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Effects of wine and grape polyphenols on blood pressure, endothelial function and sympathetic nervous system activity in treated hypertensive subjects

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ABSTRACT

In a randomized double-blind crossover trial, the effect of 8 week supplementation with grape and wine polyphenols on functional and structural vascular parameters and autonomic activity was evaluated in 40 essential hypertensive patients treated with diuretic monotherapy. Ambulatory blood pressure, brachial artery flow mediated dilation (FMD) and pulse-wave velocity (PWV) were measured at baseline and after each 8-week intervention. Forearm resistance artery endothelial function and muscle sympathetic nerve activity (MSNA) response to mental stress and cold-pressor test were measured in two separate subgroups. No statistically significant differences were found across time or between groups in either blood pressure, FMD, PWV, or resistance artery endothelial function. The MSNA response to the two stressors was non-significantly attenuated after grape-wine polyphenol supplementation. These results do not support the hypothesis that daily consumption of a high dose of grape and wine polyphenols lowers blood pressure or affects vascular function in patients already on antihypertensive medication.

1. Introduction

Mediterranean dietary patterns may confer beneficial effects on the progression of cardiovascular disease (CVD) (Sofi, Abbate, Gensini, & Casini, 2010). These diets are particularly rich in polyphenols, which represent secondary plant metabolites purported to mediate these beneficial effects on human health (Rothwell et al., 2013; Vogiatzoglou et al., 2015). Wine is an important component of the Mediterranean diet and is rich in polyphenols. Epidemiological studies demonstrate that moderate wine drinkers show lower mortality rates than non-drinkers (O'Keefe,

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Bhatti, Bajwa, DiNicolantonio, & Lavie, 2014) and potential protective effects of grape derived polyphenols against certain types of cancer, diabetes, obesity and cardiovascular disease have also been reported (Shahidi & Ambigaipalan, 2015). Polyphenols are potent antioxidants and have been shown to have anti-inflammatory and anti-atherogenic properties, such as inhibition of peroxyl radical-induced DNA strand breakage, protection of low density lipoprotein from oxidative damage, and inhibition of platelet aggregation and of the expression of adhesion molecules and of monocytes/macrophages adhesion to the endothelium (de Camargo, Regitano-d'Arce, Biasoto, & Shahidi, 2014; Denny et al., 2014; Dohadwala & Vita, 2009). Moreover, recent work has also suggested that these compounds act as inhibitors of alpha-glucosidase and lipase activity (de Camargo, Regitano-d'Arce, Biasoto, & Shahidi, 2016). Consequently, these properties may contribute to the health benefits of increased polyphenol intake in humans.

Hypertension is one of the primary risk factors for CVD-related morbidity and mortality. Human intervention studies demonstrate that consumption of products rich in grape and wine polyphenols lowers blood pressure, although the data are not entirely consistent (Botden et al., 2012; Chiva-Blanch et al., 2012; Dohadwala et al., 2010; Droste et al., 2013; Mellen, Daniel, Brosnihan, Hansen, & Herrington, 2010; van Mierlo, Zock, van der Knaap, & Draijer, 2010; Ward et al., 2005). The blood pressure lowering effects of grape-derived polyphenols may be mediated by improvement in resistance artery function and/or decreases in peripheral artery vascular tone. For example, studies with wine and grape extracts have demonstrated improved endothelial function in conduit and resistance arteries (Botden et al., 2011; Siasos et al., 2014; Stein, Keevil, Wiebe, Aeschlimann, & Folts, 1999), possibly via nitric oxide dependent pathways (Botden et al., 2011). In addition, studies with tea and cocoa, i.e. prominent sources of dietary polyphenols, found improvement in indirect measures of sympathetic nervous system (SNS) activity patterns, possibly contributing to lowering of peripheral vascular tone (Steptoe et al., 2007; Wirtz et al., 2014).

To date, most previous studies investigating the blood pressure lowering effects of wine and/or grape extracts were conducted in healthy participants or in non-medicated hypertensives (Li, Zhao, Tian, Chen, & Cui, 2015). Such studies poorly translate to the majority of hypertensive patients who typically receive lifelong antihypertensive medication. Accordingly, the objective of the current study was to determine whether 8-week consumption of a polyphenol-rich grape-wine extract mix affects ambulatory blood pressure, endothelial function and muscle sympathetic nerve activity (MSNA) in drug treated patients with essential hypertension. We hypothesized that intake of a high daily dose of polyphenols lowers blood pressure, regardless of antihypertensive medication use, an effect mediated through improvement in resistance artery endothelial function and reduction in MSNA.

2. Methods

2.1. Participants

Fifty-one hypertensive patients on diuretic monotherapy were recruited from the outpatient clinic of the University of Pisa (starting December 2009). Inclusion criteria were office systolic BP values ≥140 mmHg and/or office diastolic BP values ≥90 mmHg, which were confirmed on repeated occasions within one month according to current guidelines, if untreated or controlled (BP <140–90 mmHg) by diuretic therapy (Mancia et al, 2013). Exclusion criteria were as follows: previous cardiovascular or cerebrovascular events, clinically significant arrhythmia, diabetes mellitus, smoking, clinically apparent liver disease or kidney damage, current treatment with statins and/or hormone replacement therapy, reported alcohol consumption >28 units/week. The study protocol was approved by the local ethical committee of University Hospital of Pisa and was in accordance with guidelines in the Declaration of Helsinki. Patients gave their written informed consent to participation in the study after an explanation of its nature and purpose.

2.2. Experimental design

This study adopted a randomized, placebo-controlled, double-blind crossover design with two 8-week intervention periods. At an initial screening visit, eligible patients were given dietary advices for a standard Mediterranean diet and informed to drink no more than two units of alcohol per day. Moreover, the patients were instructed to moderate their intake of polyphenol-rich products throughout the study (less than two daily cups of coffee and/or tea; avoid dark chocolate and red wine). For the 48-h preceding the experimental days, subjects were instructed to avoid consumption of all polyphenol-rich foods in order to fully exclude the impact of background dietary polyphenols.

Following a 4-week run-in period, patients were randomly allocated to either grape-wine extract or placebo treatments. After an 8-week intervention, patients were crossed over to the other treatment. The diuretic dose was kept stable throughout the run-in and intervention periods. Measurements were performed on three different occasions, at baseline and immediately after each 8-week treatment period. Invasive measurements (forearm resistance vessel endothelial function and muscle sympathetic nerve activity) were conducted before and after the first 8-week intervention period only. Therefore, data on these measures are available in two different subsets of the study population (Fig. 1).

2.3. Intervention

The grape-wine extract mix comprised 870 mg of red wine extract (Provinols™; Seppic, Puteaux, Cedex, France) and 540 mg grape juice extract (MegaNatural™ Rubired; Polyphenolics, Heber City, UT, USA). The total polyphenol content of the extract mix amounted to 800 mg (defined as gallic acid equivalents): 550 mg from the wine extract and 250 mg from the grape juice extract.

The polyphenol composition of the red wine and grape juice extracts was determined in duplicate by means of high-performance liquid chromatography with diode array detection (HPLC-DAD) and HPLC with electrospray ionization mass spectrometry (HPLC-ESI-MS) using an Agilent (Palo Alto, CA, USA) HPLC series 1100 equipped with ChemStation software as previously reported (van Dorsten et al., 2010). For determination of anthocyanins a mobile phase consisting of water, formic acid and acetonitrile and a Betasil C18 column (Thermo Scientific,