Myocardium as contributor of plasminogen activator to blood

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It is suggested that the myocardium contributes plasminogen activator to the blood circulation, and, further, that the increased activator content in venous as compared to arterial blood may be the reason why coronary sinus thrombosis is rare.

The plasminogen activator content in the circulating blood has hitherto been thought to derive largely from the endothelium of the veins (Messer, Celander, and Guest, 1962; Chakrabarti, Birks, and Fearnley, 1963; Warren, 1964), though this has been difficult to prove and several other hypotheses have been put forward. Pandolfi and his colleagues (1967), for instance, believe that the plasminogen activator is liberated from the vasa vasorum of the veins, and it has recently been suggested that the blood during its passage through the kidneys (Buluk and Furman, 1962; Menon and Dewar, 1967; Menon, 1968a, b; Menon, Dewar, and Newell, 1968b), muscles (Menon *et al.*, 1968a; Menon, 1969), brain (Menon *et al.*, 1970b), uterus (Maki *et al.*, 1965; Menon *et al.*, 1970a), and stomach (Menon and Dewar, 1970) receives this factor from the organs mentioned. It has further been suggested that the lymphatic system through its chyle is a potent contributor of this activator to the circulation (Menon, Weightman, and Dewar, 1970c).

The present investigation was carried out in order to examine the part the myocardium might play in the contribution of activator to the blood. With this object we compared the plasminogen activator content in blood obtained from a coronary sinus with the activator content in blood from the right atrium and a femoral artery.

Subjects and methods

During cardiac catheterization undertaken for the investigation of heart disease, blood samples were collected before heparin was given from 11 patients who were sedated with 100 mg quinalbarbitone sodium. All the patients were free from signs

of congestive cardiac failure and central cyanosis but suffered from rheumatic valvular disease.

Arterial blood was obtained by direct puncture of the femoral artery and venous blood by right heart catheterization using a Teflon catheter. This was inserted into the femoral vein or the anterior cubital vein and advanced centrally under fluoroscopic visualization into the right atrium. Before catheterization was carried out local anaesthetic (1% lignocaine) was administered at the puncture site.

After obtaining blood samples from the right atrium, a coronary sinus, and the femoral artery, 5 patients were given trinitrate tablets, as this drug is known to increase the rate of blood flow through the myocardium. Five minutes later a further blood sample was withdrawn from all three sites.

The plasminogen activator content was estimated in all the blood samples by the euglobulin lysis time method using a euglobulin lysis time recorder (Menon, Martin, and Weightman, 1969a). The advantages of this method, apart from its reproducibility, are that large groups of patients can be compared and that some conclusions can be drawn about the nature of the fibrinolytic system.

All estimations were made in duplicate. In a previous study duplicate samples of blood in succession were taken for control purposes from 30 healthy medical students and analysed for euglobulin lysis time. No statistically significant difference ($P > 0.2$) was found (Menon, Weightman, and Dewar, 1969b).

The euglobulin lysis time has been expressed in units by multiplying the reciprocal of the lysis time in minutes by 10,000. In fibrinolytic assays it has been shown that activity is a direct function of the reciprocal of the lysis time, and accordingly a logarithmic plot of lysis against units of activity shows a linear relation (Sherry and Alkjaersig, 1957). Sherry *et al.* (1959) have suggested that euglobulin lysis time could usefully be expressed in terms of arbitrary units of activity derived from such a plot. Moreover, we believe that by express-

ing the euglobulin lysis time in such units rather than in minutes, the interpretation of the results is facilitated since the higher the value the larger the activator content and *vice versa* (Menon *et al.*, 1969b).

Results

For the correct interpretation of the results we feel that some elaboration with regard to the methods used is necessary.

The small amount of local anaesthetic used at the site of the needle puncture is unlikely to produce any change in the activator level. We have previously investigated the possibility of such a change occurring in 10 normal subjects by comparing the euglobulin lysis time in blood samples from the sites of puncture in the anterior cubital vein before and after administration of local anaesthetic. No significant difference ($P > 0.05$) in the euglobulin lysis time was found between the two samples (Menon *et al.*, 1969b).

For this study the activator content in the coronary artery was assumed to be the same as that in the femoral artery. This assumption appears to be justifiable since an earlier study (Menon *et al.*, 1969b) had shown the activator content in the left atrium to be similar to that in blood from a femoral or brachial artery ($P > 0.05$).

It must be stressed that no heparin was given during cardiac catheterization until all the blood specimens for our investigation had been withdrawn.

Though all samples from the coronary sinus and femoral artery were obtained 5 to 15 minutes after withdrawal of the right atrial blood, it is unlikely that the fibrinolytic activity would change during so short a period. We have investigated the euglobulin lysis time in a femoral artery at time intervals varying between 15 and 30 minutes. No significant difference in lysis times was observed ($P > 0.05$). In the same study we investigated the activator content in blood from subclavian veins collected during cardiac catheterization at time intervals of between 15 and 30 minutes. No noteworthy difference ($P > 0.05$) in the lysis times could be shown (Menon *et al.*, 1969b).

A comparison between the activator content in the blood samples from a coronary sinus, the right atrium, and a femoral artery showed a higher activator level in the venous than in the arterial blood (Fig. 1 and 2). The finding that the activator content in the blood from a coronary sinus is larger than in that from an artery confirms the belief that the heart contributes activator to the blood. The increased activator content in the blood from a coronary

sinus compared to that from the right atrium indicates that the heart contributes much more activator than other organs to the venous blood.

Estimations of the activator content in the blood from the coronary sinus before and after trinitrate administration showed a considerable increase after the patients had taken the tablets (Fig. 2). On the other hand, the drug had no significant effect on the activator content in the blood obtained from the arterial

FIG. 1 Plasminogen activator levels.

FIG. 2 Plasminogen activator levels before and after trinitrate.

sites and the right atrium. This experiment shows that by accelerating the rate of blood flow through the heart muscle the activator content in the coronary sinus is increased, presumably due to a larger amount of activator being released from the myocardium into the coronary sinus.

Discussion

It has been shown (Menon *et al.*, 1968b), that the kidneys add an average of 6 per cent plasminogen activator to the circulating blood and that the brain contributes 2.7 per cent of the activator content to the blood (Menon *et al.*, 1970b).

It has further been shown that the splanchnic circulation decreases the level of plasminogen activator in the blood by an average of 1.36 per cent. The lungs, on the other hand, reduce the activator content in the circulation by as much as 16.7 per cent (Menon *et al.*, 1969b). Consequently the lungs and liver together reduce the plasminogen activator by an average of 18.06 per cent ($16.7 + 1.36$). Since this removal is only offset by an average contribution of 6 per cent from the kidneys and 2.7 per cent from the brain it is obvious that a substantial amount must come from other sources. The finding in the present study shows the myocardium to be one of these sources. Work is in progress which seems to indicate that the suprarenals, ovaries, testes, skin, and stomach (Menon and Dewar, 1970), uterus (Menon *et al.*, 1970a), muscles (Menon *et al.*, 1968a; Menon, 1969), and lymphatic system (Menon *et al.*, 1970c) also contribute activator to the blood.

The increased activator content in the coronary sinus blood, which we have shown, may be the reason why coronary sinus thrombosis is a rare occurrence. The increased activator content in venous blood compared to arterial blood may explain why despite the sluggish blood flow in the veins the incidence of venous thrombosis is less than would be expected.

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References

- Buluk, K., and Furman, M. (1962). On the controlling function of the kidneys in fibrinolysis. *Experientia*, **18**, 146.
- Chakrabarti, R., Birks, P. M., and Fearnley, G. R. (1963). Origin of blood fibrinolytic activity from veins and its bearing on the fate of venous thrombi. *Lancet*, **1**, 1288.
- Maki, M., Nagayama, M., Sasaki, K., and Yoneya, T. (1965). A model of local fibrinolysis: marked elevation of fibrinolytic activity of blood obtained from vasa efferentia of the uterus. *Tohoku Journal of Experimental Medicine*, **86**, 43.
- Menon, I. S. (1968a). The role of the kidney in fibrinolytic activity of the blood and urinary tract. *Antiseptic*, **65**, 15.
- Menon, I. S. (1968b). Urokinase and the possible role of the kidney in its production. *Antiseptic*, **65**, 903.
- Menon, I. S. (1969). Muscles as a possible source of plasminogen activators to the circulation. *Journal of the Association of Physicians of India*, **17**, 141.
- Menon, I. S., Barron, S. L., Weightman, D., and Dewar, H. A. (1970a). The uterus as contributor of plasminogen activator to the blood. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **77**, 591.
- Menon, I. S., Burke, F. D., Dewar, H. A., Smith, P. A., and Newell, D. J. (1968a). A study of the possible causes of increased fibrinolytic activity during exercise. In *International Conference on Microcirculation, Gothenburg, 24th to 28th June*, p. 107.
- Menon, I. S., and Dewar, H. A. (1967). The role of the kidney in fibrinolytic activity of the blood and urinary tract. In *First International Symposium on Tissue Factors in Homeostasis of the Coagulation-Fibrinolysis System, Florence, 2nd to 5th May*, p. 301.
- Menon, I. S., and Dewar, H. A. (1970). The role of the heart, the stomach and the uterus in the contribution of plasminogen activator to the circulation. In *VIIth International Conference on Microcirculation, Aalborg, 22nd to 26th June*, p. 120.
- Menon, I. S., Dewar, H. A., and Newell, D. J. (1968b). Role of the kidney in fibrinolytic activity of blood. *Lancet*, **1**, 785.
- Menon, I. S., Martin, A., and Weightman, D. (1969a). Estimation of euglobulin lysis time using a time-saving recorder. *Laboratory Practice*, **18**, 1186.
- Menon, I. S., Muscat-Baron, J., Weightman, D., and Dewar, H. A. (1970b). The brain as contributor of plasminogen activator to the blood. *Clinical Science*, **38**, 85.
- Menon, I. S., Weightman, D., and Dewar, H. A. (1969b). The role of the lung in blood fibrinolysis. *Clinical Science*, **36**, 427.
- Menon, I. S., Weightman, D., and Dewar, H. A. (1970c). The lymphatic system as contributor of plasminogen activator to the blood. *Angiologica*, **7**, 177.
- Messer, D. L., Celander, D. R., and Guest, M. M. (1962). Stability of fibrin contiguous to intima of veins. *Circulation Research*, **11**, 832.
- Pandolfi, M., Nilsson, I. M., Robertson, B., and Isacson, S. (1967). Fibrinolytic activity of human veins. *Lancet*, **2**, 127.
- Sherry, S., and Alkjaersig, N. (1957). Studies on the fibrinolytic enzyme of human plasma. *Thrombosis et Diathesis Haemorrhagica*, **1**, 264.
- Sherry, S., Lindemeyer, R. I., Fletcher, A. P., and Alkjaersig, N. (1959). Studies on enhanced fibrinolytic activity in man. *Journal of Clinical Investigation*, **38**, 810.
- Warren, B. A. (1964). Fibrinolytic activity of vascular endothelium. *British Medical Bulletin*, **20**, 213.