Effects of Pomegranate Juice Consumption on Myocardial Perfusion in Patients With Coronary Heart Disease

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Pomegranate juice contains antioxidants such as soluble polyphenols, tannins, and anthocyanins and may have antiatherosclerotic properties. However, no study has investigated the effects of pomegranate juice on patients who have ischemic coronary heart disease (CHD). We investigated whether daily consumption of pomegranate juice for 3 months would affect myocardial perfusion in 45 patients who had CHD and myocardial ischemia in a randomized, placebo-controlled, double-blind study. Patients were randomly assigned into 1 of 2 groups: a pomegranate juice group (240 ml/day) or a placebo group that drank a beverage of similar caloric content, amount, flavor, and color. Participants underwent electrocardiographic-gated myocardial perfusion single-photon emission computed tomographic technetium-99m tetrofosmin scintigraphy at rest and during stress at baseline and 3 months. Visual scoring of images using standardized segmentation and nomenclature (17 segments, scale 0 to 4) was performed by a blinded independent nuclear cardiologist. To assess the amount of inducible ischemia, the summed difference score (SDS) was calculated by subtracting the summed score at rest from the summed stress score. The experimental and control groups showed similar levels of stress-induced ischemia (SDS) at baseline ($p > 0.05$). After 3 months, the extent of stress-induced ischemia decreased in the pomegranate group (SDS -0.8 ± 2.7) but increased in the control group (SDS 1.2 ± 3.1, $p < 0.05$). This benefit was observed without changes in cardiac medications, blood sugar, hemoglobin A1c, weight, or blood pressure in either group. In conclusion, daily consumption of pomegranate juice may improve stress-induced myocardial ischemia in patients who have CHD. **(Am J Cardiol 2005;96:810–814)**

Pomegranate juice may have antiatherosclerotic properties in mice and humans.[1] It contains antioxidants such as soluble polyphenols, tannins, and anthocyanins[2] and may decrease carotid artery intima-media thickness after 1 year in humans.[3] However, the effects of pomegranate juice on ischemic coronary heart disease (CHD) are unknown. We evaluated the effects of daily consumption of pomegranate juice or a placebo for 3 months on myocardial perfusion in patients who had CHD and inducible ischemia as measured by single-photon emission computed tomography in a randomized double-blind study.

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Methods

Participants: The research protocol received approval from the institution review board and written informed consent was obtained from participants before entering the study. Forty-five patients who had stable CHD were enrolled. All were confirmed to have stress-induced ischemia that was documented by ≥1 reversible myocardial perfusion defect on single-photon emission computed tomographic technetium-99m tetrofosmin scintigraphy and confirmed by an independent observer. Patients were excluded from participating for any of the following reasons: a history of debilitating stroke or transient ischemic attack, myocardial infarction during the preceding 6 weeks, surgically untreated left main coronary artery lesion with >50% diameter narrowing, coronary revascularization procedure during the preceding 6 months, current unstable angina pectoris, abnormal lung uptake on previous scintigram or positron emission tomogram, class IV congestive heart failure, or ejection fraction <30% at time of study entry, significant co-morbidity, current use of tobacco products, or alcohol or drug abuse.

Randomization and blinding: Eligible patients were randomly assigned identification numbers without stratifi-

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cation or blocking in sealed envelopes by 1 investigator who had no contact with patients. Those who administered the intervention and those who assessed the outcomes were blinded to group assignment.

Intervention: Subjects in the experimental group drank 240 ml/day of pomegranate juice (POM Wonderful, Los Angeles, California). Those in the placebo group drank a modified sports beverage of similar caloric content, amount, flavor, and color.

Risk factors: Risk factors were measured at baseline and 3 months. Blood pressure at rest was measured by a trained health professional who used a calibrated sphygmomanometer in a sitting position after 5 minutes of rest and ≥30 minutes of no food or caffeine (average of 3 measurements). Venous blood was obtained after a 12-hour fast for determination of lipid profiles, glucose, and hemoglobin A1c.

Myocardial perfusion imaging: Patients underwent radionuclide exercise treadmill or pharmacologic (adenosine or dipyridamole) stress testing by gated, single-isotope myocardial perfusion single-photon emission computed tomography using technetium-99m tetrofosmin (Myoview, GE Healthcare, Princeton, New Jersey). One sublingual metered 0.4-mg nitroglycerine spray was given before administration of the radiotracer. Ten millicuries of technetium-99m Myoview was injected within 5 minutes of the administration of nitroglycerin. Images at rest were obtained after ≥25 minutes and consumption of a small quantity of water. The second injection of 31 mCi of technetium-99m Myoview was administered at peak exercise (1 to 2 minutes before completion of the treadmill test), at the midway (3-minute) point in the adenosine test, or 2 minutes after dipyridamole infusion. Images during stress were obtained 25 to 30 minutes after the second administration of the radiotracer.

All patients who were capable of undergoing a treadmill test exercised on the Welch Allyn Cardioperfect treadmill system (Welch Allyn, Inc., Skaneateles Falls, New York) according to a multistage or a modified Bruce's protocol. Blood pressure was measured with a sphygmomanometer every 2 minutes during exercise. The electrocardiogram was recorded continuously during the exercise phase and for up to 10 minutes during recovery with the standard 12 leads and 3 right precordial leads (V_3R, V_4R, and V_5R). The results of each set of leads were recorded and analyzed separately. Exercise was terminated when the patient achieved maximum predicted heart rate or whenever a patient had severe angina, fatigue, dyspnea or arrhythmias; 3-mm ST-segment depression; 2-mm ST-segment elevation; or a decrease ≥20 mm Hg in systolic blood pressure.

For patients who were unable to perform a treadmill exercise test, a pharmacologic stress test using adenosine or dipyridamole was performed. For adenosine, the dose was calculated at 0.28 mg of adenosine per kilogram of body weight and administered through a computerized pump at a constant rate over a 6-minute period. For dipyridamole, the dose was calculated at 0.57 mg of dipyridamole per kilogram of body weight and administered at a constant rate over 4 minutes. After radiotracer administration, 100 mg of aminophylline was given. Blood pressure in the pharmacologic stress test was measured in the same fashion as exercise treadmill testing. Infusion was terminated early for severe angina, severe dyspnea, arrhythmias, significant pauses, or ST-segment changes accompanied by severe discomfort at the discretion of the attending cardiologist.

All images were acquired with the ADAC Genesys single-head gamma camera (GE Healthcare) using a photopeak of 140 keV and a 20% window. The detector head was fitted with a low-energy, high-resolution parallel-hole collimator. The camera was started at a position 45° to the right of the patient and followed a 180° circular orbit to the left and around the patient's chest, with the heart in the field of view.

The camera acquired 32 images at 5.625° per stop. Each image in the study at rest was acquired at 30 seconds per view. The stress images were gated for 8 frames per view at 20 seconds of gated data per stop. Patients were imaged in the supine position, with the left arm elevated out of the field of view, and in the prone position as needed. Processing was done with the ADAC Pegasys computer workstation. Projection files were processed with a Butterworth filter using a cutoff of 0.40 and an order of 5. Images were corrected for motion artifact, displayed using a standard display format, and printed. The AutoQuant program (AutoQuant Imaging, Inc., Troy, New York) was used to display the images and gated study in cine mode so that an ejection fraction could be calculated and any additional measurements that were desired by the reader.

Beta blockers, angiotensin-converting enzyme inhibitors, calcium antagonists, and nitrates were withheld for 24 hours before stress testing. Patients were instructed to avoid caffeine consumption for 24 hours before testing. The baseline testing procedure was replicated at 3 months, with the same stressor (exercise protocol or pharmacologic stress test) and dose of radiotracer. The exercise stress test was terminated when the patient achieved the preintervention rate–pressure product.

A semiquantitative scoring method was used to analyze radiotracer uptake in 17 myocardial segments for each subject. For each segment, a 5-point scoring system was used to describe technetium-99m tetrofosmin uptake (0 = normal uptake to 4 = absent uptake). Scores were recorded through visual analysis of each myocardial segment by an experienced nuclear medicine physician who was blinded to clinical status and experimental condition and validated by a second reader. A summed stress score and a summed rest score were calculated by adding the scores of the 17 segments of single-photon emission computed tomographic images at rest and during stress, respectively. A summed difference score (SDS) was derived as the difference between the summed stress and summed rest scores. The SDS,

Table 1
Patient characteristics at baseline

Variable	Pomegranate Juice (n = 26)	Placebo (n = 19)
Age (yrs)	69 ± 11	69 ± 9
Men	22 (85%)	18 (95%)
White	23 (89%)	16 (84%)
Diabetes mellitus	5 (19%)	6 (32%)
Previous myocardial infarction	8 (31%)	11 (58%)
Hypertension	16 (62%)	11 (58%)
Hyperlipidemia*	25 (96%)	19 (100%)
Body mass index (kg/m^2)	28 ± 6	29 ± 5
Systolic blood pressure (mm Hg)	130 ± 13	127 ± 13
Diastolic blood pressure (mm Hg)	72 ± 11	77 ± 10
Total cholesterol (mg/dl)	168 ± 42	170 ± 36
High-density lipoprotein (mg/dl)	49 ± 14	46 ± 10
Low-density lipoprotein (mg/dl)	91 ± 33	92 ± 33
Triglycerides (mg/dl)	138 ± 98	155 ± 95
Hemoglobin A1c (%)	5.9 ± 1.2	6.1 ± 1.7
Glucose (mg/dl)	113 ± 30	116 ± 51
Medication		
Angiotensin-converting enzyme inhibitors	11 (42%)	8 (42%)
Anticoagulants	23 (89%)	19 (100%)
Antihypertensives	10 (39%)	7 (37%)
β Blockers	16 (62%)	15 (79%)
Calcium channel blockers	7 (27%)	7 (37%)
Diabetic agents	4 (15%)	5 (26%)
Diuretics	8 (31%)	5 (26%)
Lipid-lowering agents	26 (100%)	19 (100%)
Nitrates	9 (35%)	6 (32%)

Values are as mean ± SD or numbers of patients (percentages). There were no statistically significant differences in any measurement.

* Hyperlipidemia was defined as a low-density lipoprotein cholesterol level >100 mg/dl, a high-density lipoprotein cholesterol level ≤40 mg/dl, or a triglyceride level ≥200 mg/dl (National Cholesterol Education Program guidelines, Adult Treatment Panel III, for patients who have CHD).

a measurement of inducible myocardial ischemia, predicted myocardial infarction in a large prospective study of patients who have CHD.[4]

Statistical analyses: Between-group comparisons of baseline demographic, medical, and psychosocial factors were performed with 2-sample *t* tests (for continuous variables) and chi-square tests (for categorical variables). To test for the effects of experimental condition and time (and their interaction) on medical characteristics, 2 (experimental vs placebo) × 2 (baseline vs 3 months) analyses of variance for repeated measurements were run. Statistical analyses were performed using SPSS 12.0 (SPSS, Inc., Chicago, Illinois).

Results

At baseline, there were no statistically significant differences between groups with respect to age, demographic characteristics, clinical status, risk factors, or medications (Table 1). Participants in the experimental and placebo control groups reported drinking the beverage 97% and 96% of the time, respectively. One elderly subject in each group dropped out of the study due to multiple co-morbidities before 3-month testing could be conducted, and 2 patients (1 in the experimental group and 1 in the control group) had unreadable perfusion tests.

At baseline, the 2 groups showed similar levels of inducible ischemia (SDS). After 3 months, the extent of stress-induced ischemia decreased in the experimental group but increased in the control group ($F[1,37] = 4.22$, $p < 0.05$; Table 2). This benefit was observed without changes in cardiac medications or revascularization in either group. Also, there were no significant changes in plasma lipids, blood glucose, hemoglobin A1c, body weight, or blood pressure during the study (Table 3). There was no significant change in the summed stress or summed rest score in the experimental group, suggesting that the relative improvement in the SDS was due to decreased ischemia rather than to infarction of jeopardized myocardium. Angina episodes decreased by 50% in the experimental group (from 0.26 to 0.13) but increased by 38% in the control group (from 0.53 to 0.75), although this difference was not statistically significant.

No patient in the experimental group had a clinical event as a direct result of the intervention. There was 1 suspected silent myocardial infarction reported in a patient who was on long-term steroid therapy in the experimental group and 1 nontransmural myocardial infarction in the control group. One patient in the intervention group was hospitalized for a syncopal event with subsequent pacemaker insertion 3 days after study entry. Two patients in the intervention group were hospitalized overnight within 1 month of study entry: 1 for observation of angina pectoris and 1 for a diagnostic angiogram. One patient in each group developed rhabdoid myalgia after being prescribed statin medications, and these were discontinued. One patient in the control group was diagnosed with prostate cancer.

Table 2
Single-photon emission computed tomography of myocardial perfusion

	Pomegranate Juice (n = 23)	Placebo (n = 16)
Summed rest score		
Baseline	1.9 ± 2.6	3.8 ± 4.7
At 3 mo	2.2 ± 2.9	3.1 ± 3.9
Summed stress score		
Baseline	6.4 ± 3.5	9.6 ± 6.5
At 3 mo	6.0 ± 4.3	10.2 ± 7.9*
SDS		
Baseline	4.5 ± 3.1	5.9 ± 4.3
At 3 mo	3.7 ± 3.7	7.1 ± 5.5†

Data are presented as mean ± SD.

* $p < 0.05$, main effect among groups, 2-way analysis of variance.

† $p < 0.05$, interaction among study time points and groups, 2-way analysis of variance.

Table 3
Anthropometric characteristics and serum profile

Variable	Pomegranate Juice	Placebo
Weight (lbs)		
Baseline	187 ± 36	199 ± 37
At 3 mo	187 ± 34	202 ± 39
Systolic blood pressure (mm Hg)		
Baseline	131 ± 13	128 ± 13
At 3 mo	130 ± 15	126 ± 25
Diastolic blood pressure (mm Hg)		
Baseline	73 ± 10	77 ± 10
At 3 mo	70 ± 12	72 ± 11
Total cholesterol (mg/dl)		
Baseline	166 ± 41	171 ± 36
At 3 mo	170 ± 42	157 ± 32
High-density lipoprotein (mg/dl)		
Baseline	49 ± 14	47 ± 10
At 3 mo	48 ± 11	46 ± 12
Low-density lipoprotein (mg/dl)		
Baseline	91 ± 33	92 ± 33
At 3 mo	91 ± 33	80 ± 35
Triglycerides (mg/dl)		
Baseline	130 ± 91	157 ± 97
At 3 mo	149 ± 107	155 ± 102
Hemoglobin A1c (%)		
Baseline	5.92 ± 1.27	6.11 ± 1.70
At 3 mo	5.81 ± 0.92	6.24 ± 1.94
Glucose (mg/dl)		
Baseline	113 ± 30	117 ± 52
At 3 mo	116 ± 31	121 ± 63

Data are presented as mean ± SD. There were no statistically significant differences in any of these measurements.

Discussion

The results of this study demonstrate, for the first time, that daily consumption of pomegranate juice for 3 months may decrease myocardial ischemia and improve myocardial perfusion in patients who have ischemic CHD as measured by the SDS. This effect occurred without change in perfusion abnormalities at rest as measured by the summed rest score. The clinical significance of this finding is further illustrated by an average improvement of 17% in myocardial perfusion in the experimental group and an average worsening of 18% in the control group (i.e., a 35% relative between-group difference) after only 3 months. Also, there were no negative effects on lipids, blood glucose, hemoglobin A1c, body weight, or blood pressure.

Dietary supplementation with polyphenolic antioxidants inhibits low-density lipoprotein oxidation and macrophage foam cell formation and attenuates development of atherosclerosis in animals.[5,6] The antioxidative and antiatherogenic characteristics of pomegranate juice also occur in atherosclerotic apolipoprotein E–deficient (E^0) mice.[1] Pomegranate juice is rich in polyphenols and demonstrates high capability in scavenging free radicals and inhibiting low-density lipoprotein oxidation in vitro and in vivo.[2,7,8]

Our findings are consistent with results reported by others who have demonstrated beneficial effects of beverages high in polyphenols. For example, purple grape juice may decrease platelet aggregation, increase platelet-derived nitric oxide release, and decrease superoxide production.[9] Red wine may increase endothelial function.[10] However, neither grape juice nor red wine has been shown to improve myocardial ischemia in humans who have CHD.

Although the sample in this study was relatively small, the strength of the design and the clinically significant and statistically significant improvements in myocardial perfusion observed in the experimental group over a rather short period suggest that daily consumption of pomegranate juice may have important clinical benefits in this population. In a recent study of 2,686 patients, the best predictor of nonfatal myocardial infarction was the amount of ischemia as indicated by the SDS.[4]

Further studies appear to be warranted to determine the effects of pomegranate juice on myocardial perfusion in a larger sample of patients over a longer period. In addition, it would be of interest to assess the effects of pomegranate juice on coronary atherosclerosis using methods such as quantitative coronary arteriography and intravascular ultrasound.

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