Abnormalities of Hemorheological, Endothelial, and Platelet Function in Patients With Chronic Heart Failure in Sinus Rhythm

Effects of Angiotensin-Converting Enzyme Inhibitor and β-Blocker Therapy

Christopher R. Gibbs, MRCP; Andrew D. Blann, PhD; Robert D.S. Watson, MD; Gregory Y.H. Lip, MD

**Background**—To investigate the hypothesis that abnormalities of hemorheological (fibrinogen, plasma viscosity), endothelial (von Willebrand factor [vWF]), and platelet (soluble P-selectin) function would exist in patients with chronic heart failure (CHF) who are in sinus rhythm, we conducted a cross-sectional study of 120 patients with stable CHF (median ejection fraction 30%). We also hypothesized that ACE inhibitors and β-blockers would beneficially affect the measured indices.

**Methods and Results**—In the cross-sectional analysis, plasma viscosity ($P=0.001$), fibrinogen ($P=0.02$), vWF ($P<0.0001$), and soluble P-selectin ($P<0.001$) levels were elevated in patients with CHF compared with healthy controls. Women demonstrated greater abnormalities of hemorheological indices and vWF than males (all $P<0.05$). Plasma viscosity ($P=0.009$) and fibrinogen ($P=0.0014$) levels were higher in patients with more severe symptoms (New York Heart Association [NYHA] class III–IV), but there was no relationship with left ventricular ejection fraction. When ACE inhibitors were introduced, there was a reduction in fibrinogen (repeated-measures ANOVA, $P=0.016$) and vWF ($P=0.006$) levels compared with baseline. There were no significant changes in hemorheological, endothelial, or platelet markers after the introduction of β-blocker therapy, apart from a rise in mean platelet count ($P<0.001$).

**Conclusions**—Abnormal levels of soluble P-selectin, vWF, and hemorheological indices may contribute to a hypercoagulable state in CHF, especially in female patients and in those with more severe NYHA class. Treatment with ACE inhibitors improved the prothrombotic state in CHF, whereas the addition of β-blockers did not. These positive effects of ACE inhibitors may offer an explanation for the observed reduction in ischemic events in clinical trials. (**Circulation. 2001;103:1746-1751.**)

Key Words: platelets ‣ von Willebrand factor ‣ fibrinogen ‣ heart failure

Chronic heart failure (CHF) is associated with an increased risk of thromboembolism, whether or not concomitant atrial fibrillation is present. Small observational studies have suggested that pulmonary thromboembolism and stroke are common in dilated cardiomyopathy, whereas observational data from large heart failure trials suggest that mild to moderate CHF is associated with an annual stroke risk of 1.5%. However, this is increased in severe CHF, with the annual stroke risk increasing to 4%. Indeed, one report found an inverse relationship between left ventricular ejection fraction (LVEF) and stroke. Such events contribute to the high morbidity in CHF, from stroke and myocardial ischemia/infarction, which have thrombosis as the underlying pathophysiological process. Clearly, the pathophysiology of thromboembolism is complex and multifactorial, although CHF is known to be associated with a hypercoagulable or prothrombotic state, even in sinus rhythm. Furthermore, there is accumulating data to indicate that certain drug treatments reduce the risk of ischemic and thrombotic events, and the beneficial effects of β-blockers in reducing reinfarction rates after myocardial infarction (MI) may perhaps be related to anti-ischemic and antithrombotic properties. Studies in hypertensive and post-MI patients have also reported beneficial effects of some agents in improving hemorheology, endothelial, and platelet function. Although there is a long-established association between elevated hemostatic factors and the risk of future cardiovascular events, there are few studies addressing the

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in vivo effects of treatment with established therapy (ACE inhibitors and \(\beta\)-blockers) on the hypercoagulable state in CHF.11

We hypothesized that abnormalities of hemorheological (fibrinogen, plasma viscosity), endothelial (von Willebrand factor [vWF]), and platelet (soluble P-selectin) function would exist in patients with CHF who are in sinus rhythm and that these abnormalities would correlate with sex, the degree of left ventricular dysfunction, and the severity of symptoms. Second, we hypothesized that therapy with ACE inhibitors or \(\beta\)-blockers would beneficially affect these indices, as possible mechanisms for their clinical benefits in CHF. First, we performed a cross-sectional study of patients with stable CHF, and next, we prospectively studied 2 entirely separate treatment groups: group 1 consisted of ACE-inhibitor–naïve patients, in whom ACE inhibitors were introduced, and group 2 was composed of patients with CHF who were already receiving maintenance therapy with ACE inhibitors for \(>6\) months, in whom \(\beta\)-blockers were introduced.

**Methods**

Ambulant patients who were in sinus rhythm with stable CHF (New York Heart Association [NYHA] class II-IV) and an LVEF of \(\leq40\%\), as assessed by 2D echocardiography, were studied. The cause of heart failure was determined, in each patient, from clinical assessment and relevant investigations. Patients with uncontrolled CHF (requiring hospital admission for deteriorating CHF within 3 months), regular angina (>2 episodes/week), significant renal impairment (creatinine >200 \(\mu\)mol/L), active infection, neoplastic or connective tissue disease, a recent (<2 months) acute ischemic event (MI, unstable angina, or cerebrovascular event), atrial fibrillation or pacemakers, or previous thromboembolism and those taking warfarin, antithrombotic agents other than aspirin (eg, nonsteroidal agents, clopidogrel), or hormone replacement therapy were excluded.

In group 1 (20 patients), ACE-inhibitor–naïve patients were commenced on lisinopril (with a single captopril 6.25-mg test dose in selected patients), which was titrated up to a target maintenance dose of lisinopril (20 mg once daily) or to the highest tolerated dose level. In group 2 (20 patients), a \(\beta\)-blocker (either carvedilol or bisoprolol) was introduced at low dose and titrated up to the target maintenance dose of each agent (carvedilol 25 mg twice daily, bisoprolol 10 mg once daily) or to the highest tolerated dose level. Minor alterations in the dose of diuretics were permitted, although patients requiring further alterations to cardiovascular therapy were excluded. Serial blood samples were obtained from all subjects at baseline (before further alterations to cardiovascular therapy were excluded. Serial blood samples were obtained from all subjects at baseline (before ACE inhibitor or \(\beta\)-blocker therapy) and then at 3 and 6 months after the start of treatment.

Control subjects were drawn from among healthy hospital staff and from healthy subjects attending hospital for hernia repairs, varicose vein procedures, or other minor operations. All were “healthy” by careful clinical history and physical examination.

**Blood Samples and Assays**

Citrated plasma was obtained from venous blood by centrifugation at 2500 rpm for 15 minutes at 4°C. Aliquots were stored at \(-70\)°C to allow batch analysis. Soluble P-selectin and vWF were measured by ELISA (R&D Systems and Dako-Patts). Plasma fibrinogen (g/L) was measured by the Clauss technique on a Pacific Hemostasis coagulometer, and reagents were from Alpha Laboratories. An EDTA sample was analyzed in the routine hematology autoanalyzers for serial assays of hemoglobin (Hemocue), hematocrit (Hawksley), and plasma viscosity (Coulter viscometer) levels. Intra-assay coefficients of variation for all analyses were \(<5\%\); interassay variabilities were \(<10\%\).

**Power Calculation, Analysis of Data, and Statistics**

In the cross-sectional study, we based our power calculation on the hypothesis that fibrinogen would be increased by a factor of half a standard deviation in patients compared with controls.16 To detect a \(P\) value of \(<0.05\) with a power (\(\beta\)) of 0.80, we needed 64 cases and 64 controls. Because we intended to perform other analyses (eg, vWF and plasma viscosity), we recruited 120 in each group to provide the additional confidence required of multiple analyses and subanalyses, such as that for disease severity. In the latter case, the difference in fibrinogen provides a power of 0.91 from sample numbers of 38 per group. For the treatment study, we expected the introduction of either ACE inhibitor or \(\beta\)-blocker therapy to reduce systolic blood pressure by \(\sim1\) SD as a crude measure of a hemodynamically significant dose. To achieve this for \(P<0.05\) and a \(\beta\) of 0.80, the power calculation requires 15 patients; to ensure good data and adequate power, we recruited 20 patients in each of the 2 arms.

Clinical data are expressed as mean (SD) except for soluble P-selectin, which is nonparametrically distributed and is expressed as median (interquartile range). Data between patients and controls were analyzed by unpaired \(t\) test or the Mann-Whitney \(U\) test, as appropriate. Stepwise multiple regression analysis was performed with relevant clinical variables and the measured indices as predictors. Serial data (before and after treatment) were analyzed by Friedman’s repeated-measures ANOVA (RMANOVA) to compare variables at baseline and 3 and 6 months. Correlations between changes in hemodynamic parameters and circulating markers were performed with Spearman’s rank correlation. A \(P\) value of \(<0.05\) was considered statistically significant.

**Results**

We studied 120 study participants (92 men; mean age 64±12 years) with CHF (median LVEF 30\%, range 16\% to 40\%), who were compared with matched controls (96 men; mean age 64±8 years). Patients with CHF were taking standard therapy for heart failure (Table 1). Plasma viscosity (\(P<0.001\)), fibrinogen (\(P=0.006\)), vWF (\(P<0.0001\)), and soluble P-selectin (\(P<0.0001\)) levels were elevated in CHF compared with controls (Table 2).

CHF patients with ischemic heart disease (n=108) were older (65±11 versus 54±8 years, \(P=0.0007\)) but had lower mean diastolic blood pressure (77±6 versus 85±10 mm Hg, \(P=0.022\)) and serum cholesterol (5.1±0.9 versus 6.1±1.0 mmol/L, \(P=0.077\)) levels than those without ischemic heart disease (n=12). There were no significant differences in plasma viscosity, fibrinogen, and soluble P-selectin concentrations between CHF patients with and without ischemic heart disease (data not shown). Women with CHF were older but demonstrated greater abnormalities of hemorheological indices (hematocrit, plasma viscosity, and fibrinogen) and vWF than men (Table 3). Afro-Caribbean patients had higher mean systolic and diastolic blood pressures (both \(P<0.05\)) but lower median soluble P-selectin (\(P=0.002\)) than white and Indo-Asian patients, despite having similar mean age and ejection fraction levels.

There were no significant differences in plasma viscosity, fibrinogen, vWF, or soluble P-selectin levels when patients with mild left ventricular dysfunction (LVEF \(\geq30\%)\) were compared with patients with more severe impairment of left ventricular function (LVEF <30\%) (Table 4). Plasma viscosity (\(P=0.009\)) and fibrinogen (\(P=0.0014\)) levels were higher in CHF patients with more severe symptoms (NYHA class III-IV) than in those with milder symptoms (NYHA class II). There was a nonsignificant trend toward higher levels of vWF.
We recruited 40 patients (30 men; age 65±11 years) with stable CHF in sinus rhythm with a mean LVEF of 30% (range 16% to 38%) for this substudy. Baseline indices in patients enrolled in the 2 treatment groups were similar (including mean ejection fraction levels), apart from higher mean age (68 versus 61 years, *P=0.024) and plasma fibrinogen levels (3.4 versus 2.8 g/L, *P=0.02) in group 1 versus group 2 (Table 1).

In group 1 (n=20), the median maintenance dose of lisinopril was 10 mg (range 2.5 to 20 mg), whereas in group 2 (n=20), 14 patients received bisoprolol at a median maintenance dose of 5 mg (range 2.5 to 10 mg) and 6 received carvedilol at a median maintenance dose of 25 mg daily (range 12.5 to 50 mg daily). As expected, drug treatment was associated with a fall in mean systolic blood pressure levels in both of the treatment groups (Table 5). There was also a fall in mean diastolic blood pressure in both groups.

In group 1, ACE inhibitor therapy was associated with a reduction in fibrinogen (RMANOVA, *P=0.016) and vWF (*P=0.006) concentrations compared with baseline. There was a nonsignificant trend toward lower soluble P-selectin levels. There were no significant correlations between changes in systolic blood pressure and changes in either plasma fibrinogen (Spearman *r=−0.3; *P=0.2) or vWF (*r=0.2; *P=0.5). In group 2, there were no changes in any hemorheological, endothelial, or platelet markers after treatment, although the addition of β-blockers was associated with a rise in the mean platelet count (*P<0.001). There were no significant changes in mean hemoglobin, hematocrit, creatinine, cholesterol, or HDL cholesterol levels after treatment in either group compared with baseline (some data not shown).

### Spearman Correlations and Stepwise Multiple Regression Analyses

In the cross-sectional study, there were no significant correlations between LVEF and plasma viscosity (*r=0.13, *P=0.17), fibrinogen (*r=−0.06, *P=0.5), vWF(*r=−0.08, *P=0.4), or soluble P-selectin (*r=0.14, *P=0.15). Fibrinogen levels were correlated with age (*r=0.19, *P=0.036), vWF (*r=0.30, *P=0.001), and plasma viscosity (*r=0.434, *P<0.001). There were no other correlations between the measured indices. Stepwise regression analysis with relevant clinical variables (eg, age, sex, ejection fraction, previous diabetes, and hypertension) as predictors/determinants and
the measured indices demonstrated that sex and diastolic blood pressure were independent predictors for plasma viscosity levels ($R^2=10.8$, $P<0.05$), whereas sex was the only independent predictor for plasma fibrinogen levels ($R^2=7.7$, $P<0.05$). Similarly, sex was the only independent predictor for plasma vWF levels ($R^2=4.2$, $P<0.05$). Ethnicity was the only independent predictor for soluble P-selectin levels ($R^2=5.3$, $P<0.05$).

**Discussion**

This study represents one of the largest cohorts exploring the relationship between hemorheological factors, vWF, and soluble P-selectin and CHF. In the present study, the abnormal baseline hemorheological markers, vWF and soluble P-selectin, are consistent with observations of a hypercoagulable state in CHF, but in addition, we observed a relationship to sex and the severity of CHF, as indicated by NYHA class. Furthermore, the introduction of ACE inhibitor therapy but not β-blockers was associated with a reduction in plasma fibrinogen and vWF levels.

CHF is more common in men than women, although the effect of female sex on prognosis is not clear. In general, the studies evaluating CHF have been conducted in predominantly male populations. The SOLVD (Studies Of Left Ventricular

### Table 3. Effects of Sex and Ethnicity on Hemorheological Markers, vWF, and Soluble P-Selectin in CHF

|Sex| Males (n=92) | Females (n=28) |
P|---|---|---|
|Age| 63±11 | 69±9 | 0.0045 |
|Systolic blood pressure, mm Hg| 135±22 | 144±21 | 0.067 |
|Diastolic blood pressure, mm Hg| 78±7 | 78±5 | 0.84 |
|Creatinine, µmol/L| 111±28 | 106±30 | 0.52 |
|Cholesterol, mmol/L| 5.0±1.0 | 5.6±1.0 | 0.0031 |
|Ejection fraction, %| 29±6 | 29±6 | 0.64 |
|Hematocrit, %| 41.5±3.9 | 37.1±3.1 | <0.0001 |
|Plasma viscosity, mpa| 1.74±0.12 | 1.83±0.15 | 0.0077 |
|Fibrinogen, g/L| 3.0±0.7 | 3.4±0.8 | 0.0078 |
|vWF, IU/dL| 133±26 | 146±27 | 0.034 |
|Soluble P-selectin, ng/mL| 47 | 40 | 0.193 |

### Table 4. Relationship Between Ejection Fraction, NYHA Class, and Hemorheological Markers, vWF, and Soluble P-Selectin in CHF

<table>
<thead>
<tr>
<th>Variable</th>
<th>≥30% (n=66)</th>
<th>&lt;30% (n=54)</th>
<th>P</th>
<th>Mitr CHF (NYHA Class II) (n=38)</th>
<th>Moderately- to Severe CHF (NYHA Class III–IV) (n=82)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td>40.0±4.2</td>
<td>41.1±4.1</td>
<td>0.16</td>
<td>41.4±0.8</td>
<td>40.4±0.5</td>
<td>0.28</td>
</tr>
<tr>
<td>Plasma viscosity, mpa</td>
<td>1.78±0.14</td>
<td>1.74±0.13</td>
<td>0.25</td>
<td>1.71±0.10</td>
<td>1.78±0.15</td>
<td>0.009</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.1±0.8</td>
<td>3.1±0.7</td>
<td>0.82</td>
<td>2.8±0.5</td>
<td>3.3±0.8</td>
<td>0.0014</td>
</tr>
<tr>
<td>vWF, IU/dL</td>
<td>134±28</td>
<td>139±25</td>
<td>0.32</td>
<td>129±26</td>
<td>139±27</td>
<td>0.078</td>
</tr>
<tr>
<td>Soluble P-selectin, ng/mL</td>
<td>43 (35–63)</td>
<td>43 (32–57)</td>
<td>0.41</td>
<td>40 (34–50)</td>
<td>48 (33–70)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or median (interquartile range).
Table 5. Effects of Therapy on Blood Pressure, Hemorheological Markers, vWF and Soluble P-Selectin in CHF

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (ACE Inhibitors)</th>
<th>Group 2 (β-Blockers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 mo</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>148±22</td>
<td>...</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83±8</td>
<td>...</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>13.7±1.4</td>
<td>13.5±1.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>42.1±4.1</td>
<td>42.1±4.4</td>
</tr>
<tr>
<td>Plasma viscosity, mpa</td>
<td>1.76±0.15</td>
<td>1.71±0.12</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>3.4±0.8</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>vWF, IU/dL</td>
<td>148±22</td>
<td>138±17</td>
</tr>
<tr>
<td>Platelet count, 1000×10^3</td>
<td>200±73</td>
<td>216±54</td>
</tr>
<tr>
<td>Soluble P-selectin, ng/mL</td>
<td>59±50</td>
<td>48±16</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. Analysis by repeated-measures ANOVA, apart from blood pressure changes, compared by paired t-test.

Dysfunction) patient registry, of which 26% were female patients, found that women had a significantly higher risk of morbidity and mortality, with more hospitalizations (33% versus 25%) and deaths (22% versus 17%). In the present study, female patients with CHF had greater abnormalities of hemorheological indices and vWF than male patients, which could contribute in part to the higher (thrombosis related) event rates in female CHF patients. Indeed, sex was an independent predictor for plasma viscosity, fibrinogen, and vWF levels on multiple regression analyses. Importantly, population studies have not shown any substantial sex-related differences in levels of these measured indices within the 55- to 64-year-old age group.18

Hoffmeister et al16 recently reported a negative correlation between plasma viscosity and LVEF in CHF. Although we did not observe such a relationship, there was a strong association between plasma viscosity and fibrinogen with the clinical severity of CHF indicated by the NYHA classification. The latter closely correlates with prognosis, and thus, abnormal hemorheological indices may have an important role in the pathogenesis of adverse outcomes. Importantly, the presence of underlying ischemic heart disease did not appear to be the major determinant of hemorheological, endothelial, and platelet abnormalities, because no significant differences were observed between patients with ischemic and nonischemic left ventricular dysfunction.

Abnormalities of hemorheological indices, vWF, and soluble P-selectin could relate to the prothrombotic or hypercoagulable state in CHF in many ways. For example, plasma fibrinogen is a major determinant of fibrin formation, which contributes to blood flow abnormalities and a prothrombotic state in a variety of disorders.19 Elevated fibrinogen levels have been correlated with nonfatal thromboembolic events after acute MI and an increased long-term risk of cardiovascular death.19 Fibrinogen, therefore, appears to predispose to the development of intracardiac thrombus, in situ thrombosis, and vascular occlusion, so that the elevated levels in severe CHF may, in part, account for the increased incidence of thromboembolic events in these patients.

CHF is associated with impaired endothelium-dependent vasodilatation and impaired release of endothelium-derived nitric oxide in response to stimuli, which contributes to the peripheral vasoconstriction that is characteristic of heart failure.20 Consequently, the elevated baseline vWF levels reflect preexisting endothelial dysfunction in CHF, and as a procoagulant product of the endothelium, vWF may further enhance the prothrombotic state through its effects on platelet aggregation and platelet adhesion to the endothelium.21 Indeed, elevated vWF levels are associated with an increased risk of reinfarction and mortality in post-MI patients.22 Elevated vWF levels have previously been observed in patients with left ventricular aneurysms,23 but there was no relationship between vWF and LVEF, as in the present study. Although there was a trend toward higher vWF levels in patients with more severe symptoms (NYHA class III–IV), these differences were not statistically significant. The elevated soluble P-selectin levels are consistent with other studies that have reported abnormal circulating markers of platelet function, abnormal platelet morphology, and enhanced platelet aggregation in CHF.24–26 In the present study, there was no evidence of a relationship between platelet activation and LVEF, although there was a nonsignificant trend toward higher soluble P-selectin levels in NYHA class III–IV. We also observed lower median soluble P-selectin levels in Afro-Caribbean patients, despite this patient group having higher mean blood pressures and despite the relationship between soluble P-selectin and hypertension.27 Although the origin of platelet activation in CHF remains to be established, increased platelet activity might be related to elevation of cytosolic free calcium concentrations28 and to the fact that platelets may be affected by enhanced sympathetic activation and catecholamine release in CHF.29

In the present study, the observed beneficial effects of ACE inhibitors on plasma fibrinogen and vWF levels may offer a potential explanation for the reduction in (thrombosis related) ischemic events with the use of these agents in clinical trials.12 The precise mechanism for a reduction in plasma fibrinogen and vWF levels with ACE inhibitors in CHF remains to be established, although in the present study, the changes in plasma fibrinogen and vWF levels did not appear to be directly related to the reduction in blood pressure. Similar effects on fibrinogen in hypertensive patients have been linked to the effects of ACE inhibitors on insulin sensitivity.30 Perhaps blockade of the renin-angiotensin-aldosterone system, combined with the effects of ACE inhibitors on bradykinin metabolism, may also be important factors in the modulation of circulating vWF concentrations. We did not observe any changes in plasma fibrinogen and vWF levels with β-blockade, but the signif-
ificant rise in mean peripheral platelet count after the addition of β-blockers in our patients is a well-documented response to alterations in the adrenergic control of the circulating and splenic platelet pool.  

If the mechanisms of thromboembolism in CHF are not simply mechanical but are also related to an underlying hypercoagulable state, measurement of suitable markers associated with thrombogenesis may perhaps be useful in identifying high-risk patients and in determining the nature, duration, and intensity of antithrombotic therapy. Moreover, many of these markers have already been shown to have prognostic implications in cardiovascular disease, but further information is needed on their predictive value in patients with CHF, as well as large trials of antithrombotic therapy in such patients.

We recognize that there are limitations to our cross-sectional study design. However, all patients had documented systolic dysfunction, and patients with atrial fibrillation were excluded in view of the study design. However, all patients had documented systolic dysfunction, and patients with atrial fibrillation were excluded in view of the study design. However, all patients had documented systolic dysfunction, and patients with atrial fibrillation were excluded in view of the study design.

In conclusion, we have demonstrated abnormal soluble P-selectin, vWF, and hemorheological indices in CHF, which may contribute to a hypercoagulable state. Plasma viscosity and fibrinogen were also correlated with symptomatic severity, and long-term treatment with ACE inhibitors improved the prothrombotic state, but the addition of β-blockers did not. These positive effects of ACE inhibitors may offer a potential explanation for the observed reduction in ischemic events associated with the use of these agents in large-scale trials.

References

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