T he relationship between alcoholic beverage consumption and cardiovascular disease is complex and not fully elucidated. The idea that drinking moderately protects against coronary heart disease prevails among physicians and the public at large. There are 218 reviews in MedLine under the search terms “coronary heart disease alcohol,” limited to title and abstract, almost all asserting that the consumption of moderate amounts of alcoholic beverages is beneficial for cardiovascular health. Wine is the beverage typically associated with cardioprotection, being presumably a determinant of the low incidence of CHD in France, the French paradox. The epidemiological evidence comes along with the demonstration of beneficial effects of alcohol or other wine products on some mediators of cardiovascular disease, such as blood lipoproteins, clotting and fibrinolytic factors, insulin sensitivity, endothelin, NO, and LDL susceptibility to oxidation. However, not all epidemiological studies have shown a cardiovascular protection derived from the moderate consumption of alcoholic beverages. In blacks, this amount of consumption was associated with an increased risk for coronary heart disease incidence.1 The observational design of studies that have demonstrated the beneficial effect of alcoholic beverages precluded the full control of confounding by a healthier lifestyle of moderate drinkers. In addition, other negative cardiovascular effects of alcohol could nullify its beneficial effects. Among the harmful effects of alcoholic beverages is their blood pressure–raising effect. Drinkers of alcoholic beverages have higher blood pressure2 or are at higher risk for developing hypertension.3 A J-shaped relationship between blood pressure and ingestion of alcoholic beverages has been described by some studies, with lower blood pressure at moderate levels of consumption.4 However, the habit of drinking 2 to 3 drinks per day is an unequivocal threshold dose for increasing of blood pressure. The evidence from epidemiological studies was corroborated by human experimental studies, which have shown that alcohol ingestion increases blood pressure,5 and withdrawing of alcoholic beverages lowers blood pressure.6

Contrasting effects of alcohol and some components of alcoholic beverages, such as antioxidant polyphenols, could eventually explain the paradoxical effects of alcohol and alcoholic beverages, particularly wine, on cardiovascular regulation. In this issue of Hypertension, Zilkens et al present the results of an experiment addressing this possibility.7 Twenty-eight healthy male individuals, regular daily drinkers, were assigned to 4 periods of a 4-week open-label crossover study. The 4 interventions included abstinence from all alcohol and grape products (control period), 375 mL daily of red wine (39 g alcohol), 375 mL of the same red wine dealcoholized, and 1125 mL daily (41 g alcohol) of beer. Ambulatory daily systolic blood pressure was 1.9 and 2.9 mm Hg higher at the end of the beer and wine periods, respectively, compared with the abstinence period. Blood pressure at the end of the dealcoholized red wine period did not differ from the abstinence period. None of the interventions had an effect on flow and glyceryl trinitrate mediated dilatation of the brachial artery. Urinary endothelin-1 (ET-1) excretion was higher in the alcohol (beer or wine) periods than in the nonalcohol (abstinence or dealcoholized wine) periods.

The results of this experiment add 2 more pieces to the whole picture of effects of alcohol and alcoholic beverages on the cardiovascular system. First, it confirms that the most active component of alcoholic beverages is alcohol itself. Blood pressure increased with the intake of 39 g daily of ethanol carried on indistinctly by beer or wine. Second, it shows that other components of red wine have negligible, if any, sustained effect on cardiovascular parameters of human beings. Four weeks of daily intake of 375 mL of wine without alcohol, with ~700 mg of polyphenols, did not produce any detectable effect on blood pressure, heart rate, endothelial function, or endothelin secretion. In this respect, these findings contradict the results of other experiments, which have shown that grape juice or dealcoholized wine improved endothelium-dependent vasodilation.8–10 Zilkens et al attributed these contradictory results to the noncontrolled design of 2 experiments8,9 but did offer an explanation for the differences with the results of the experiment of Agewall et al.10 These differences may be attributable to chance or the evaluation of endothelial function just after the ingestion of wine or dealcoholized wine by Agewall et al. The results of the experiment of Zilkens et al, with a controlled design and adequate statistical power, suggest that the effects of alcohol or other components of wine on potential mediators of their beneficial effects on cardiovascular system may in fact be null or pharmacologically irrelevant. In this regard, these findings strengthen the interpretation that drinking moderately may be a surrogate marker of a healthier behavior.
responsible for the lower incidence of coronary artery
disease.\textsuperscript{1}

Zilkens et al suggested that the vasopressor effect of
alcohol was caused, at least in part, via an alcohol-induced
increase in ET-1, which was higher in the 24-hour urine
collections at the end of wine and beer ingestion periods.
Corder et al showed that polyphenols from red wine de-
creased ET-1 synthesis in cultured bovine aortic endothelial
cells.\textsuperscript{11} If this effect happens in vivo, it may be overridden by
a subsequent increase in endothelin synthesis, secondary to a
dual effect of ethanol on blood pressure regulation. Epidemi-
ological\textsuperscript{12} and experimental\textsuperscript{13,14} studies have demonstrated that
the ingestion of alcohol is associated with an immediate
decreasing of blood pressure (an effect typical of vasodila-
tors), which is followed by a rebounding elevation of blood
pressure. Heart rate increases in response to vasodilation and
decreases thereafter. The rebound effects of acute alcohol
ingestion on blood pressure and heart rate may be mediated
by sympathetic modulation. Structural adaptation of the
resistance vessels exposed to the recurrent cardiovascular
effects of ethanol would lead to chronic hypertension.

Regardless of source, alcohol consumption, above a certain
threshold level, raises blood pressure, and this effect does not
appear to be counteracted by other components of wine. In
view of the large risk for cardiovascular disease attributable
to blood pressure $>115/75$ mm Hg,\textsuperscript{15} physicians should caution their patients against excess alcohol consumption.

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