

tween advertisement placement and readership. It may be that 84% of alcohol advertising is seen by readers older than 21 years. Our analysis suggests that the remaining 16% of alcohol advertising seen by adolescents is more than what would be expected by chance if advertisements were placed only as a function of adult readership.

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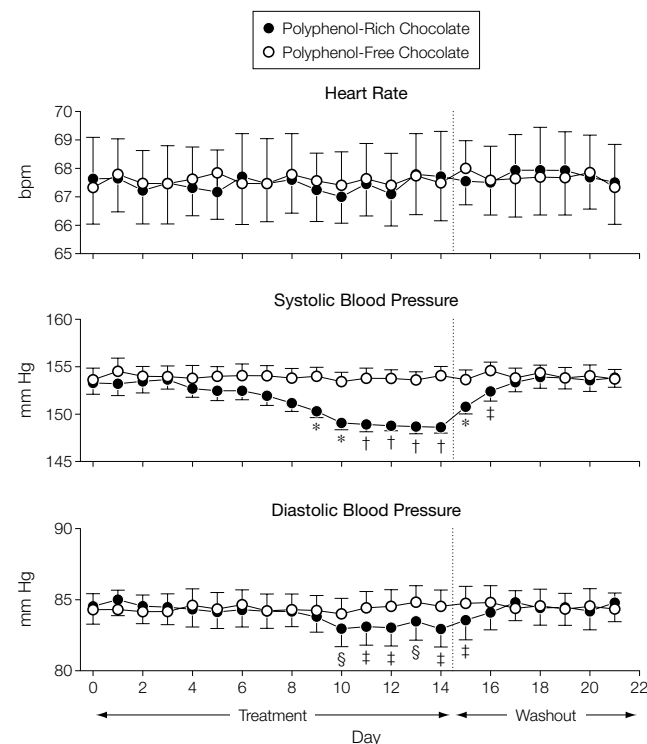
RESEARCH LETTERS

Chocolate and Blood Pressure in Elderly Individuals With Isolated Systolic Hypertension

To the Editor: Chocolate may have beneficial cardiovascular effects, possibly due to cocoa polyphenols.¹ Experiments in animals suggest that plant polyphenols decrease blood pressure (BP)²; however, evidence from human clinical trials is lacking. We examined whether dark chocolate (polyphenol-rich chocolate [PRC]) may lower BP in individuals with mild isolated hypertension.

Methods. We conducted a randomized crossover trial in 13 otherwise healthy individuals (6 men and 7 women, aged 55-64 years, with body mass index of 21.9-26.2 [calculated as weight in kilograms divided by the square of height in meters]) with recently diagnosed and untreated stage 1 mild isolated systolic hypertension (mean [SD] systolic BP, 153.2 [3.9] mm Hg; mean [SD] diastolic BP, 83.8 [3.5] mm Hg). After a cocoa-free run-in phase of 7 days, participants were randomly assigned to receive 14 consecutive daily doses of either 100-g dark PRC bars containing 500 mg of polyphenols and 480 kcal of energy (Ritter Sport Halbbitter, Alfred Ritter, Waldenbuch, Germany), or 14 days of 90-g white chocolate (polyphenol-free chocolate [PFC]) bars that also contained 480 kcal and similar amounts of cocoa butter, macronutrients, fiber, electrolytes, and vitamins (Milka Weisse Schokolade, Kraft Foods, Bremen, Germany). After a cocoa-free washout phase of 7 days, participants were crossed over to the other condition. Participants were asked to substitute the chocolate bars for foods of similar energy and macronutrient composition. Overall diet during the study period was assessed by reports of daily food intake and by measurement of body weight, plasma concentrations of lipids and glucose, and urinary excretion of sodium, potassium, and nitrogen at the run-in phase and after each intervention period.

Figure. Time Course of Mean Blood Pressure and Heart Rate During a 14-Day Diet With PRC or PFC and a Subsequent 7-Day Washout Period



* $P < .05$; † $P < .001$; ‡ $P = .04$; and § $P = .03$, indicating significant differences in blood pressure between diets with polyphenol-rich or polyphenol-free chocolate, adjusted to a baseline blood pressure difference of zero (paired 2-tailed t tests, individual P values are adjusted for multiple comparisons by the method of Holm). All other P values are $> .05$. Error bars indicate SEM.

The BP was recorded daily, in a blinded fashion, with participants in a seated position, 12 hours post-dose, in the left upper arm with a validated oscillometer (Omron HEM 722C, Omron, Mannheim, Germany). A systolic BP of more than 170 mm Hg or a diastolic BP of more than 100 mm Hg at a single visit was necessary for referral for antihypertensive pharmacological treatment. At the end of the study participants were referred to their physician for further monitoring and management of BP. We received approval for our study from the ethics committee of the Medical Faculty of the University of Cologne; all participants gave written informed consent.

Results. Participants had significantly lower systolic and diastolic BPs within 10 days of beginning PRC, but this effect was not seen during the PFC period (FIGURE). At the end of the 14-day PRC intervention, mean (SD) systolic BP had declined by 5.1 (2.4) mm Hg ($P < .001$; paired 2-tailed t test) and mean (SD) diastolic BP by 1.8 (2.0) mm Hg ($P = .002$; paired 2-tailed t test) compared with PFC. After discontinuation of PRC consumption, BP returned to preintervention values within 2 days. Heart rate was not affected by either treatment. There were no sex differences in the effects of chocolate on BP. None of the participants reached the pre-

defined threshold that would have required antihypertensive drug therapy. Daily energy intake and macronutrient composition remained stable throughout the study. Body mass index, 24-hour urinary excretion of sodium, potassium, and total nitrogen, as well as fasting plasma concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose were not significantly different between the run-in phase and the postintervention periods.

Comment. A calorie-balanced increase in consumption of dark chocolate may favorably affect BP in previously untreated elderly hypertensive individuals. Control meals using PFC differed from PRC meals only by the lack of cocoa solids. Plant polyphenols are major constituents of the cocoa solids,³ have significant bioavailability,⁴ and appear to be responsible for the reductions in BP. The long-term clinical effects, however, remain unknown.

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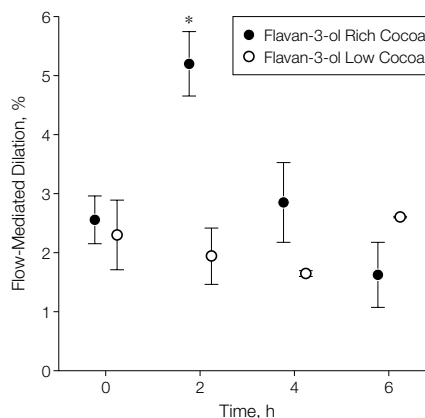
Vascular Effects of Cocoa Rich in Flavan-3-ols

To the Editor: In vitro studies have suggested that flavonoids may have specific vascular effects, but their mechanism of action has not been clarified.¹ A subclass of flavonoids—flavan-3-ols and their oligomers (procyanidins)—are constituents of cocoa beans, which can be detected in human plasma after ingestion of cocoa.² In turn, plant extracts rich in flavan-3-ols can increase the activity of nitric oxide synthase (NOS) in endothelial cells.³ Nitric oxide is an essential signaling molecule in vascular physiology. Nitric oxide bioactivity can be preserved in human plasma in a circulating pool via increases in a number of nitrosated compounds.^{4,5} Thus, it is possible that cocoa rich in flavan-3-ols may lead to improved endothelium-dependent dilation via an increase of nitric oxide bioactivity.

However, commercially available cocoa drinks contain only small amounts of flavan-3-ols due to roasting and alkalization of cocoa beans, which are known to degrade flavan-3-ols. We tested the hypothesis that ingestion of flavan-3-ol rich cocoa can increase the circulating pool of nitric oxide in human plasma, thus increasing endothelium-dependent dilation.

Methods. Participants were 26 outpatients with at least 1 cardiovascular risk factor, including history of coronary artery dis-

Figure 1. Time Course of Flow-Mediated Dilation After Ingestion of 100 mL of Cocoa Drink Containing High (176 mg mL; n=6) or Low (<10 mg mL; n=3) Amounts of Flavan-3-ols



Data given as mean (SEM). *Indicates significant difference from baseline ($P < .001$).

ease, hypertension, hyperlipidemia, diabetes, or current tobacco use. Individuals were excluded if they had C-reactive protein levels greater than 0.5 mg/dL, atrial fibrillation, acute coronary syndrome, or New York Heart Association class III or IV heart failure. Individuals were studied in the morning after a 12-hour fasting period.

In an initial study involving the first 6 participants, we assessed the time course of flavan-3-ol effects on flow-mediated dilation (FMD). This was measured at 0, 2, 4, and 6 hours after ingestion of 100 mL of cocoa drink containing 176 mg of flavan-3-ols (70 mg of epicatechin plus catechin, 106 mg of procyanidins [The Positive Food Co, Wokingham, England]) (n=6) or control (100 mL cocoa drink with <10 mg of flavan-3-ols [Dovedrink, Mars Inc, Hackettstown, NJ] or water) (n=3).

We then used these results to guide the timing of a double-blind crossover study. Twenty participants received 100 mL of cocoa drinks with high or low levels of flavan-3-ols, in random order, on 2 consecutive days. The sum of nitrosylated and nitrosated species (collectively referred to as RNO) was measured by reductive chemiluminescence assay 2 hours after ingestion on both days.⁴ Nitrate and nitrite levels were measured as previously described.⁶ Endothelium-dependent dilation was assessed by measuring FMD of the brachial artery. In addition, we measured a number of other vascular parameters that would not be expected to change as a result of flavan-3-ol, including blood pressure, heart rate, and plasma levels of nitrite and nitrate. Similarly, we measured endothelium-independent dilation of the brachial artery following sublingual application of 400 µg of glyceroltrinitrate, diameter of the brachial artery, and forearm blood-flow at rest and during reactive hyperemia, as assessed by venous occlusion plethysmography. (Technical details are available from the authors.)

All variables except endothelium-independent dilation were measured both before and after ingestion of the cocoa. Endo-