first reports on these calcium antagonists were published without knowledge of their mechanism, Fleckenstein later ascribed their action and the loss of contractility to calcium deficiency. These drugs abolish the contractile response of heart muscle without interfering with the action potential. Apparently calcium antagonists block only the transmembrane calcium influx without affecting simultaneous Na+ movements which are connected to the action potential. This electromechanical dissociation leads to diminished ATP consumption by the heart muscle, and to diminished contractile force of the myocardium. As a result, both creatine phosphate and ATP levels in heart muscle increase with the diminution of orthophosphate fraction. The essential feature of these drugs in their antanginal use is a diminution in myocardial O2 demand of the heart muscle.

These effects of calcium antagonists have other interesting metabolic sequelae. For example, some of these drugs favorably reduce the effects of myocardial ischemia. It has been shown that administration of one of these drugs (diltiazem) to dogs with regional myocardial ischemia resulting from ligation of branches of the left descending coronary artery,
results in a 50% reduction in the decline of ATP in the ischemic region, lessens the inhibition of anaerobic glycolysis, lowers the tissue levels of lactic acid and free fatty acids, and markedly improves contractility of glycerinated heart muscle, prepared from ischemic heart muscle fibers.74 Previously, Smith et al. had demonstrated the amelioration of myocardial ischemia by calcium antagonists.70 This latter finding, although not well understood, illustrates a preservation of the contractile elements of heart muscle secondary to the improved biochemical status.70

The possibility that mitochondrial dysfunction is part of the deficiency in myocardial failure has been raised by a number of investigators. Schwartz71 and Dhalla72 have described mitochondria isolated from failing human hearts as defective with respect to respiratory control and calcium accumulation. Renewed interest in the relationship of mitochondrial functions to myocardial contractility was aroused by the finding that electrophysiological and structural changes in heart muscle occur when ischemic heart muscle is being reperfused.73, 74 The result is diminished cardiac contractility. Apparently, the severity and duration of ischemia is influential in determining the degree of damage.75, 76 This damage to the myocardium has been ascribed to rapid reoxygenation of the heart muscle. Hearse stated that the sudden changes resulting from reoxygenation or reperfusion are strikingly similar to the calcium paradox.74 When hearts are perfused with calcium-free medium, readmission of calcium causes severe myocardial damage.77 It is believed that readmission of oxygen after prolonged ischemia, when the electron transfer system is blocked but remains functional, results in massive respiration-linked uptake of calcium.74 This is supposed to occur as an alternative to oxidative phosphorylation. It was discovered that, if the ischemia is severe (70–95% of control coronary flow), mitochondrial respiration is severely impaired, while calcium uptake is unimpaired and calcium binding is reduced. Reperfusion of areas of lesser degrees of ischemia appears to have little effect on myocardial function.79

Therefore, under certain conditions, the relationship of mitochondria to calcium sequestration is very important in influencing contractility. It has been found that mitochondria from heart muscle, in contrast to liver mitochondria, have a low-energy linked rate of calcium uptake and that calcium uptake by mitochondria from heart muscle is not accompanied by an increase in their oxygen utilization.78 In the heart mitochondria oxidative phosphorylation can compete effectively with calcium transport for the energy made available by the respiratory chain. In liver mitochondria, under similar conditions, calcium transport is preferred over oxidative phosphorylation. Apparently reperfusion of the acutely ischemic myocardium may change this; under these conditions, Ca++ binding diminishes, and oxidative phosphorylation cannot compete effectively with ion transport for the energy made available by the respiratory chain.

Finally, defects in contractile or regulatory protein may contribute to the development of myocardial failure. The end organs of excitation-contraction coupling are the contractile proteins, actin and myosin, which combine to actomyosin during contraction. They are composed of several subunits of low-molecular weight, heavy and light meromyosin; the former determines the rate of ATP hydrolysis and the interaction with actin.79 In addition, as mentioned above, there are the regulatory or modulatory proteins, troponin and tropomyosin. The troponin complex is also composed of subunits. Apparently the sensitization of actomyosin to calcium requires all of the troponin components in addition to tropomyosin.79

Diminished contractility, the hallmark of myocardial failure, could therefore result from a variety of disturbances on the molecular level. It has been proposed that there is a relationship between specific links of the excitation-contraction coupling chain and specific contractile functions.79 For example, changes in the rate of development of tension in the contractile elements (dp/dt) may reflect alterations in the rate at which Ca++ is bound to troponin. An increase in maximal tension (P0) may be due to the amount of Ca++ in the contractile proteins. Vmax (the maximal shortening velocity at zero load) could be dependent on myosin ATPase activity. Therefore, in myocardial failure, deficiencies in Ca++ delivery systems of excitation-contraction coupling, or the myosin ATPase activity, could be responsible for the diminution in cardiac contractility. Katz in 1970 had stated that the rate of ATP hydrolysis by actomyosin in vitro reflects the maximum rate of energy liberation by the intact muscle.80 He based his conclusion on the difference in the ATPase activity of myosin from red and white skeletal muscle and the existence of a causal relationship between ATPase activity and the maximal shortening velocity of the muscle as described by Bárány.81 But equally, the diminution in contractility may result from deficiencies in mitochondrial respiration, from interference with activities of the sarcolemma or SR. Finally, alterations in the activity of calcium uptake and release by the SR may be a factor. Therefore, many factors may be responsible for the loss of contractility in myocardial failure. We have the tools to investigate this problem which, because of its clinical significance, deserves attention.

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Circulation. 1978;58:965-970
doi: 10.1161/01.CIR.58.6.965

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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