REGULAR HEAVY ETHANOL CONSUMPTION has been associated with a type of nonischemic dilated cardiomyopathy termed “alcoholic cardiomyopathy” (ACM), which is clinically expressed as an impairment of left ventricular function (nonsymptomatic stage) and occasionally as overt heart failure (symptomatic stage) (19). ACM is a specific heart muscle disease diagnosed primarily on the basis of a long-standing history (>10 yr) of heavy alcohol consumption (>80 g/day, i.e., ~6 to 7 standard drinks/day) and the absence of any other evident etiology. The toxic effects of heavy ethanol drinking persist for the heart because they have been identified mainly after reports of almost complete reversal of the heart muscle disease after total alcohol abstinence in a very limited number of cases (12, 13). On the other hand, the protective effect of moderate ethanol intake, owing mainly to a reduction in fatal and nonfatal coronary heart disease, has been recognized (4, 8, 10). In recent years, moderate and chronic ethanol consumption has even been reported to result in a lower risk of congestive heart failure (1, 20). Furthermore, in patients with established left ventricular dysfunction enrolled in the randomized trials, Studies of Left Ventricular Dysfunction (6) and Survival and Ventricular Enlargement (2), moderate alcohol consumption had no significant effect on prognosis even for those with nonischemic left ventricular dysfunction (6).

These ambiguous effects of ethanol suggest that the relationship between ethanol and heart diseases and the effects of ethanol on left ventricular function are much more complex than previously suspected. Basic research exploring the effect of ethanol on cardiomyocyte contractility is therefore obviously needed to propose new concepts and mechanisms. In this issue of American Journal of Physiology—Heart and Circulatory Physiology, the study by Aistrup et al. (3) is very welcome in this context.

Ethanol has been shown to interfere with a number of myocardial metabolic steps and cellular mechanisms. However, no single key factor for the development of ACM can be pointed out, although it is well established that ethanol can affect intracellular organelles, contractile proteins, and calcium homeostasis and induce oxidative stress and cell death (18). Animal models of ACM have significantly contributed to our understanding of human ACM. These models have demonstrated that both acute (14) and chronic (17) ethanol exposure decreases myocardial lipid peroxidation and protein oxidation and reduces mitochondrial GSH content, suggesting that reactive oxygen species play an important role in the onset of cardiac toxicity.

In addition to the possible link between oxidative stress and ethanol toxicity, there is substantial literature reporting an alteration of contractile function in the stress due to alcohol exposure (16). It is well established that ethanol impairs excitation-contraction coupling, leading to impaired cardiac contractility (18). In isolated cardiomyocytes, acute ethanol treatment induces a dose-dependent reduction of maximum shortening. This negative inotropic effect is significant at very low concentrations (0.05%), and the dose-response relationship is not linear, which suggests that ethanol may act upon cardiac myocyte contraction in several ways (9).

More than thirty years ago, Bing et al. (5) were the first to demonstrate that ethanol exposure results in a decline in calcium uptake by the sarcoplasmic reticulum in dog cardiomyocytes. Several studies on acute alcohol consumption have since confirmed that ethanol can cause a dose-dependent depletion of the sarcoplasmic reticulum calcium content (7) and affect cellular calcium homeostasis, probably through direct effects on calcium channels (15). However, the mechanisms by which acute and chronic ethanol exposure induces inotropic effects are probably different, because Figueredo et al. (11) have shown that changes in myocardial contractility due to chronic ethanol exposure do not result from altered calcium management but rather from changes at the myofilament level.

Most studies about the cardiac effects of ethanol so far have focused either on acute ethanol consumption or on long-term chronic ethanol exposure. The study by Aistrup et al. (3) provides an example of a strict approach, sophisticated methodology, and cautious interpretation of the results. This careful report expands our understanding of the changes in cellular excitation-contraction coupling in cardiac myocytes during the transition period where acute ethanol exposure becomes chronic. These results show that so long after the onset of chronic ethanol consumption, the well-documented negative inotropic effect of acute ethanol exposure is temporarily counteracted by adaptive mechanisms, leading to the expression of a temporary positive inotropic effect. This observation on how the acute effects of ethanol on excitation-contraction coupling at the cellular level translate into chronic conditions and the onset of ethanol-induced cardiac disease may be of fundamental significance. They may help understand the ambiguous effect of ethanol on the heart in the clinical setting. Finally, identifying the precise mechanisms responsible for this compensatory adaptation and its subsequent loss may allow us to design new approaches for the prevention and treatment of ACM.

REFERENCES