Drawing-up of coagulation standards in sheep - precondition for extracorporeal oxygenation of premature lambs

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Sheep have been used as an animal model in experimental perinatology as well as in the evaluation of artificial lungs; in both fields a lack of excessive bleeding was observed. The extracorporeal oxygenation of premature lambs was used as an animal model for prolonged respiratory support for the newborn with a membrane oxygenator. The animal model not only demonstrated excellent oxygenation and CO_2 removal to the premature lamb, but also seemed to be relatively innoxious to the subject. So it was surprising that the application of the same method led to hemorrhagic complications. In order to make experiments of the extracorporeal oxygenation of the animal model premature lamb more comparable to the situation of the newborn human infant, more has to be known about the coagulation system of sheep blood. Coagulation standards were drawn up from 100 mature female merino-sheep at the age of 2 to 3 years, taken from several herds in Berlin, and compared to normal human ranges.

First we examined the routine methods used clinically

	x	96% range	normal human range	Vk %
Prothrombin time (%)	95	62-250	70-140	3,4
Activated partial thromboplastin time (sec)	30,3	20,5 -51,7	30-40	2,1
Thrombin time (sec)	14,8	11,8 -22,1	14,5-17,5	4,2
Reptilase time(sec)	19,8	14,8 -26,0	20	5,3
Fibrinogen level(g/l)	2,25	1,4 -5,0	2-4	3,0

Thus in these methods we did not find those obvious differences which would lead to a comprehension of the different experimental and clinical findings. In addition citrated whole sheep blood, still recalcified, was examined by thrombelastrographic tracing. Here there were clear differences to human values:

	r(min)	k(min)	G_{max}	G_{60}	G_{90}	G_{120}
96% range	2-9	1-3, 5	144-488	144-455	144-488	144-488
25 percentile	3	1,5	201	190	201	199
median: X	4,13	1,88	245	239	245	245
75 percentile	5,25	2,5	335	322	335	326
normal human range	3-6	1-3	100-150	90-130	80-120	80-110

Whereas r-time and k-time were similar to those of humans we did find higher amplitudes, and so higher shear modulus, and a later reaching of the maximal amplitude.

The activity of antithrombin III was also examined. In our opinion

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this heparine cofactor is of particular interest in experiments in which heparinisation is an important factor in order to prevent coagulation in the extracorporeal circulation. A lesser AT III activity was found (sheep 60-100% in comparison to humans 70-130%) which leads to a different heparine sensibility, the human sensibility being higher than that of the sheep. As the most important factor of the fibrinolytic system the plasminogen activity in sheep blood was examined. Since sheep plasminogen like bovine plasminogen does not react with streptokinase, we used human euglobulin fraction as a plasminogen proactivator. Here we were able to show the biological distribution of the plasminogen activities in sheep, but it was impossible to compare the results of this estimation specially suited to sheep and bovine plasminogen with normal human activities. For this reason we had to resort to another method, which is based on the activation of plasminogen through urokinase and which can be used in sheep plasma as well as in human plasma. The results found with the streptokinase method and related to a sheep pool moved in a range between 64% and 143% with a fixed median value of 100%. By means of the urokinase method related to a human pool, the activities moved in a range between 7% and 16%, with a median value of 11%. So the plasminogen activity of sheep is about 1/10 that of the human plasminogen activity.

Summary:

In conclusion we can say:

1. The small coagulation status shows similar values to that of humans;
2. r-time and k-time on the thrombelastogramme are comparable with that of humans, but the shear modulus measured as amplitude are higher;
3. the AT III level of sheep is lower;
4. the plasminogen activity of sheep is clearly lower.

However, there seems to be obvious differences concerning the coagulation system in sheep and human beings; therefore these results achieved in the animal model sheep can only be related to humans to a very limited extent.

Literature from the author.

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