CHAPTER 3

The early course of D-dimer concentration following pulmonary artery embolisation

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SUMMARY

Background There is little information about the course of D-dimer concentration in patients during the first hours of a thrombotic event. We measured D-dimer concentrations following pulmonary artery embolisation in patients with pulmonary arteriovenous malformations.

Methods We studied D-dimer concentration before and during an 8-hour time period after embolisation in 13 patients; the control group were 14 patients with a diagnostic heart catheterisation without embolisation. We investigated the extent of D-dimer concentration in relation to the total volume of the parts of the embolised arteries, the improvement in pO2 and the reduction in shunt fraction.

Results The patients had significantly increased D-dimer levels at t=2, 4 and 8 hours after the procedure as compared to baseline ($p=0.001$) and to the controls ($p=0.047$). We found a correlation between D-dimer concentration and the calculated volume of the embolised arteries ($R^2=0.74$).

Conclusions There is no relevant lag time between the increase in D-dimer concentration and pulmonary embolisation. The relation between D-dimer concentration and thrombus size deserves confirmational studies.

INTRODUCTION

The onset of venous thromboembolic processes is accompanied by an increase in the concentration of D-dimers, which are products of the plasmin-mediated proteolysis of cross-linked fibrin. Measurement of D-dimer concentration is considered to be a promising tool in the reduction of additional tests to rule out venous thromboembolism (VTE). Sensitivity and negative predictive value of D-dimer tests have been investigated in several management studies (1-4). Although some authors suggest that anticoagulant therapy can be withheld in patients with normal D-dimer levels (5;6), studies about the accuracy of different D-dimer tests show large variations in sensitivity and negative predictive value (7-9). A source of variation in D-dimer concentration may be the time of D-dimer determination in relation with the duration of symptoms or the onset of the thromboembolic process (10;11). Data about the course of D-dimer concentration in patients with VTE are limited to a study during the first days of heparin treatment in patients with deep venous thrombosis (12). It is of clinical importance to be informed about the time of increase and decrease in D-dimer concentration to establish the optimal time of D-dimer testing and to define the time-period before and after which a D-dimer test may have reduced accuracy. In addition, it is of interest to be informed about the correlation between the size of the thrombus and the extent of D-dimer concentration, as large thrombi may lead to a more aggressive therapeutic approach and to a more careful monitoring.

We studied the course of D-dimer concentrations in patients undergoing embolisation of pulmonary arteries because of pulmonary arteriovenous malformations (PAVM) that caused hypoxemia and right-to-left shunts. We also calculated the correlation between D-dimer concentrations and the estimated size of the thrombus.

PATIENTS AND METHODS

Patients

We studied 13 patients with hereditary hemorrhagic teleangiectasia (HHT) or Rendu-Osler-Weber disease who underwent embolisation because of PAVM causing hypoxemia and increased right-to-left shunts. Embolisation in patients with PAVM induces thrombus formation due to local haemostasis in the presence of thrombogenic fibres attached to coils. The patient group consisted of 13 individuals (3 men and 10 women) with a mean age of 39.9 ± 12.2 years (range: 23-66 years). The control group consisted of 14 patients (8 men and 6 women) with a mean age of 56.3 ± 17.5 years (range: 23-82 years) who underwent a diagnostic right and/or left heart catheterisation procedure with pulmonary or coronary angiography without any intervention. The individuals in the control group were suspected of aortic or mitral insufficiency (n=4), aortic stenosis (n=1), coronary insufficiency (n=2), HHT (n=3), pulmonary hypertension (n=2), Scimitar syndrome (n=1) or screened for lung transplantation (n=1). Patients and controls did not use oral anticoagulants.

Methods

The catheterisation in both groups was carried out by right heart catheterisation through a femoral approach. The quantity of heparin to flush the catheter in the embolised group was at least 3000 IU with a maximum of 5000 IU depending on the length of the procedure. The control group received a standard dose of 5000 IU heparin. There was no significant difference in the median dose of heparin used in patients and controls. The duration of the procedure was 1-3 hours in both groups. For the embolisation, we used coils made of platinum with and without synthetic fibres (Cook, Denmark and Target Therapeutics, Ireland). Blood was collected two hours before, at the start of and two, four and eight hours after the procedure. We used the Asserachrom® ELISA (Diagnostica Stago, France) for the determination of D-dimer concentrations. All patients gave informed consent and the medical ethical committee of the St. Antonius Hospital approved the study protocol.

The size of the thrombus induced by the coils was estimated in three different ways. We calculated the total volume of the parts of the pulmonary arteries that were embolised ($\sum \pi r^2 x$ length).

We calculated the reduction of the right to left shunt measured with 100% oxygen, as described previously (13-15). Finally, we measured differences in pO2 (in kPascal) before and after the embolisation.

Statistics

Between groups repeated measurements ANOVA was used (α-levels were 0.05). Data are given as mean ± standard error of the mean. For calculation of correlation Pearson's correlation and p-values were used.

RESULTS

The course of D-dimer concentration determined by the Asserachrom® ELISA assay in the patient and control group is shown in Fig. 1. The results at t=-2 and t=0 hours were similar and combined at t=0 hours. At the start of the procedure, no differences in D-dimer concentration were found between the two groups. At t=2 hours, D-dimer concentration in the patient group was significantly higher as compared to D-dimer concentration at baseline (p=0.001). The D-dimer values obtained at t=4 hours and t=8 hours remained significantly higher when compared to baseline (p=0.02 and p=0.001 respectively). The control group showed no significant increase in D-dimer concentration as compared to baseline. The increase in D-dimer concentration in the patient group differed significantly from the control group (p=0.047).

We found a correlation between D-dimer concentration and the calculated volume of the parts of the pulmonary arteries that were embolised (R^2=0.74, p<0.001) (Fig. 2), but not between D-dimer concentration and the decrease of the right to left shunt or the increase in pO2 (R^2=0.26, p=0.1 and R^2= 0.06, p=0.5 respectively).

Figure 1. Course of D-dimer concentration following pulmonary embolisation in patients with pulmonary arteriovenous malformations. Controls under went diagnostic heart catheterisation without intervention.

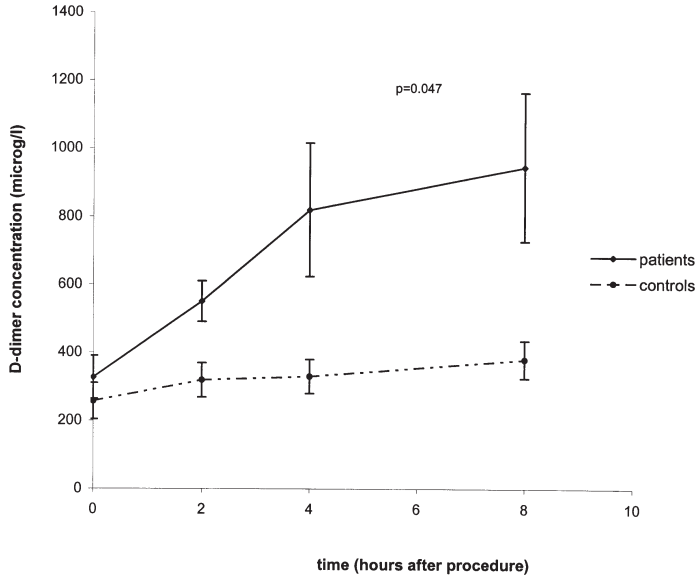
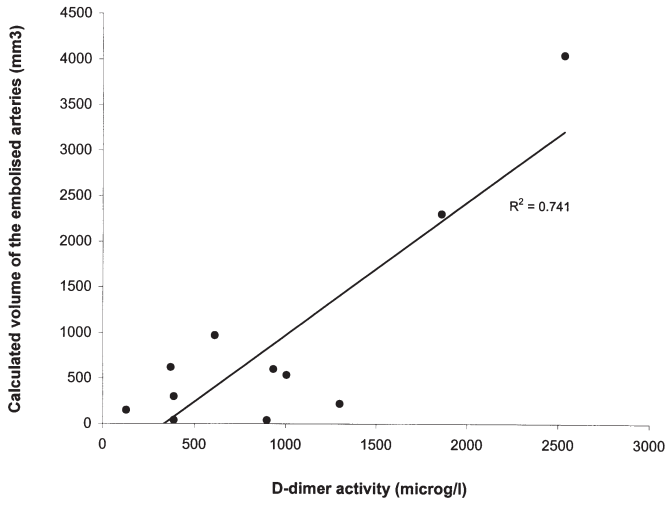


Figure 2. Relationship between D-dimer concentration and calculated surfaces of the parts of the embolised arteries following pulmonary embolisation.



DISCUSSION

Determination of D-dimer concentration is increasingly used as diagnostic tool for exclusion of VTE. The moment of D-dimer determination in pulmonary embolism (PE) varies from an immediate diagnostic procedure in patients with sudden onset of dyspnoea and chest-pain to a delayed procedure in patients with unexplained thoracic complaints for a longer period. The exact time after which D-dimer concentrations begin to rise and fall after the formation of a clot in humans is unknown. Because PE is often preceded by the formation of a thrombus in the legs, our model of PAVM-embolisation may not be identical to the events in patients with PE. Our study mimics, however, some of its aspects and provides data about the D-dimer concentration in the first hours after a thromboembolic event.

In this study in patients with PAVM undergoing embolisation, we observed a significant increase in D-dimer concentration at 2 hours after the start of embolisation, which remained significantly elevated during 8 hours. This implicates that D-dimer concentrations show an almost immediate increase after the start of embolisation and makes the existence of a lag time unlikely. A significant time by group interaction was present, which means that the differences in D-dimer concentration between patients and controls increased during the observation period of 8 hours and that the increase of D-dimer was not due to the catheterisation alone. The clinical implication of this finding is that D-dimer concentrations remain elevated for at least the first 8 hours after the onset of thrombosis.

In a previous study, a trend but not a significant correlation was found between D-dimer levels and the location of VTE (16). In the present study, we found a correlation between D-dimer concentrations and the calculated volume of the parts of the pulmonary arteries that were embolised. This may indicate higher D-dimer levels to be present in larger thrombus formations. The fact that we did not find a correlation between D-dimer levels and differences in shunt fraction and pO2 after embolisation may be due to the fact that the latter two are indirect estimates of thrombus formation, while measurement of the volume of the arteries is a more direct approach. Furthermore, there may be inter-individual differences in fibrinolytic activity after a thromboembolic event. However, as functional impairment is more relevant than the size of the thrombus, it is -in our opinion- not correct to delay further tests (such as pulmonary angiography) in patients suspected

for having PE with only small increases in D-dimer concentration and non-diagnostic ventilation-perfusion scans.
In conclusion, we found no relevant lag time between the increase in D-dimer concentration and pulmonary embolisation in patients with PAVM. D-dimer concentrations remain elevated during at least the first 8 hours of a thrombotic event. The D-dimer concentration may be helpful to predict the extent of thrombus formation.

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