STUDIES ON THE BLOOD FIBRINOLYTIC SYSTEM IN CONGESTIVE CARDIAC FAILURE

J. M. RAWLES, D. OGSTON AND A. S. DOUGLAS

Department of Medicine, University of Aberdeen

(Received 6 December 1972)

SUMMARY

1. The major components of the blood fibrinolytic enzyme system were measured in patients with congestive cardiac failure, in control patients with heart disease but not in failure, and in control subjects without heart disease.

2. Heart disease in the absence of failure was associated with an increase in fibrinogen, fibrin degradation products and $\alpha_1$-antitrypsin, but not with any alteration of plasminogen activator, plasminogen, the serum inhibitor of plasminogen activation or $\alpha_2$-macroglobulin.

3. Compared with patients with heart disease, there were decreased amounts of plasminogen activator and plasminogen and increased amounts of the serum inhibitor of plasminogen activation and the antiplasmin $\alpha_1$-antitrypsin in patients with cardiac failure. Fibrinogen, fibrin degradation products and $\alpha_2$-macroglobulin were not significantly altered.

4. Plasminogen activator as measured by the euglobulin lysis time correlated inversely with the height of the jugular venous pressure, but not with liver size, the extent of oedema, chest X-ray appearances, amounts of blood urea or bilirubin.

5. The release of plasminogen activator in response to venous stasis was decreased in patients with cardiac failure.

Key words: fibrinolysis, cardiac failure, plasminogen, plasminogen activator, fibrinogen, $\alpha_1$-antitrypsin, $\alpha_2$-macroglobulin, venous stasis.

Venous thrombosis and pulmonary embolism is a common complication of cardiac disease (Hampton & Castleman, 1940; Anderson & Hull, 1950; Levinson & Griffith, 1951; Byrne & O'Neil, 1952). In one large unselected autopsy series pulmonary embolism was found in almost 14% of patients and 55% of pulmonary emboli occurred in the patients with cardiac disease, giving an incidence in cardiac disease of almost 25%, three times as great as in non-cardiac

Correspondence: Dr J. M. Rawles, Department of Medicine, University Medical Buildings, Foresterhill, Aberdeen AB9 2ZD.
disease (Coon & Coller, 1959): although the presence of cardiac failure was not specified in this series, it has been thought to increase the risk of thrombo-embolism (White, 1940; Wood, 1968). Kucera (1968) found a higher incidence of pulmonary embolism at autopsy in cardiac patients with evidence of failure than in those without.

Immobility, venous stagnation and a decreased cardiac output may be contributory factors predisposing such patients to thrombosis. In experimental animals, however, even complete venous stasis is insufficient by itself to cause thrombosis in the absence of abnormality in the blood (Wessler, 1962; Botti & Ratnoff, 1964). Nilsson (1968) has claimed that impaired fibrinolysis may play a rôle in the causation of thrombosis, and in the present study we have examined the fibrinolytic enzyme system in cardiac failure.

**MATERIALS AND METHODS**

**Methods**

Blood for the following estimations was drawn by clean venepuncture between 09.00 and 09.30 hours.

*Plasminogen activator.* This was assessed by performing euglobulin clot lysis times (ELT) by the method of Nilsson & Olow (1962). The results were expressed by plotting the lysis times logarithmically against units of fibrinolytic activity (Sherry, Lindemeyer, Fletcher & Alkjaersig, 1959), 10 units being arbitrarily equated with a lysis time of 50 min. For statistical analyses values of less than 1.0 unit were treated as 1.0 unit. Plasminogen activator was also measured by applying 30 μl samples of resuspended euglobulin precipitate to fibrin plates prepared from 0.2% human fibrinogen (Grade L, AB Kabi, Stockholm). After incubation at 37°C for 24 h the area of lysis was estimated from the product of two diameters. A partially purified preparation of urokinase (Leo Pharmaceutical Products, Ballerup, Denmark) was used as a reference standard. The areas of lysis by the urokinase standard dilutions were plotted on a log-log scale and the fibrinolytic activity of the euglobulin precipitate obtained by extrapolation and expressed as Ploug units of urokinase (Ploug & Kjeldgaard, 1957). In a group of forty-two subjects not in cardiac failure a close correlation was found between these two techniques for the measurement of plasminogen activator ($r = 0.65; P < 0.001$).

*Plasminogen.* This was measured by the caseinolytic techniques of Alkjaersig, Fletcher & Sherry (1959a) and the results expressed in Sherry units (Alkjaersig, Fletcher & Sherry, 1959b).

*Fibrinogen.* This was assayed by a modification (Ogston & Ogston, 1966) of the method of Ratnoff & Menzie (1951).

*Serum inhibitor of plasminogen activation.* This was measured using a standard clot system as described by Bennett (1967). One unit of inhibition is equivalent to that produced by $10^{-3}$ mol of ε-aminocaproic acid.

*Alpha1-antitrypsin and alpha2-macroglobulin.* Amounts of these were assayed by single radial immunodiffusion (Mancini, Carbonara & Heremans, 1965) using reagents obtained from Hoechst Pharmaceuticals, Hounslow, Middlesex.

*Serum fibrin degradation products (FDP).* These were measured by the tanned erythrocyte haemagglutination-inhibition technique of Merskey, Kleiner & Johnson (1966).

*Haematocrit values.* These were measured by a micro-method and the serum urea and bi-
Fibrinolysis in cardiac failure
rubin were measured in the hospital chemical pathology laboratory using a Technicon Auto-Analyzer.

Venous occlusion test
Venous occlusion was effected by a sphygmomanometer cuff inflated midway between diastolic and systolic pressures. Blood was drawn from the unoccluded arm immediately after inflation of the cuff and from the occluded arm after 5 min inflation just before release of the cuff.

Patients
Twenty-nine patients with congestive cardiac failure were studied. For the purpose of this study congestive cardiac failure has been defined as increase of the jugular venous pressure more than 3 cm above the sternal angle in a patient known to have heart disease in the absence of any other known cause of fluid retention. None of the patients had had a recent myocardial infarction as this is known to cause changes in the fibrinolytic system (Bennett, Ogston & Ogston, 1967). Jugular venous pressure was measured visually by one observer (J.M.R.) in centimetres vertically above the sternal angle with the patient positioned so that the upper level of pulsation could be clearly seen. The position of the liver edge was recorded in 'finger breadths' below the right costal margin. Oedema of the ankles and sacrum was arbitrarily recorded as slight, moderate or gross. For evidence of left-ventricular failure the chest X-ray was studied by an independent observer and allotted a score with a possible maximum of 6. Hilar clouding, pulmonary clouding or a pleural effusion each scored 0, 1 or 2 depending whether the feature was absent, dubious or definite. If the total from these three features was less than 6 each of the following could score an additional point: presence of Kerley's lines, prominent upper lobe veins or prominence of the fissures.

Control patients had hypertensive, rheumatic, ischaemic or pulmonary heart disease, but at the time of investigation had no evidence of congestive heart failure.

In both groups many of the patients were on diuretics and digoxin together with other drugs which are not known to effect the fibrinolytic enzyme system. Patients with concurrent malignancy, advanced renal failure, liver disease or acute infection were excluded as those conditions might themselves alter components of the fibrinolytic system.

Control subjects without heart disease were either healthy volunteers or patients with medical conditions not known to be associated with any abnormality of the fibrinolytic enzyme system. The same individuals were not necessarily used for each of the variables studied, but the groups for each variable were age-matched.

RESULTS

Controls
In heart disease, amounts of fibrinogen, fibrin degradation products and α₁-antitrypsin were increased compared with control subjects (Table 1). The elevation of the mean amount of fibrinogen was especially marked in the four patients with pulmonary heart disease. There were no other marked differences between subgroups of patients with heart disease due to various causes and, in particular, there was no difference in the mean plasminogen activator amount between control and heart disease groups.
TABLE 1. Mean values and standard deviations of components of the fibrinolytic enzyme system in controls, patients with heart disease and patients with congestive cardiac failure

<table>
<thead>
<tr>
<th>Group (no. of subjects)</th>
<th>Age (years)</th>
<th>ELT (units)</th>
<th>Fibrin plate (UK units)</th>
<th>Plasminogen (units/ml)</th>
<th>Fibrinogen (mg/100 ml)</th>
<th>FDP (μg/ml)</th>
<th>Activation inhibitor (units)</th>
<th>α₁-antitrypsin (mg/100 ml)</th>
<th>α₂-macro-globulin (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cardiac disease (30)</td>
<td>±8·54</td>
<td>±1·88</td>
<td>—</td>
<td>4·14</td>
<td>414</td>
<td>11·8</td>
<td>3·7</td>
<td>329·1</td>
<td>257·4</td>
</tr>
<tr>
<td>Heart disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease (11)</td>
<td>62·9</td>
<td>4·1</td>
<td>0·91</td>
<td>4·5</td>
<td>414</td>
<td>11·8</td>
<td>3·7</td>
<td>329·1</td>
<td>257·4</td>
</tr>
<tr>
<td>Rheumatic heart disease (7)</td>
<td>57·4</td>
<td>4·5</td>
<td>1·41</td>
<td>4·2</td>
<td>399</td>
<td>8·2</td>
<td>4·1</td>
<td>296·0</td>
<td>304·0</td>
</tr>
<tr>
<td>Pulmonary heart disease (4)</td>
<td>67·0</td>
<td>5·5</td>
<td>1·42</td>
<td>4·0</td>
<td>519</td>
<td>7·3</td>
<td>5·2</td>
<td>293·0</td>
<td>223·0</td>
</tr>
<tr>
<td>Hypertensive heart disease (10)</td>
<td>60·1</td>
<td>4·1</td>
<td>0·94</td>
<td>3·9</td>
<td>402</td>
<td>13·4</td>
<td>3·5</td>
<td>306·0</td>
<td>255·0</td>
</tr>
<tr>
<td>'All heart disease' (32)</td>
<td>±13·1</td>
<td>±1·8</td>
<td>±0·8</td>
<td>±0·6</td>
<td>±114·8</td>
<td>±7·5</td>
<td>±1·4</td>
<td>±84·3</td>
<td>±52·0</td>
</tr>
<tr>
<td>Significance of difference from no cardiac disease (P)</td>
<td>&gt;0·1</td>
<td>&gt;0·1</td>
<td>—</td>
<td>&gt;0·1</td>
<td>&lt;0·05</td>
<td>&gt;0·1</td>
<td>&lt;0·05</td>
<td>&lt;0·05</td>
<td>&gt;0·1</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease (13)</td>
<td>74·1</td>
<td>2·3</td>
<td>0·40</td>
<td>3·2</td>
<td>419</td>
<td>12·8</td>
<td>6·0</td>
<td>332·4</td>
<td>234·4</td>
</tr>
<tr>
<td>Rheumatic heart disease (8)</td>
<td>57·8</td>
<td>1·3</td>
<td>0·42</td>
<td>3·2</td>
<td>438</td>
<td>14·5</td>
<td>5·4</td>
<td>378·7</td>
<td>266·7</td>
</tr>
<tr>
<td>Pulmonary heart disease (6)</td>
<td>60·3</td>
<td>2·0</td>
<td>0·86</td>
<td>3·4</td>
<td>434</td>
<td>10·8</td>
<td>6·0</td>
<td>392·7</td>
<td>229·3</td>
</tr>
<tr>
<td>Hypertensive heart disease (2)</td>
<td>71·0</td>
<td>1·3</td>
<td>0·25</td>
<td>2·2</td>
<td>298</td>
<td>30·0</td>
<td>6·25</td>
<td>340</td>
<td>264</td>
</tr>
<tr>
<td>'All cardiac failure' (29)</td>
<td>±13·1</td>
<td>±1·3</td>
<td>±0·3</td>
<td>±1·1</td>
<td>±121·5</td>
<td>±11·6</td>
<td>±2·3</td>
<td>±106·5</td>
<td>±55·9</td>
</tr>
<tr>
<td>Significance of difference from 'all heart disease' (P)</td>
<td>&gt;0·1</td>
<td>&lt;0·001</td>
<td>&lt;0·001</td>
<td>&lt;0·001</td>
<td>&gt;0·1</td>
<td>&lt;0·001</td>
<td>&gt;0·1</td>
<td>&lt;0·05</td>
<td>&gt;0·01</td>
</tr>
</tbody>
</table>

ELT, Euglobulin clot lysis time; FDP, fibrin degradation products; UK, urokinase.
Cardiac failure. In cardiac failure there were minor differences in mean values between different aetiological groups, but no clear pattern emerged (Table 1).

As measured by the euglobulin lysis time and the fibrin plate technique the amount of plasminogen activator was significantly decreased in cardiac failure compared with patients with cardiac disease not in failure. The decreased amount of plasminogen activator measured by the euglobulin lysis time cannot be accounted for by changes in the concentration of fibrinogen or plasminogen, since the difference was also apparent when the fibrin plate technique was used; a technique uninfluenced by the amount of plasma plasminogen or fibrinogen. The correlation between ELT and plasminogen activator amount measured by the fibrin plate technique was significant \((r = 0.43; P<0.05)\).

The amount of plasminogen was decreased and \(\alpha_1\)-antitrypsin and the serum inhibitor of plasminogen activation were significantly increased in patients with cardiac failure.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Cardiac failure</th>
<th>Treated failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ELT (units)</td>
<td>Plasminogen (units/ml)</td>
</tr>
<tr>
<td>4</td>
<td>&lt; 1.0</td>
<td>2.6</td>
</tr>
<tr>
<td>15</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>21</td>
<td>&lt; 1.0</td>
<td>3.6</td>
</tr>
<tr>
<td>22</td>
<td>2.3</td>
<td>4.3</td>
</tr>
<tr>
<td>23</td>
<td>&lt; 1.0</td>
<td>3.3</td>
</tr>
<tr>
<td>24</td>
<td>3.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Mean</td>
<td>1.7</td>
<td>3.4</td>
</tr>
<tr>
<td>SEM</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Significance of the difference (P)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ELT, Euglobulin clot lysis time; FDP, fibrin degradation products.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Jugular venous pressure (cm)</th>
<th>Liver fb(^1)</th>
<th>Oedema</th>
<th>Chest X-ray score</th>
<th>Plasminogen activator ELT (units)</th>
<th>Plate ELT (UK units)</th>
<th>Occlusion ELT (units)</th>
<th>Plasminogen (units/ml)</th>
<th>Fibrinogen (mg/100 ml)</th>
<th>FDP (μg/ml)</th>
<th>Activation inhibitor (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>35</td>
<td>F</td>
<td>VSD + Ebstein's disease</td>
<td>10</td>
<td>2</td>
<td>++</td>
<td>+</td>
<td>3·3</td>
<td>0·3</td>
<td>—</td>
<td>2·9</td>
<td>375</td>
<td>12·4</td>
<td>—</td>
</tr>
<tr>
<td>31</td>
<td>60</td>
<td>F</td>
<td>Pulmonary stenosis</td>
<td>18</td>
<td>4</td>
<td>—</td>
<td>—</td>
<td>6·2</td>
<td>2·8</td>
<td>—</td>
<td>3·5</td>
<td>355</td>
<td>21·6</td>
<td>3·2</td>
</tr>
<tr>
<td>32</td>
<td>66</td>
<td>M</td>
<td>ASD + Eisenmenger complex</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>7·6</td>
<td>3·8</td>
<td>25</td>
<td>4·7</td>
<td>490</td>
<td>12·8</td>
<td>5·4</td>
</tr>
<tr>
<td>33</td>
<td>43</td>
<td>F</td>
<td>Aorto-pulmonary window + Eisenmenger complex</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>11·0</td>
<td>2·5</td>
<td>16·5</td>
<td>5·5</td>
<td>335</td>
<td>0</td>
<td>3·5</td>
</tr>
</tbody>
</table>

\(^1\) ‘Finger breadths' below the costal margin.

ELT, Euglobulin clot lysis time; FDP, fibrin degradation products; VSD, ventricular septal defect; ASD, atrial septal defect; UK, urokinase.
Venous occlusion. The effect of venous occlusion on the plasminogen activator amount was studied in thirteen control subjects and ten patients with cardiac failure. In the control subjects the pre-occlusion amount averaged 4·3 (SD ± 2·2) units and the post-occlusion amount 9·3 (SD ± 4·3) units. In contrast, the pre-occlusion amount in patients in cardiac failure was 1·5 (SD ± 0·8) units with a mean of 4·0 (SD ± 4·7) units after venous occlusion. The individual values are illustrated in Fig. 1. The difference between the mean post-occlusion values in the control subjects and the cardiac failure patients was significant \((P<0·05)\).

Recovery from cardiac failure. Six patients were studied while in cardiac failure and after the failure had responded to treatment. After treatment the mean plasminogen activator and plasminogen amounts rose, whereas activation inhibitor fell (Table 2). The post-treatment mean values were close to those of the control group. The mean plasminogen activator response to venous occlusion was restored to normal in four subjects.

<table>
<thead>
<tr>
<th>Table 4. Correlations of euglobulin lysis time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jugular venous pressure</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Coefficient of correlation ((r))</td>
</tr>
<tr>
<td>Significance ((P))</td>
</tr>
</tbody>
</table>
**Fibrinolysis in cardiac failure**

*Congenital heart disease.* Four patients with congenital heart disease were studied (Table 3). Two patients (nos. 30 and 31) were in cardiac failure, as defined, yet had higher values of plasminogen activation than the mean value in cardiac failure. A further two patients (nos. 32 and 33) without cardiac failure had far higher values than the mean for control subjects.

**Correlations of the euglobulin lysis time.** There was a statistically significant inverse relationship between plasminogen activator amount determined by euglobulin lysis time and the jugular venous pressure (Fig. 2), but it was not related to the extent of oedema, liver size, chest X-ray score, urea or bilirubin (Table 4).

**DISCUSSION**

Sawyer, Fletcher, Alkjaersig & Sherry (1960) observed that the mean fibrinolytic activity, measured by a technique which primarily measures plasminogen activator, was decreased in patients with cardiac failure of unspecified aetiology and severity. Our findings have confirmed that patients with congestive cardiac failure have decreased amounts of plasminogen activator as measured either by the euglobulin clot lysis time or by the fibrin plate technique. In addition, there was a decrease in the plasminogen amount and an increase in the serum inhibitor of plasminogen activation and the antiplasmin \( \alpha_1 \)-antitrypsin. There was no significant change in the amount of the other principal antiplasmin \( \alpha_2 \)-macroglobulin, fibrinogen, or fibrin degradation products. These changes occurred to a similar extent in heart failure due to ischaemic, rheumatic, pulmonary or hypertensive heart disease and did not result from heart disease itself in the absence of cardiac failure. After successful treatment and the disappearance of signs of heart failure the abnormalities reverted towards normal.

The explanation for the alteration in components of the fibrinolytic system is uncertain. Hepatic disease is associated with changes in fibrinolysis (Fletcher, Biederman, Moore, Alkjaersig & Sherry, 1964; Ogston, Bennett & Ogston, 1971), but in the present study the amount of plasminogen activator did not correlate with the bilirubin amount, which was elevated in a number of patients with more severe heart failure. Renal disease with azotaemia is also associated with alterations in the fibrinolytic enzyme system (Bennett & Ogston, 1970). However, the urea amounts in the patients with cardiac failure did not correlate with plasminogen activator amounts.

The decreased plasminogen activator activity in congestive cardiac failure does not, therefore, appear to result from changes of renal or hepatic function, but correlates with the severity of failure as measured by the jugular venous pressure. Hypoxaemia of mixed venous blood, which reflects decrease in cardiac output (Muir, Kirby, King & Miller, 1970), might affect the release of plasminogen activator from venous endothelium. However, it has been shown that acute hypoxaemia in healthy subjects does not induce changes in the fibrinolytic enzyme system (Cunningham, Boyd, Windebank, Moran & McNicol, 1971), and in subjects with congenital heart disease fibrinolytic activity does not correlate with oxygen saturation (Menon, 1969). Indeed, in some cases of cyanotic heart disease fibrinolysis is accelerated (Goldschmidt, 1969; Johnson, Abildgaard & Schulman, 1968); this was noted in the four patients with congenital heart disease of the present study.

Venous occlusion is a potent stimulus for the production of fibrinolytic activity. It is presently believed that this is secondary to the release of plasminogen activator from vascular endothelium. In cardiac failure there was both a decrease in the amount of circulating plasminogen
activator and the amount failed to rise normally with the stimulus of venous occlusion. We conclude therefore that either the vein wall containing plasminogen activator is unresponsive to a stimulus that normally would cause release of the activator or the stores of plasminogen activator are depleted.

Depression of fibrinolysis has been reported after myocardial infarction (Bennett et al., 1967), but it is less marked than we have found in cardiac failure. Such depression also occurs after accidental and surgical trauma and may, therefore, represent a non-specific response to 'stress'. It is possible that at the onset of cardiac failure there is stimulation of fibrinolysis, similar to the initial response following accidental trauma, mediated by increased blood amounts of catecholamines known to occur in congestive cardiac failure (Chidsey, Harrison & Braunwald, 1962). If failure persists the plasminogen activator stores in venous endothelium could be depleted with consequent depression of fibrinolysis. It is known that repeated injections of nicotinic acid exhaust the fibrinolytic response that occurs initially (Weiner, de Crinis, Redisch & Steele, 1959). Against this possibility is the evidence that the enhanced fibrinolysis provoked by exercise showed no signs of abating after 4 h (Bennett, Ogston & Ogston, 1968), and that prolonged infusion or repeated injections of adrenalin resulted in increased fibrinolysis without tachyphylaxis (Genton, Kern & von Kaulla, 1961; Rahn & von Kaulla, 1964).

Even if depletion of plasminogen activator is the cause of the decreased blood amount found in cardiac failure, depletion cannot be the sole explanation for all the changes we have noted. The increased amounts of α1-antitrypsin and the serum inhibitor of plasminogen activation cannot be explained by this mechanism. Whatever the explanation of the changes in components of the fibrinolytic enzyme system, the decrease in plasminogen activator and increase in inhibitors may contribute to the genesis of the thrombo-embolic complications found in cardiac failure.

ACKNOWLEDGMENTS

We are grateful to Dr D. S. Short for reading the chest X-rays and to the physicians of the Aberdeen Teaching Hospitals for permission to study their patients. Mrs H. Lee and Mrs N. Hoogstadt provided careful technical assistance.

REFERENCES


