 Influence of Altered Blood Rheology on Ventricular-Vascular Response to Exercise

James E. Sharman, Joseph Brown, David J. Holland, Graeme Macdonald, Karam Kostner, Thomas H. Marwick

Abstract—Blood (or plasma) rheology is related to cardiovascular risk. Mechanisms of this association are unclear but may be partially related to impaired left ventricular (LV) function and increased central blood pressure (BP) during light activity. This study aimed to test these hypotheses. Twenty patients (14 men; aged 61 ± 12 years) with polycythemia rubra vera (n = 16) or hemochromatosis (n = 4) were studied at rest and during exercise at ~50% of maximal heart rate before and after venesection (500 mL; volume replaced with saline) to elicit an acute decrease in plasma viscosity at stable BP. Controls (n = 20) underwent the same protocol with 25-mL venesection. Central BP and augmentation index were determined by tonometry. Resting LV systolic (peak longitudinal systolic strain rate and strain) and diastolic functions were determined by tissue-Doppler echocardiography. Venesection with blood volume replacement decreased viscosity (1.46 ± 0.10 to 1.41 ± 0.11 centipoise), protein, and hemoglobin (P < 0.05 for all) and increased strain rate and strain (P < 0.001 for both) in patients but not in controls (P > 0.10 for all). There was no change in LV diastolic function (P > 0.12 for all). Exercise augmentation index in patients was reduced after venesection (24 ± 12% to 17 ± 9%; P = 0.001) despite no significant change in other BP variables. Hemodynamics (resting or exercise) were not significantly changed in controls. Exercise central systolic BP correlated with triglycerides (r = 0.59; P < 0.001). However, neither exercise hemodynamic changes nor LV functional changes correlated with any biochemical changes after venesection (P > 0.05). We conclude that an acute change in blood rheology improves ventricular-vascular interaction by enhanced LV systolic function and reduced light-exercise central BP. (Hypertension. 2009;54:1092-1098.)

Key Words: blood pressure ■ hemodynamics ■ blood viscosity ■ heart ventricles ■ exercise

Several studies have demonstrated associations between blood rheological variables (eg, fibrinogen, hematocrit, blood, and plasma viscosity) and cardiovascular risk factors, including elevated blood pressure (BP),1 raised carotid intima media thickness,2 increased aortic pulse wave velocity,3 incident hypertension,4 incident cardiovascular disease,5 and vascular and nonvascular mortality.6 Few studies have investigated the possible mechanisms behind these associations. Recent data suggest that studying the central (ascending aortic) BP response to exercise may reveal important information relating to left ventricular (LV) function and cardiovascular risk that would otherwise be undetectable under resting conditions.7 This could be because of the large individual variations that may exist between brachial and central systolic BPs (SBP) during exercise.8 These changes can be seen even with light-intensity activity, similar to that of daily life.9,10 Thus, “true” LV afterload may be significantly different between individuals with similar brachial SBP during physical activity.

Using radial tonometry to estimate central BP from arterial waveforms, we found recently that men with hypercholesterolemia had significantly elevated augmentation index (AIx) and blunted pulse pressure amplification (ratio of brachial: central pulse pressure) during light exercise.11 This was representative of increased central systolic loading (possibly affecting normal LV function) and occurred despite similar brachial SBP compared with controls. We hypothesized that this abnormal response may be related to plasma rheology, including factors such as increased viscosity, which may retard peripheral blood runoff and increase exercise AIx. The aim of this current study was to determine the effect of an acute change in plasma rheology (by 500-mL venesection and replacement of blood with normal saline to maintain stable BP and large artery stiffness) on exercise central hemodynamics and LV function. The intervention was expected to improve central BP during exercise and resting LV function.

Received April 30, 2009; first decision May 15, 2009; revision accepted August 11, 2009.

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DOI: 10.1161/HYPERTENSIONAHA.109.135525
Table 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n=20)</th>
<th>Patients (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33±10</td>
<td>61±12</td>
<td>&lt;0.001</td>
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<tr>
<td>Height, cm</td>
<td>174±6</td>
<td>172±7</td>
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</tr>
<tr>
<td>Weight, kg</td>
<td>71±12</td>
<td>85±19</td>
<td>0.009</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.5±3.0</td>
<td>28.8±5.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>9 (45)</td>
<td>6 (30)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Data are mean±SD unless otherwise specified.

Methods

Subjects

The intervention population was composed of patients who were regularly venesected (ie, every 3 to 6 months) as part of their usual medical care for either polycythemia rubra vera (n=16) or hemochromatosis (n=4). Control subjects (n=20) were recruited from the community and hospital staff. All of the subjects were otherwise healthy. Exclusion criteria included a history of coronary artery disease or any condition that may be aggravated by exercise (acute myocardial infarction, unstable angina before a period of stabilization, uncompensated severe congestive heart failure, advanced atrioventricular block or life-threatening arrhythmias, acute myocarditis or pericarditis, ejection fraction <40%, severe aortic stenosis, or severe resting hypertension). Characteristics of the study population are shown in Table 1. Procedures were carried out in accordance with the Declaration of Helsinki (2000). The research was approved by the Princess Alexandra Hospital Human Research Ethics Committee, and participants provided informed consent.

Study Protocol

Participants attended the hospital in the morning after an overnight fast on one occasion (Figure 1). During this visit, participants underwent a cardiovascular testing procedure in which resting and exercise data were recorded (preintervention data). The testing procedure was then repeated after venesection (postintervention data). The following measures were recorded in the supine resting state: brachial and aortic pulse wave velocity (as indices of large artery stiffness), echocardiography (for LV function), and brachial and central BPs. Participants then performed light exercise for ~10 minutes at ~50% of age-predicted maximal heart rate on an upright bicycle ergometer. Both brachial and central BPs were recorded during exercise. Approximately 20 minutes after exercise (ie, approximately the same time period for the patients to be venesected), a 25-mL sample of blood was drawn from each of the control participants. After a further 20-minute rest period, the above resting and exercise protocol was repeated in the controls, including another 25-mL sample of blood at the conclusion of the second bout of light exercise. The patient population, on the other hand, had 500 mL of blood venesected at the conclusion of the first exercise bout (25 mL of this sample was stored for analysis and baseline comparison with the controls). The 500-mL blood draw was chosen on the basis that this is the typical venesecution volume to obtain a reduction in plasma viscosity, hematocrit, and iron levels in the patient populations. Blood volume was replaced with 500 mL of normal saline with the aim of eliciting an acute decrease in plasma viscosity but keeping BP stable (this process aimed to take approximately the same time as the 40-minute rest period given to the controls). Patients then repeated the resting and light-exercise protocol and had a further 25-mL sample of blood drawn at the conclusion of the second exercise bout. The 25-mL blood samples were used to measure blood biochemistry before and after intervention.

Brachial and Central BPs

Supine and light-exercise brachial BPs were recorded by mercury sphygmomanometer in duplicate and the results averaged according to guidelines.12 Central BP was estimated by hand-held radial applanation tonometry at rest or using a servo-controlled device (Colin CBM-7000; Colin Corp) during exercise. In both cases, a generalized transfer function with customized software (SphygmoCor 7.01; AtCor Medical) was used to derive a central BP waveform. We have shown this methodology to be valid13 and reproducible during exercise.14 From these exercise data we calculated that the study would have 92% power to detect a 15% difference in exercise pulse pressure amplification (mean±SD: 1.45±0.20)14 with 20 participants per group and α at 0.05. Brachial SBP and diastolic BP were used to calibrate the radial pressure waveform. Mean arterial pressure was derived by integration of the radial pressure waveform.

Large Artery Stiffness

ECG-gated sequential applanation tonometry of the carotid to femoral arteries (for aortic pulse wave velocity) and the carotid to radial arteries (for brachial pulse wave velocity) were recorded during supine rest using commercial equipment (SphygmoCor 7.01) as measures of regional artery stiffness.15 The time to the first inflection point on the central pressure waveform was recorded as a surrogate marker of aortic stiffness.16 A marker of systemic arterial stiffness was estimated by the AIx on the central waveform, which was calculated as follows: (P2−P1/pulse pressure)×100, where P2 and P1 indicate the pressure at the second and first systolic inflection points, respectively.17 The augmented pressure was defined as P2−P1. We and others have shown these tonometric techniques to have good reproducibility.14,18 Pulse pressure amplification was also calculated (ratio of brachial:central pulse pressure) as an indicator of large artery stiffness.19

Echocardiography

All of the participants underwent transthoracic echocardiography with a 2.5-MHz phased array probe using commercially available equipment (Vivid 7; GE Medical Systems). Color-coded tissue...
Doppler images were used to extract LV strain and strain-rate curves with peak systolic longitudinal strain and strain rate (SR) measured offline by a single blinded observer (Echopac; GE VingMed) and reported as the average of 6 basal segments. LV strain is a measure of tissue deformation analogous to ejection fraction, whereas SR quantifies the velocity of myocardial deformation and is an analogue of LV contractility. LV end-diastolic volume, end-systolic volume, and ejection fraction were recorded from the apical 4- and 2-chamber views using the Simpson’s biplane method, as per the American Society of Echocardiography guidelines. Left atrial area was measured from the apical 4-chamber view at end systole. Doppler interrogation of the mitral inflow was used to measure the early diastolic deceleration time as well as early (E) and late (A) mitral inflow velocities. Pulse wave Doppler of the septal mitral annulus was used to measure the peak systolic tissue velocity and the early diastolic tissue velocity (Em). LV filling pressures were estimated by the ratio of E:Em. Stroke volume was obtained in accordance with LV contractility, LV end-diastolic volume, and systolic volume, and ejection fraction were recorded from the apical 4- and 2-chamber views using the Simpson’s biplane method, as per the American Society of Echocardiography guidelines. Cardiac output was calculated as stroke volume×heart rate. Peripheral vascular resistance was defined as mean arterial pressure/cardiac output and expressed as peripheral resistance units. Total arterial compliance was calculated by the ratio of stroke volume:central pulse pressure. Effective arterial elastance was determined by the ratio of end systolic pressure:stroke volume. The pressure variables for these calculations were acquired from the derived central pressure waveform.

**Blood Biochemistry**

Assays for plasma viscosity, lipids, protein, hemoglobin, hematocrit, and red cell count were performed as per approved procedures at the Princess Alexandra Hospital Queensland Health Pathology and Scientific Services. Plasma viscosity was measured using a Low Shear 30 viscometer (Contraves) at 37°C.

**Data Analysis**

Data were presented as mean±SEM (except where specified), and P<0.05 was considered significant. Within-group differences between preintervention and postintervention variables were analyzed by paired t tests. Between-group comparisons for continuous variables were analyzed using SPSS software version 17.0 (SPSS Inc). Pearson product moment correlation (data are mean±SD; P<0.05 was considered significant. Within-group differences between preintervention and postintervention variables were analyzed by paired t tests. Between-group comparisons for continuous variables and Spearman r for categorical variables. Data were analyzed using SPSS software version 17.0 (SPSS Inc).

**Results**

**Subject Characteristics**

As shown in Table 1, the patient population was significantly older and heavier, but there were no sex or height differences between groups. Patients also had significantly higher plasma viscosity, hematocrit, red cell count, and triglyceride levels compared with controls (Table 2). Table 3 details the baseline hemodynamic differences between groups.

**Changes With Venesection (Resting Data)**

From preintervention to postintervention (venesection), there were significant decreases in plasma viscosity, total protein, hemoglobin, red cell count, and total cholesterol levels in the patients but not in the controls (Table 2). Neither the patients nor controls showed significant changes in resting heart rate, arterial stiffness measures, brachial or central BPs, or LV diastolic parameters (data not shown) from before to after intervention. On the other hand, resting cardiac output was significantly decreased, whereas peripheral vascular resistance, LV strain, and SR were significantly increased in the patients but not in the controls (Table 3 and Figure 2).

**Correlations for Changes With Venesection (Resting Data)**

Strain was significantly correlated with plasma viscosity and triglycerides (r=0.48; P=0.008 for both) in the patients. However, for the controls, strain was not significantly correlated with either plasma viscosity (r=−0.002; r=0.99) or triglycerides (r=0.16; P=0.34). There was no significant association between the change in LV function and the change in any biochemical variable in either group (P>0.05 for all).

**Changes With Venesection (Exercise Data)**

From before to after intervention, there was a significant increase in exercise pulse pressure amplification, together with a significant decrease in exercise-augmented pressure and AIX in the patient population but not in the controls (Table 4 and Figure 2). These changes in the patients were observed despite no significant change in exercise brachial or central BPs, mean arterial pressure, or heart rate (although this was of borderline significance; P=0.05; Table 4). There were no different significances between groups for the heart rate during exercise (before or after intervention; P>0.30 for both; Table 3). However, the percentage of estimated maximal heart rate was lower in the controls before (51±5% versus 58±6%) and after (51±4% versus 60±8%) intervention (data are mean±SD; P<0.001 for both).

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**Table 2. Blood Biochemistry for Patients (n=20) and Controls (n=20) Before and After Intervention**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma viscosity, cP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1.46±0.03</td>
<td>1.41±0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Controls</td>
<td>1.38±0.03</td>
<td>1.37±0.02</td>
<td>0.61</td>
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<tr>
<td>Total protein, g/L</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>75.1±1.0</td>
<td>70.9±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Controls</td>
<td>74.3±1.3</td>
<td>74.8±1.0</td>
<td>0.61</td>
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<tr>
<td>Hemoglobin, g/L</td>
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<td></td>
</tr>
<tr>
<td>Patients</td>
<td>144±3</td>
<td>140±3</td>
<td>0.005</td>
</tr>
<tr>
<td>Controls</td>
<td>144±3</td>
<td>143±3</td>
<td>0.55</td>
</tr>
<tr>
<td>Hematocrit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>0.46±0.008*</td>
<td>0.45±0.01</td>
<td>0.19</td>
</tr>
<tr>
<td>Controls</td>
<td>0.43±0.009</td>
<td>0.43±0.008</td>
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<tr>
<td>Red cell count, ×10^12/L</td>
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<td></td>
<td></td>
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<tr>
<td>Patients</td>
<td>5.3±0.1*</td>
<td>5.2±0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Controls</td>
<td>4.7±0.1</td>
<td>4.7±0.1</td>
<td>0.59</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
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<td></td>
</tr>
<tr>
<td>Patients</td>
<td>4.5±0.2</td>
<td>4.3±0.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Controls</td>
<td>4.8±0.2</td>
<td>4.8±0.2</td>
<td>0.72</td>
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<tr>
<td>Triglycerides, mmol/L</td>
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<tr>
<td>Patients</td>
<td>2.1±0.2*</td>
<td>1.9±0.2</td>
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</tr>
<tr>
<td>Controls</td>
<td>0.97±0.09</td>
<td>1.0±0.09</td>
<td>0.47</td>
</tr>
</tbody>
</table>

P values are for the within-group comparison from preintervention to postintervention. cP indicates centipoise, a unit of dynamic viscosity. *P<0.05 indicates a significant difference from controls at baseline.
Table 3. Resting Hemodynamic Variables for Patients (n=20) and Controls (n=20) Preintervention and Postintervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients 136±4*</td>
<td>135±3</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Controls 112±3</td>
<td>112±3</td>
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<tr>
<td>Brachial diastolic BP, mm Hg</td>
<td></td>
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<tr>
<td>Patients 82±2*</td>
<td>82±2</td>
<td>0.96</td>
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<tr>
<td>Controls 71±2</td>
<td>70±1</td>
<td>0.37</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients 100±2*</td>
<td>99±2</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Controls 84±2</td>
<td>83±2</td>
<td>0.36</td>
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<tr>
<td>Central SBP, mm Hg</td>
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<td></td>
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<tr>
<td>Patients 123±3*</td>
<td>122±2</td>
<td>0.56</td>
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</tr>
<tr>
<td>Controls 99±3</td>
<td>98±2</td>
<td>0.66</td>
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<tr>
<td>Brachial pulse pressure, mm Hg</td>
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<td></td>
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<tr>
<td>Patients 54±3*</td>
<td>53±3</td>
<td>0.64</td>
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</tr>
<tr>
<td>Controls 41±2</td>
<td>42±2</td>
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<tr>
<td>Central pulse pressure, mm Hg</td>
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<tr>
<td>Patients 40±3*</td>
<td>39±3</td>
<td>0.62</td>
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<tr>
<td>Controls 27±2</td>
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<td>0.75</td>
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<tr>
<td>Pulse pressure amplification, ratio</td>
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<tr>
<td>Patients 1.38±0.04</td>
<td>1.38±0.04</td>
<td>0.80</td>
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<tr>
<td>Controls 1.59±0.04</td>
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<td>0.53</td>
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<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>Patients 76±3</td>
<td>77±3</td>
<td>0.65</td>
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</tr>
<tr>
<td>Controls 69±3</td>
<td>69±3</td>
<td>0.83</td>
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<tr>
<td>Augmented pressure, mm Hg</td>
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<tr>
<td>Patients 11±2*</td>
<td>9±2</td>
<td>0.21</td>
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<tr>
<td>Controls 3±1</td>
<td>3±1</td>
<td>0.86</td>
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<td>AIx, %</td>
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<tr>
<td>Patients 25±3*</td>
<td>21±3</td>
<td>0.14</td>
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<tr>
<td>Controls 8±3</td>
<td>9±3</td>
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<tr>
<td>Time to first inflection point, ms</td>
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<tr>
<td>Patients 132±3*</td>
<td>137±4</td>
<td>0.14</td>
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<tr>
<td>Controls 142±3</td>
<td>148±3</td>
<td>0.06</td>
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</tr>
<tr>
<td>Aortic pulse wave velocity, m/s</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients 8.8±0.4*</td>
<td>8.7±0.4</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Controls 6.4±0.2</td>
<td>6.6±0.3</td>
<td>0.13</td>
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<tr>
<td>Brachial pulse wave velocity, m/s</td>
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<tr>
<td>Patients 8.4±0.3</td>
<td>8.5±0.3</td>
<td>0.46</td>
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<tr>
<td>Controls 7.9±0.3</td>
<td>8.1±0.2</td>
<td>0.42</td>
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</tr>
</tbody>
</table>

(Continued)

Table 3. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, L/min</td>
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</tr>
<tr>
<td>Patients 3.8±0.2*</td>
<td>3.3±0.2</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Controls 3.2±0.2</td>
<td>3.1±0.2</td>
<td>0.33</td>
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</tr>
<tr>
<td>Peripheral vascular resistance, PRU</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients 28.0±2.1</td>
<td>33.0±2.4</td>
<td>0.004</td>
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<tr>
<td>Controls 27.7±1.5</td>
<td>27.7±1.5</td>
<td>0.99</td>
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<tr>
<td>Total arterial compliance, ml/mm Hg</td>
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<td></td>
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</tr>
<tr>
<td>Patients 1.43±0.13*</td>
<td>1.40±0.14</td>
<td>0.76</td>
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</tr>
<tr>
<td>Controls 2.25±0.23</td>
<td>2.11±0.19</td>
<td>0.59</td>
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<tr>
<td>Effective arterial elastance, mm Hg/mL</td>
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<tr>
<td>Patients 2.30±0.14*</td>
<td>2.45±0.19</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Controls 1.79±0.09</td>
<td>1.78±0.08</td>
<td>0.86</td>
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</tr>
<tr>
<td>Left ventricular longitudinal strain rate, 1/s</td>
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<td></td>
</tr>
<tr>
<td>Patients −1.21±0.03</td>
<td>−1.35±0.03</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Controls −1.28±0.04</td>
<td>−1.27±0.03</td>
<td>0.81</td>
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</tr>
<tr>
<td>Left ventricular strain, %</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients −17.1±0.7*</td>
<td>−20.3±0.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Controls −19.6±0.6</td>
<td>−20.1±0.6</td>
<td>0.11</td>
<td></td>
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</tbody>
</table>

P values are for the within-group comparison from preintervention to postintervention. PRU indicates peripheral resistance units.

*P<0.05 indicates a significant difference from controls at baseline.

Correlations for Changes With Venesection (Exercise Data)

From preintervention to postintervention, the change in peak systolic longitudinal SR was significantly correlated with the changes in augmented pressure (r=0.49; P=0.002), AIx (r=0.47; P=0.004), and pulse pressure amplification (r=−0.39; P=0.02) during exercise for the whole study population. Furthermore, in the whole study population, exercise central SBP was significantly correlated with triglycerides (r=0.59; P<0.001; Figure 3), and exercise AIx was of borderline significance with plasma viscosity (r=0.25; P=0.05). However, the change in exercise central SBP and exercise AIx was not significantly correlated with the change in any blood biochemistry variable. The change in augmented pressure during exercise was of borderline significance when correlated with the change in total protein (r=0.32; P=0.06) but not with the change in other biochemical variables.

Discussion

The main results of this study were that venesection with saline replacement of venesected volume was associated with a significant improvement in resting LV systolic function (evidenced by increased LV strain and SR), together with a significant improvement in exercise central systolic loading (evidenced by decreased AIx and augmented pressure but increased pulse pressure amplification). Importantly, the changes in exercise central parameters were observed in the absence of major modification to brachial BP, thereby highlighting the indepen-
dence between central and brachial BP during exercise, even at a light intensity similar to that of daily life. In addition, the improved LV function was significantly correlated with improved exercise central hemodynamics, indicating an overall enhancement of the ventricular-vascular relationship.

**LV Function**

Despite increased peripheral vascular resistance and reduced cardiac output (as expected from blood loss),25 LV peak systolic longitudinal strain and SR were both improved after venesection. Other gross cardiovascular alterations do not account for the LV systolic improvements, particularly because neither heart rate nor BP was appreciably changed. The lack of associations between changes in LV systolic function and changes in any laboratory parameters may suggest that some rheological or biochemical factor(s), other than that measured, may play a role in the observed LV improvements. Venesection may increase coronary microvascular blood flow (and, therefore, increase LV strain and SR) by reducing the aggregation of proteins bound to red blood cells and reducing microvasculature resistance.26 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27 This hypothesis may help to explain some of the data showing potential harm from high hemoglobin targets (using erythropoietin-stimulating agents) in the setting of heart failure.27

We favor an alternative explanation, that improved LV systolic function may be related to the significant reduction in light-exercise central systolic loading, specifically the reduced augmented pressure and AIx. To our knowledge, this is the first study to assess the effect of changes in blood rheology on AIx. The AIx is commonly regarded as a composite marker of systemic arterial stiffness and wave reflection, with increased values indicating raised LV afterload and wasted LV energy.28 Indeed, several studies have found a relationship between higher AIx and adverse LV structure and function, as well as cardiovascular risk under resting conditions. The significant associations observed between light-exercise central loading conditions and resting LV function may seem paradoxical, because resting loading conditions should be expected to explain resting LV function. Alternatively, the central hemodynamic milieu during light physical activity, similar to that of daily life, may be more representative of the chronic pressure load faced by the left ventricle compared with resting BP values. Indeed, this proposition is also supported by a recent observation (in a larger population than this current study) that resting LV systolic function was correlated with light-exercise central BP, independent of resting BP, as well as 24-hour ambulatory BP monitoring.32 Interestingly, although LV systolic function was significantly changed, none of the LV diastolic function parameters (ie, deceleration time, E/A, or E/Em) improved after venesection, perhaps indicating a subtle LV afterload effect, considering that large (experimentally induced) changes in afterload will alter relaxation characteristics.33

**Exercise-Central BP**

In a cohort of 62 men, we have previously observed a strong negative (and independent) relationship between plasma cholesterol and light exercise–induced pulse pressure amplification.11 We found that men with high blood cholesterol had higher central SBP and AIx compared with controls subjects who had similar brachial SBP during light exercise. A similar correlation between blood lipids and exercise-central BP was also observed in this current study (Figure 3). Together, the data imply that central hypertension may play a role in the relation between hypercholesterolemia and increased cardiovascular risk. In particular, raised central pressure (not apparent from brachial BP) may predispose hypercholesterolemic individuals to adverse cardiac remodeling. This is of interest given that LV hypertrophy is associated with high blood cholesterol through uncertain mechanisms that are not thought to be associated with BP.34 Considering that we found no correlation between the change in blood lipids (postvenesection) and the change in exercise BP variables in this current study, it may be that the effect of lipids on exercise central hemodynamics is related to chronic alteration in vascular properties (eg, increased large artery
stiffness),35 which is quite separate to the influence of blood rheology. On the other hand, an “acute” vascular response to blood lipid changes may not be noticeable for some hours.36

**Limitations**

We have made comparisons between a healthy population and individuals with known disease. Although we screened each participant to determine whether there was a history of coronary artery disease, we cannot rule out the possibility of subclinical cardiac disease caused by treatment associated with polycythemia rubra vera or occult iron overload in patients with hemochromatosis.37 This seems unlikely, because there was no significant difference in preintervention LV SR between patients and controls. Alternatively, the changes in response to intervention that were observed in the patients but not controls may reflect differences in age and general cardiovascular risk profile (eg, body mass index) between groups. We contend, however, that this is unlikely, because we observed significant correlations between the changes in our main outcome measures (ie, LV SR and exercise-central BP parameters) postvenesection for all of the participants, which would argue against the skewing of a treatment effect toward to one group. Moreover, we have tested the reproducibility of our tonometric measures in healthy individuals and used this information to determine sample size.14 Others have examined reproducibility in older patient populations with high risk of cardiovascular events and shown that only small study numbers are required (ie, less than this present study).38 Nonetheless, an optimal study design would have incorporated a more closely matched control group. Finally, it would be expected for there to be a shift of saline from the blood into the extracellular fluid resulting in a drop in circulating blood volume with saline infusion. Against this being a major issue was the significant fall in hemoglobin drop in circulating blood volume with saline infusion. Against this we observed significant correlations between the changes in our main outcome measures (ie, LV SR and exercise-central BP parameters) postvenesection for all of the participants, which would argue against the skewing of a treatment effect toward to one group. Moreover, we have tested the reproducibility of our tonometric measures in healthy individuals and used this information to determine sample size.14 Others have examined reproducibility in older patient populations with high risk of cardiovascular events and shown that only small study numbers are required (ie, less than this present study).38 Nonetheless, an optimal study design would have incorporated a more closely matched control group. Finally, it would be expected for there to be a shift of saline from the blood into the extracellular fluid resulting in a drop in circulating blood volume with saline infusion. Against this we observed significant correlations between the changes in our main outcome measures (ie, LV SR and exercise-central BP parameters) postvenesection for all of the participants, which would argue against the skewing of a treatment effect toward to one group. Moreover, we have tested the reproducibility of our tonometric measures in healthy individuals and used this information to determine sample size.14 Others have examined reproducibility in older patient populations with high risk of cardiovascular events and shown that only small study numbers are required (ie, less than this present study).38 Nonetheless, an optimal study design would have incorporated a more closely matched control group. Finally, it would be expected for there to be a shift of saline from the blood into the extracellular fluid resulting in a drop in circulating blood volume with saline infusion. Against this being a major issue was the significant fall in hemoglobin after saline replacement, indicating a dilution of hemoglobin by additional fluid maintained in the circulation.

**Perspectives**

This study found that an acute change in blood rheology, brought about by venesection, significantly improved resting LV systolic function and central systolic loading during physical activity, despite no significant change in traditional brachial BP measures. These results are likely to be of medical relevance given that both our echocardiographic and tonometric measures have independent associations with mortality (albeit in different clinical situations to this current study). Our findings are suggestive of enhanced ventricular-vascular interaction and, thus, provide a possible explanation for the link between plasma rheology and cardiovascular risk.1,2,4–6 More studies will be required to confirm this conjecture.

---

**Table 4. Exercise Hemodynamic Variables for Patients (n=20) and Controls (n=20) Preintervention and Postintervention**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention</th>
<th>Postintervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>155±4</td>
<td>154±4</td>
<td>0.68</td>
</tr>
<tr>
<td>Controls</td>
<td>127±4</td>
<td>128±4</td>
<td>0.85</td>
</tr>
<tr>
<td>Brachial diastolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>86±2</td>
<td>85±2</td>
<td>0.45</td>
</tr>
<tr>
<td>Controls</td>
<td>69±3</td>
<td>73±2</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>111±2</td>
<td>108±2</td>
<td>0.11</td>
</tr>
<tr>
<td>Controls</td>
<td>88±3</td>
<td>90±2</td>
<td>0.36</td>
</tr>
<tr>
<td>Central SBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>138±4</td>
<td>134±3</td>
<td>0.07</td>
</tr>
<tr>
<td>Controls</td>
<td>107±3</td>
<td>107±3</td>
<td>0.57</td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>69±3</td>
<td>69±4</td>
<td>0.85</td>
</tr>
<tr>
<td>Controls</td>
<td>60±3</td>
<td>55±3</td>
<td>0.19</td>
</tr>
<tr>
<td>Central pulse pressure, mm Hg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>50±3</td>
<td>47±3</td>
<td>0.28</td>
</tr>
<tr>
<td>Controls</td>
<td>35±2</td>
<td>32±2</td>
<td>0.13</td>
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<tr>
<td>Pulse pressure amplification, ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>1.41±0.04</td>
<td>1.49±0.04</td>
<td>0.009</td>
</tr>
<tr>
<td>Controls</td>
<td>1.71±0.04</td>
<td>1.73±0.04</td>
<td>0.50</td>
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<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
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<tr>
<td>Patients</td>
<td>92±3</td>
<td>95±3</td>
<td>0.05</td>
</tr>
<tr>
<td>Controls</td>
<td>95±2</td>
<td>96±2</td>
<td>0.85</td>
</tr>
<tr>
<td>Time to first inflection point, ms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Patients</td>
<td>129±3</td>
<td>137±5</td>
<td>0.15</td>
</tr>
<tr>
<td>Controls</td>
<td>140±2</td>
<td>144±5</td>
<td>0.33</td>
</tr>
<tr>
<td>Augmented pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>13±2</td>
<td>9±1</td>
<td>0.005</td>
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<tr>
<td>Controls</td>
<td>1±1</td>
<td>0±1</td>
<td>0.40</td>
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<tr>
<td>Alx, %</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>24±3</td>
<td>17±2</td>
<td>0.001</td>
</tr>
<tr>
<td>Controls</td>
<td>3±3</td>
<td>2±3</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*P* values are for the within-group comparison from preintervention to postintervention.
Acknowledgments
We are very grateful for the clinical advice and assistance from Dr Helen Fairweather.

Sources of Funding
This work was supported by a University of Queensland Early Career Researchers Grant. J.E.S. was supported by a National Health and Medical Research CouncilAustralian Clinical Research Fellowship (reference 409940) and a National Health and Medical Research Council Career Development Award (reference 569519).

Disclosures
J.E.S. has research collaborations with AtCor Medical.

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Sources of Funding This work was supported by a University of Queensland Early Career Researchers Grant. J.E.S. was supported by a National Health and Medical Research Council Australian Clinical Research Fellowship (reference 409940) and a National Health and Medical Research Council Career Development Award (reference 569519).
Influence of Altered Blood Rheology on Ventricular-Vascular Response to Exercise
James E. Sharman, Joseph Brown, David J. Holland, Graeme Macdonald, Karam Kostner and Thomas H. Marwick

Hypertension. 2009;54:1092-1098; originally published online August 31, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.135525

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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