Dose-related effects of red wine and alcohol on hemodynamics, sympathetic nerve activity, and arterial diameter

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Spaak J, Merlocco AC, Soleas GJ, Tomlinson G, Morris BL, Picton P, Notarius CF, Chan CT, Floras JS. Dose-related effects of red wine and alcohol on hemodynamics, sympathetic nerve activity, and arterial diameter. Am J Physiol Heart Circ Physiol 294: H605–H612, 2008.—The cardiovascular benefits of light to moderate red wine consumption have often been attributed to its polyphenol constituents. However, the acute dose-related hemodynamic, vasodilator, and sympathetic neural effects of ethanol and red wine have not been characterized and compared in the same individual. We sought to test the hypotheses that responses to one and two alcoholic drinks differ and that red wine with high polyphenol content elicits a greater effect than ethanol alone. Thirteen volunteers (24–47 yr; 7 men, 6 women) drank wine, ethanol, and water in a randomized, single-blind trial on three occasions 2 wk apart. One drink of wine and ethanol increased blood alcohol to 38 ± 2 and 39 ± 2 mg/dl, respectively, and two drinks to 72 ± 4 and 83 ± 3 mg/dl, respectively. Wine quadrupled plasma resveratrol (P < 0.001) and increased catechin (P < 0.03). No intervention affected blood pressure. One drink had no heart rate effect, but two drinks of wine increased heart rate by 5.7 ± 1.6 beats/min; (P < 0.001). Cardiac output fell 0.8 ± 0.3 l/min after one drink of ethanol and wine (both P < 0.02) but increased after two drinks of ethanol (+0.8 ± 0.3 l/min) and wine (+1.2 ± 0.3 l/min) (P < 0.01). One alcoholic drink did not alter muscle sympathetic nerve activity (MSNA), while two drinks increased MSNA by 9–10 bursts/min (P < 0.001). Brachial artery diameter increased after both one and two alcoholic drinks (P < 0.001). No beverage augmented, and the second wine dose attenuated (P = 0.02), flow-mediated vasodilation. One drink of ethanol dilates the brachial artery without activating sympathetic outflow, whereas two drinks increase MSNA, heart rate, and cardiac output. These acute effects, which exhibit a narrow dose response, are not modified by red wine polyphenols.

microneurography; sympathetic nervous system; blood pressure; cardiovascular diseases; risk factors

THE CONCEPT OF A PROTECTIVE effect of light to moderate alcohol intake against coronary heart disease, ischemic stroke, and heart failure has been distilled from the results of >60 observational studies (13, 16, 22). For example, in the Male Health Professional study (n = 38,077), compared with less than one drink per week, alcohol consumption between 3 and 7 days per week was associated with approximately one-third less risk of myocardial infarction (22). A meta-analysis involving 10 studies (n = 176,042) provides further support for the existence of a J-shaped rather than linear relationship between the use of alcohol and the risk of suffering a cardiovascular event (7, 16).

Although it has been hypothesized that polyphenols in red wine should contribute to such benefit, no clear distinction between alcoholic beverages with respect to cardiovascular risk reduction has emerged from these analyses (16, 22). Consequently, the American Heart Association Nutrition Committee does not comment on whether any particular alcoholic beverage is preferred but advises that men who drink alcohol should limit their consumption to two drinks per day and women to one daily drink. In this context, because they contain a comparable amount of alcohol (15–18 g), each of a 12-oz bottle of beer (355 ml), a 4-oz glass of wine (120 ml), and a 1.5-oz (44 ml) shot of spirits is considered one standard “drink” (10, 18).

The potential benefits of alcohol may relate to its metabolic, antithrombotic, anticoagulant, antioxidant, or anti-inflammatory properties or to effects on hemodynamics, vascular endothelial function, and neurohumoral regulation of the circulation; these latter actions are the focus of the present study. Intoxicating doses of ethanol have been shown to dilate conduit arteries, increase heart rate (HR), and stimulate sympathetic nervous system activity, causing an increase in blood pressure that is sustained for hours after vasodilation dissipates (3, 11, 26, 30). These acute sympathoexcitatory and pressor effects, if replicated with each drink, could account in part for the sustained elevations in ambulatory awake blood pressure and asleep HR observed in a randomized crossover trial when 40 g of ethanol was consumed daily for 4 wk as either beer or red wine (35) and could also contribute to the dose-dependent relationship with blood pressure observed when more than two alcoholic drinks daily are consumed chronically (24). In contrast, there has been no systematic dose-response evaluation of the hemodynamic and vascular effects of one and two standard drinks of red wine or ethanol in the same person, or any direct comparison of such responses between red wine and ethanol.

The purpose of this randomized, single-blind, water-controlled study involving healthy subjects was to answer four questions: 1) Does low or moderate red wine and/or alcohol ingestion affect central sympathetic outflow and endothelium-dependent dilation? 2) If so, are these effects dose dependent? 3) What is the relationship between the amount of wine or ethanol ingested and blood pressure or sympathetic nerve traffic? 4) Does a red wine with verified high polyphenol content differ from alcohol in its effects on vascular responsiveness or the sympathetic nervous system?
METHODS

Subjects. We studied healthy nonsmoking adult men and nonpregnant women of non-Asian background. Both heavy drinkers and total alcohol abstainers were excluded. The study was approved by our Institutional Research Ethics Board, and all subjects provided written informed consent.

Detailed instructions to abstain from caffeine, alcohol, and flavonoid-rich drinks (such as fruit juices) and food (fruits, dark chocolate, etc.) from the afternoon of the day before each session were provided. Subjects were instructed to eat a light breakfast in the morning before each study.

Protocol. Subjects attended three morning sessions, during which one of red wine, ethanol, or water was administered at random. To rest the fibular nerve between microneurographic recordings these sessions were scheduled at least 2 wk apart, and since muscle sympathetic nerve activity (MSNA) demonstrates between-leg congruence (33), alternate legs were studied on each session to minimize the potential for nerve trauma. Subjects were seated in a reclined chair, and an antecubital vein was canulated for blood sampling. A respiratory belt was wrapped around the abdomen to ensure that all signals were obtained during spontaneous breathing. HR was determined continuously from the ECG. Blood pressure was recorded automatically by an upper-arm cuff (Dinamap Pro 100, Critikon). A micro-neurographic electrode was placed in a sympathetic efferent fiber of the fibular nerve as previously described (2). After 10 min of quiet rest, stroke distance was determined by Doppler ultrasound directed above the aortic annulus (23). Brachial artery diameter and flow at rest plus increases in these variables following deflation of a lower-arm cuff inflated to 50 mmHg above systolic pressure for 4.5 min were determined by high-resolution ultrasound using a 7- to 10-mHz linear array transducer and Doppler, respectively (5). In brief, the artery was scanned 2–5 cm above the elbow. Postischemic reactive hyperemia was induced by inflating a lower-arm blood pressure cuff to 50 mmHg above systolic pressure for 4.5 min. A second scan was acquired, commencing 30 s before cuff deflation. Doppler flow measurements were obtained during the resting scan and during the first 10 s of reactive hyperemia. Blood was then drawn, and blood pressure, HR, and efferent MSNA were recorded over 8 min of quiet rest.

The first drink was then ingested over 5 min. When a peak blood alcohol concentration (BAC) of 40 mg/dl was achieved, after ~10 min, all measurements were repeated (Fig. 1). Once BAC had fallen to 25–30 mg/dl, the second drink was ingested. A third set of data was acquired once BAC peaked, at ~90 mg/dl. At the conclusion of the protocol, subjects voided for urinalysis.

Subjects were provided lunch and remained in the laboratory until BAC fell below 10 mg/dl. Transportation home was arranged, and subject status was determined later that day by telephone.

Selection of red wine and controls. The Quality Assurance Laboratory of the Liquor Control Board of Ontario (Toronto), selected a moderately priced pinot noir with high resveratrol content (Wolf Blass, Australia, 2001). Ethanol (95%) was provided by the hospital pharmacy, diluted with bottled Perrier water to a volume and concentration equal to the wine, and flavored with a sugar-free artificial flavoring (Crystal-Light, <1.3 g) for palatability. Equal volumes of Perrier water were provided as water control.

Target blood alcohol concentrations. Classical pharmacokinetics were used to calculate the one-drink dose required to achieve a BAC of 40 mg/dl in each subject, e.g., for a 68-kg male, 155 ml of wine with 12% alcohol content (18.6 g of ethanol) (Fig. 1). This was then doubled (310 ml) for the second dose. BAC was assessed with a breathalyzer (Intoxilyzer SD-5, CMI, Owensboro, KY; accuracy <0.5 mg/dl).

Analytic methods. Concentrations of free resveratrol, catechin, and quercetin in the bottle of wine, in venous plasma, and in urine were determined from gas chromatography (29). Plasma epinephrine, norepinephrine (NE), dopamine (DA), atrial natriuretic peptide (ANP), arginine vasopressin (AVP), adrenocorticotropic hormone (ACTH), and cortisol concentrations were determined by HPLC with electrochemical detection.

Continuous data were digitized and stored with LabView (National Instruments, Austin, TX; Ref. 2). Blinded analysis of data was performed after the conclusion of all studies by trained investigators. Stroke volume (SV) was calculated using the mean-time velocity integral and the area of the aortic annulus orifice (23), and cardiac output (CO) was calculated as the product of SV and simultaneous HR. Brachial artery diameter was determined with edge-tracing software (5). Flow-mediated dilation (FMD) was calculated as the percent increase in brachial artery diameter from baseline elicited by hyperemia (5). MSNA was quantified as burst frequency (bursts/min), burst incidence (bursts/100 heartbeats), and integrated nerve activity normalized to the maximum burst amplitude detected during each recording (NIMSNA) (8).

Statistical analysis. Values are expressed as means ± SE. A linear mixed-effects model was used to account for repeated measurement after zero, one, and two drinks on three different days. Comparisons were made by linear contrasts on the results of the fitted model. A linear contrast was also constructed to test for equal trends over time for the ethanol and wine days. Statistical significance was accepted if P < 0.05.
RESULTS

Subjects. Seven men and six women, aged 35 (24–47) yr [mean (range)], with a body mass index of 23 (18.4–27.6) kg/m², completed all three arms of this protocol.

Interventions. The red wine selected was determined to have high t-resveratrol (9.36 mg/l) and catechin (67.2 mg/l) concentrations and an average quercetin concentration (11.4 mg/l). Wine alone caused significant increases in both plasma and urine resveratrols and catechins (Fig. 2; Table 1). Similar BACs were achieved with the two alcohols after one and two drinks (P = 0.58 and 0.07, respectively): for ethanol 36.5 ± 2 and 81.4 ± 2 mg/dl and for wine 36.1 ± 2 and 71.4 ± 2 mg/dl (for 1 and 2 drinks, respectively, P < 0.00001 from baseline for all).

Hemodynamic responses. There was no significant change in blood pressure after one or two drinks of water, ethanol, or wine (Fig. 3; Tables 2–4). HR fell after one (5.0 ± 1.6 beats/min; P = 0.0027) and after two (7.2 ± 1.6 beats/min; P = 0.0001) drinks of water (Fig. 3). The first alcoholic drink had no effect on HR, whereas the second drink of wine increased HR (+5.7 ± 1.6 beats/min; P = 0.0007). However, overall there were no differences in the effects of either alcoholic beverages on HR (P = 0.44).

SV was not affected by drinking water, whereas there was a biphasic effect of both alcoholic beverages, with a reduction after one dose (P = 0.038 for ethanol vs. baseline) and a return toward baseline after two doses (Fig. 3; Tables 2–4). SV was 7.8 ± 3.8 ml higher after two drinks of wine than after two drinks of water (P = 0.04), but overall there was no difference between the effects of ethanol and wine on SV (P = 0.73).

CO fell by 0.8 ± 0.3 l/min after two drinks of water (P = 0.004) and after one drink of both ethanol (P = 0.008) and wine (P = 0.015), whereas compared with two drinks of water, CO rose significantly after two drinks of both ethanol (+0.8 ± 0.3 l/min; P = 0.009) and wine (+1.2 ± 0.3 l/min; P = 0.0002) (Fig. 3; Tables 2–4). Overall, there was no difference between the effects of ethanol and wine on CO (P = 0.66).

Table 1. Polyphenol concentrations before drinking, after first drink, and after second drink on day when red wine was given

<table>
<thead>
<tr>
<th></th>
<th>Predrink Mean±SE</th>
<th>After Drink 1 Mean±SE</th>
<th>After Drink 2 Mean±SE</th>
<th>P_mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-resveratrol</td>
<td>11.1±2.3</td>
<td>24.8±5.8</td>
<td>43.0±9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-catechin</td>
<td>59.6±16</td>
<td>65.1±17</td>
<td>70.8±19</td>
<td>0.03</td>
</tr>
<tr>
<td>P-quercetin</td>
<td>74.3±6.1</td>
<td>80.5±7.8</td>
<td>82.9±7.7</td>
<td>0.28</td>
</tr>
<tr>
<td>U-resveratrol</td>
<td>15.8±3.1</td>
<td>427±151</td>
<td>427±151</td>
<td>0.02</td>
</tr>
<tr>
<td>U-catechin</td>
<td>116±33</td>
<td>261±52</td>
<td>261±52</td>
<td>0.02</td>
</tr>
<tr>
<td>U-quercetin</td>
<td>150±42</td>
<td>225±68</td>
<td>225±68</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Values are expressed in micrograms per liter. P, plasma; U, urine. P values refer to changes from predrink values. P_mixed refers to the test of nonzero difference in changes between wine and ethanol.

Fig. 2. Confirmation of polyphenol absorption after acute intake of red wine. Plasma (P) resveratrol concentration increased significantly 30 min after 1 wine drink (Post-1), and rose further after the second dose (Post-2) (a). Red wine also increased catechin but not quercetin plasma concentrations. Corresponding increases in urine (U) polyphenol concentrations (bottom) indicate the potential for biological action at these doses. Water (■) or ethanol alone (●) had no effect on plasma or urine polyphenol concentrations. All values shown are means ± SE; *P < 0.05 compared with predrink levels.
Fig. 3. Comparison of acute hemodynamic effects of red wine, ethanol, and water. No beverage affected systolic arterial pressure (SAP). One drink (Post-1) did not affect heart rate (HR), but two drinks (Post-2) of wine or ethanol evoked a marked positive chronotropic response. SV fell significantly after 1 glass of ethanol and tended to fall after 1 glass of red wine, while the second dose caused a return toward predrink levels. The drop in cardiac output (CO) after 1 alcoholic drink was more pronounced, and even though it returned toward predrink levels after the second dose there was a marked difference between the alcoholic drinks and the control (water) intervention. When compared directly, there were no significant differences between the effects of red wine and ethanol alone. All values shown are means ± SE. †P < 0.05 compared with predrink levels; *P < 0.05 compared with water day.

Sympathoneural and neuroendocrine responses. On the water day, MSNA burst frequency fell 3.5 ± 1.7 bursts/min (P = 0.044) after two drinks, whereas MSNA burst incidence did not change (P = 0.64) (Fig. 4; Tables 2–4). There was no effect of one alcoholic drink on burst frequency. In contrast, two drinks of both ethanol and wine increased MSNA from the predrink baseline (+5.1 ± 1.8 and +6.2 ± 1.7 bursts/min, respectively; P < 0.01). Compared with two drinks of water, MSNA was 9.7 ± 2.5 bursts/min higher after two ethanol drinks (P = 0.0002) and 9.6 ± 2.5 bursts/min higher after two wine drinks (P = 0.0003). There was no significant difference between the two alcoholic beverages with respect to burst frequency (P = 0.74).

Because of the concurrent increase in HR, neither alcoholic beverage increased MSNA burst incidence significantly above respective baseline values, and there was no significant difference between the alcoholic beverages with respect to burst incidence (P = 0.57). NIMSNA showed a pattern similar to that of MSNA burst frequency (Fig. 4).

Plasma NE concentration was not significantly affected by either beverage, but there was considerable variability within these data. Two wine drinks increased plasma epinephrine concentration by 0.09 pmol/l from baseline (P = 0.048), although there was no significant difference in this effect between ethanol and wine (P = 0.48). Neither water nor ethanol increased plasma DA concentration. In striking contrast, one glass of wine increased plasma DA concentration by 0.44 ± 0.12 pmol/l (P = 0.004), and two glasses increased plasma DA concentration by 0.81 ± 0.12 pmol/l (P < 0.0001). These effects of two red wine drinks on DA were significantly greater than those of both water (P < 0.00001) and ethanol (P = 0.00005), and there was a significant difference for trends over time between wine and ethanol (P = 0.0001).

None of these interventions affected plasma concentrations of ANP or AVP. Plasma ACTH concentrations increased 80% after wine (P = 0.006), but not after ethanol or water. ACTH concentrations after two drinks of wine were significantly greater than after two drinks of ethanol (P = 0.017) or water (P = 0.043). Trends for ACTH over time were significantly different during the wine and ethanol sessions (P = 0.041). With the exception of a fall after one drink of ethanol (P = 0.041), none of the interventions affected plasma cortisol and there was no difference in trends over time between the two alcoholic beverages.

Brachial artery diameter and responsiveness to flow. There was no change in resting brachial arterial diameter after one or two drinks of water (Fig. 5; Tables 2–4). By contrast, there were significant increases in diameter after one and two drinks of both alcoholic beverages, with no difference between ethanol and wine (P = 0.39). Compared with two drinks of water, brachial diameter was 0.39 ± 0.10 mm larger after two drinks of ethanol (P = 0.0001) and 0.40 ± 0.10 mm larger after two drinks of wine (P < 0.0001).

Hyperemia induced a transient 8- to 12-fold increase in brachial artery flow, with no significant difference between experimental conditions. With the exception of the flow-mediated dilator response to one drink of wine, which was 4.4 ± 1.9% less than that to two drinks of water (P = 0.02), the differences between ethanol and wine compared with water and compared with each other (P = 0.61) were not significant.
DISCUSSION

Our objectives in this study were to characterize, simultaneously, the acute hemodynamic, neural, vascular, and neurohumoral responses to one and two standard doses of red wine and ethanol, achieving identical BAC, and to determine whether red wine with verified high polyphenol content exerts greater hemodynamic or vascular actions than ethanol alone. Previous investigators have focused their attention on one or two aspects of these actions of red wine or ethanol, without determining or comparing the integrated responses to acute consumption of these alcohols at low doses in the same person.

Our principal findings were that 1) there is a U-shaped relationship between BAC and CO; 2) one alcoholic drink induces conduit artery vasodilation without eliciting direct or reflex increases in HR or MSNA; 3) compared with water, two alcoholic drinks evoke significant increases in MSNA, HR, and CO, yet brachial dilation is sustained and blood pressure does not increase; 4) neither alcoholic beverage augments FMD; 5) despite significantly increasing plasma polyphenols, red wine exerts hemodynamic, sympathoneural, and vascular actions similar to those of ethanol alone; and 6) in contrast to ethanol, red wine increases plasma DA and ACTH concentrations.

Hemodynamic actions of alcohols. There is little information as to the effects of red wine or ethanol in the doses given in the present study on systemic hemodynamics. A dose of ethanol that raised the BAC in normal subjects to 62 ± 7 mg/dl had no

<table>
<thead>
<tr>
<th>Substance</th>
<th>Predrink Mean±SE</th>
<th>After Drink 1 Mean±SE</th>
<th>P1, P2</th>
<th>After Drink 2 Mean±SE</th>
<th>P1, P2</th>
<th>χ²</th>
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</thead>
<tbody>
<tr>
<td>BAC, mg/dl</td>
<td>0±0</td>
<td>38.5±1.9</td>
<td>&lt;0.001</td>
<td>83.3±2.4</td>
<td>&lt;0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>112±4.0</td>
<td>108±4.3</td>
<td>0.08, 0.92</td>
<td>114±4.5</td>
<td>0.65, 0.27</td>
<td>0.19</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>64.3±2.6</td>
<td>64.0±2.1</td>
<td>0.88, 0.22</td>
<td>67.2±3.0</td>
<td>0.24, 0.52</td>
<td>0.75</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>65.5±1.8</td>
<td>68.2±2.0</td>
<td>0.15, 0.27</td>
<td>71.7±2.3</td>
<td>&lt;0.001, 0.005</td>
<td>0.38</td>
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<tr>
<td>SV, ml</td>
<td>76.1±3.2</td>
<td>68.2±3.4</td>
<td>0.04, 0.26</td>
<td>70.9±4.0</td>
<td>0.21, 0.19</td>
<td>0.73</td>
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<td>CO, l/min</td>
<td>5.17±0.20</td>
<td>4.43±0.28</td>
<td>0.008, 0.45</td>
<td>4.89±0.34</td>
<td>0.33, 0.009</td>
<td>0.66</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>30.4±1.3</td>
<td>28.4±1.9</td>
<td>0.24, 0.89</td>
<td>35.6±2.5</td>
<td>0.005, &lt;0.001</td>
<td>0.74</td>
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<tr>
<td>MSNA, bursts/100 beats</td>
<td>46.1±2.3</td>
<td>41.4±2.2</td>
<td>0.056, 0.63</td>
<td>49.6±3.0</td>
<td>0.17, 0.030</td>
<td>0.57</td>
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<td>FMD, mm</td>
<td>15.3±0.69</td>
<td>13.9±0.97</td>
<td>0.20, 0.54</td>
<td>18.8±1.9</td>
<td>0.004, &lt;0.001</td>
<td>0.98</td>
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<tr>
<td>P-E, pmol/l</td>
<td>57±20</td>
<td>100±37</td>
<td>0.56, 0.38</td>
<td>150±22</td>
<td>0.15, 0.86</td>
<td>0.28</td>
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<td>P-NE, nmol/l</td>
<td>1.14±0.25</td>
<td>1.27±0.19</td>
<td>0.88, 0.49</td>
<td>1.20±0.16</td>
<td>0.91, 0.26</td>
<td>0.39</td>
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<tr>
<td>P-DA, pmol/l</td>
<td>28.6±18</td>
<td>33.3±21</td>
<td>0.98, 0.95</td>
<td>16.7±17</td>
<td>0.93, 0.98</td>
<td>0.0001</td>
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<td>P-ANP, pg/ml</td>
<td>45.7±13.6</td>
<td>31.8±4.5</td>
<td>0.27, 0.41</td>
<td>46.0±11.1</td>
<td>0.98, 0.45</td>
<td>0.75</td>
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<td>P-AVP, pmol/l</td>
<td>1.67±0.21</td>
<td>1.00±0.00</td>
<td>0.26, 0.15</td>
<td>1.38±0.18</td>
<td>0.56, 0.46</td>
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<td>P-ACTH, pmol/l</td>
<td>2.13±0.52</td>
<td>1.63±0.38</td>
<td>0.50, 0.99</td>
<td>1.50±0.38</td>
<td>0.40, 0.37</td>
<td>0.04</td>
</tr>
<tr>
<td>P-cortisol, nmol/l</td>
<td>251±43</td>
<td>202±41</td>
<td>0.04, 0.71</td>
<td>214±29</td>
<td>0.12, 0.09</td>
<td>0.61</td>
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<tr>
<td>FMD, mm</td>
<td>0.237±0.040</td>
<td>0.204±0.033</td>
<td>0.54, 0.14</td>
<td>0.211±0.041</td>
<td>0.62, 0.31</td>
<td>0.48</td>
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<td>FMD, %</td>
<td>6.92±1.2</td>
<td>6.09±1.1</td>
<td>0.58, 0.99</td>
<td>5.64±1.0</td>
<td>0.42, 0.16</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 3. Significant P values are in bold.

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effect on CO but increased superior mesenteric and digital skin blood flow (20), whereas a higher dose (BAC 112 ± 4 mg/dl) increased HR, CO, and blood pressure (17). The present observations are in agreement with previous studies demonstrating a fall or no change in blood pressure and a 4–12 beat/min increase in heart rate following acute intake of higher doses (e.g., ≈500 ml) of red wine but not dealcoholized red wine (3, 12, 19, 21). We observed similar dilation of the brachial artery with ethanol and red wine, and similar increases in HR, CO, and MSNA, indicating that alcohol, rather than other red wine constituents, elicits these effects.

**Sympathoneural effects of alcohol.** The present observations concerning MSNA are unique in two respects. First, there are no published data comparing the effects of ingested red wine and ethanol on MSNA in the same person. Second, one standard drink of ethanol or wine did not increase MSNA in our subjects. Thus the concept that ethanol is sympathoexcitatory (31) is based on findings of studies involving higher doses (BACs ranging between 48 and 107 mg/dl) (11, 14, 30).

**Brachial artery dilation.** Several groups have compared the effects of single doses of wine, dealcoholized wine, ethanol, and water on endothelium- or flow-mediated (FMD) and nitrate-mediated dilation (1, 4, 12, 32). All described an alcohol-induced increase in brachial artery diameter, but the reported effects on FMD were not consistent, possibly because of the influence of a higher baseline diameter on the denominator of this ratio. In the present study, one alcoholic drink increased brachial artery diameter, and a further increase was seen after two drinks, but there was no difference in the effects of red wine and ethanol on this response.

Of the polyphenols in red wine, resveratrol appears to have the greatest impact on vascular endothelial nitric oxide synthase activity (27). In the present study, two drinks of wine increased the plasma concentration of resveratrol 4-fold and urinary concentration 27-fold, but the flow-mediated vasodilation after two drinks of wine was significantly less than after two drinks of water. This attenuated vasodilator response cannot be attributed entirely to a reduction in brachial endothelial shear stress (4), because ethanol also diluted the brachial artery yet did not reduce FMD significantly. The key conclusion, therefore, is that the polyphenol constituents of red wine...
do not augment ethanol-induced vasodilation acutely either at rest or in response to a hyperemic stimulus.

Limitations. It is conceivable that the present sample size may have obscured true differences between the acute actions of red wine and ethanol, but it can be argued on the basis of the present paired comparison study design that, if present, these should be quite small and of doubtful biological significance. The report by Randin et al. (26) suggests that further increases in MSNA might have been detected had we continued our recordings for an hour or more after the last drink; however, the protocol had some time constraints imposed by the bladder fullness stimulated by these interventions. Greater vascular or neurohumoral responses might have been elicited by higher oral intake of polyphenols, but these are unlikely to be achieved in a practical way through the medium of red wine as currently produced, and this protocol aimed to replicate normal social use of alcohol.

In conclusion, one drink of alcohol caused conduit artery vasodilation without activating sympathetic outflow, whereas two drinks increased sympathetic nerve firing rate, HR, and CO. Despite the abundant literature describing the potential cardiovascular benefits of polyphenols, and greater increases in plasma DA and ACTH after two wine drinks, there was no evident distinction between the acute cardiovascular actions of red wine and ethanol. The present findings do not exclude the possibility that evidence of such benefit might emerge with chronic red wine consumption.

Increases in HR and sympathetic outflow are well-described risk markers for hypertension, hypothyreosis, heart failure, and cardiovascular death (9, 28). Although it is not possible to infer the chronic actions of alcohol ingestion from this acute dose-response comparison, the narrow dose-response relationships demonstrated may elucidate the J-shaped relationship between alcohol consumption and cardiovascular events observed in population studies.

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REFERENCES