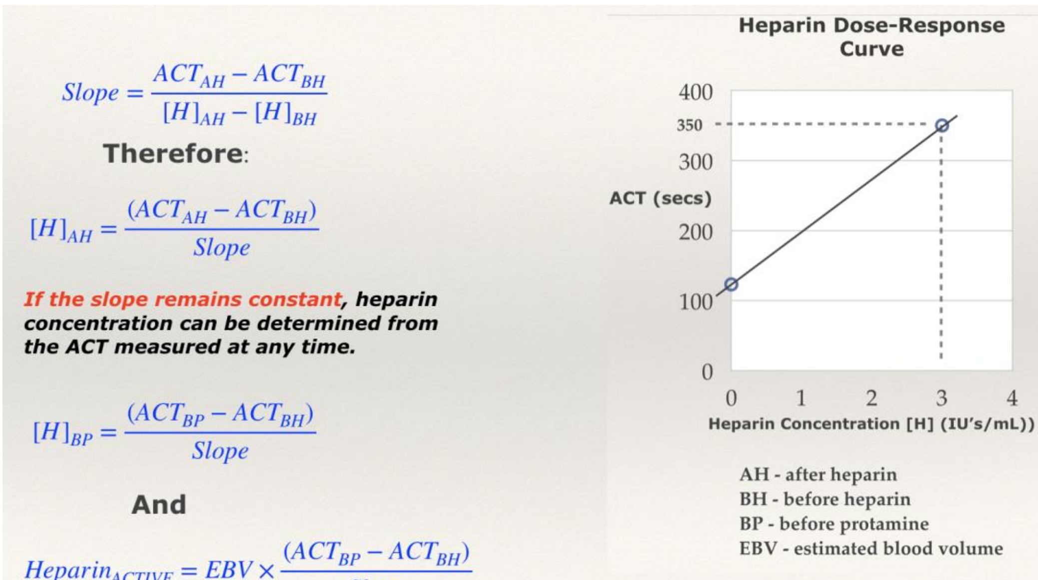
Appendix A. Explanation of methodology used in determining heparin and protamine administration

Baseline characteristics needed include age, sex, height and weight (used to estimate the EBV), oral anticoagulant, pre-heparin ACT and post-heparin ACT. The formula of Nadler[1] is used to calculate the estimated blood volume (EBV). The heparin concentration after the first dose of heparin is estimated by dividing the dose given by the EBV.



Calculated heparin Vs ACT

ACT_{AH} is the ACT after heparin is given.

ACT_{BH} is the ACT before heparin is given.

ACT_{BP} is the ACT before protamine is given.

$[H]_{AH}$ is the Heparin concentration after the initial dose of heparin is given (calculated from the total amount of heparin given, and the estimated blood volume).

$[H]_{BH}$ is the Heparin concentration before the initial dose of heparin is given. (Zero in all patients in this study)

EBV is the estimated blood volume

Calculating the slope of the HDR curve and 'active' concentration of heparin

The logic behind this approach is as follows:

- The volume of distribution of heparin has been shown to be closely approximated to the blood volume.[2]
- The 'effective' heparin concentration can be estimated by dividing the initial heparin dose by the estimated blood volume (EBV) after redistribution of the heparin has occurred.
- The initial heparin concentration before heparin is given is considered to be zero.

- The slope of the heparin:ACT dose-response curve can be estimated if the ACT is measured before and after the heparin is given.
- Knowing the individual heparin:ACT dose-response curve slope enables an estimate of the heparin concentration for a measured ACT.
- This allows estimation of subsequent doses of heparin required to maintain a desired ACT, and the protamine dose needed to reverse the active heparin at that ACT.
- The median heparin:ACT dose-response curve taken from all patient measurements can be used to estimate the initial heparin dose likely to achieve a desired ACT in future cases.

The slope of the heparin-ACT dose-response relationship (HDR) is calculated for each patient and used for individual patient calculations. The individual slopes of the HDR are averaged for each type of oral anticoagulant and used for the initial heparin dose estimation.

The slope of the individual HDR is used to adjust subsequent doses of heparin to maintain a desired ACT, and to calculate the amount of "active" heparin at any point during the procedure.

Each patient has a unique heparin dose-response relationship. The slope of this relationship can be estimated from the theoretical heparin concentration found by dividing the dose of heparin given with the EBV using Nadler's formula as follows:

A.1. $$Slope = \frac{(ACTah - ACTbh)}{([H]ah - [H]bh)}$$

Where [H] indicates heparin concentration in units/mL, ah is after heparin and bh is before heparin.

Once the slope is calculated for that individual patient, rearrangement of the equation becomes:

$$[H]ah - [H]bh = \frac{(ACTah - ACTbh)}{Slope}$$

If the heparin concentration before heparin is given is zero, this becomes:

$$[H]ah = \frac{(ACTah - ACTbh)}{Slope}$$

If the slope remains constant, the concentration of heparin actively contributing to anticoagulation ('active heparin') can be estimated for the current ACT.

A.2. $$[H]current = \frac{(ACTcurrent - ACTbh)}{Slope}$$

This should allow adjustments to heparin by infusion or by intermittent dosing (vide infra).

Calculating the initial heparin loading dose

If the average slope for a particular subgroup of patients is calculated (and recalculated with each case), the average slope moves toward the population mean. The Winsorized[1] mean is calculated in order to remove the influence of outliers. Using this mean slope, the heparin concentration for a particular ACT can be estimated, and from that, the dose required.

A.3 $$[H]for\ desired\ ACT = \frac{(ACTah - ACTbh)}{Mean\ Slope}$$

For example, if the average slope of the heparin:ACT dose response curve for patients taking Xarelto (Rivaroxaban) is 84.62, and the estimated blood volume for a particular patient is 5040 mL, with a pre-Heparin ACT of 125, the estimated heparin concentration for an ACT of 360 would be:

$$[H]\ for\ ACT\ of\ 360 = \frac{(360-125)}{84.62}$$

OR 2.78 Units/mL

If the heparin concentration is then multiplied by the estimated blood volume of 5040 mL, the loading dose needed to achieve this heparin concentration would be:

$$Loading\ dose\ (IU's)\ =\ 2.78\ Units/mL\ \times 5{,}040\ mL$$

OR

Loading dose (IU's) = 14,011 IU's of heparin

A Winsorized mean is a statistical measure of central tendency. It involves the calculation of the mean after winsorizing -- replacing given parts of a probability distribution or sample at the high and low end with the most extreme remaining values, typically doing so for an equal amount of both extremes; often 10 to 25 percent of the ends are replaced.

Once the initial loading dose is given, ten minutes is allowed to pass to allow for the initial redistribution phase of heparin. The ACT is measured again and the patient's individual heparin:ACT dose response curve can be calculated as follows:

1. Estimate the heparin concentration achieve by that dose of heparin (Equation A.2.)

Given a loading dose of 14,000 Units and an EBV of 5.040mL:

$$[H]ah\ =\ \frac{14{,}000\ units}{5{,}040\ mL}$$

OR 2.78 Units/mL

2. Estimate to skope for that individual patient using equation A.1.

If the post-Heparin ACT was 351seconds, the pre-heparin ACT was 125 and the patient had not received heparin before the procedure (ACT_{bh} = 0), we can use:

$$Slope = \frac{(351-125)}{2.78}$$

OR

81.29

Note: this individual slope is different from the mean slope, and is the slope of that individual patient's heparin:ACT dose-response curve. This is the value that should be used in all future calculations for that patient.

Calculating boluses needed to maintain the desired ACT

If the ACT measured falls below the desired ACT, a heparin bolus is required to raise the ACT to the desired level.

This amount of heparin required can be estimated by using the individual heparin:ACT response curve for the patient:

The current heparin concentration is given by equation A.2.:

$$[H]current = \frac{(ACTcurrent - ACTbh)}{Slope\ of\ the\ patient}$$

The desired Heparin concentration is given by:

$$[H]desired = \frac{(ACTdesired - ACTbh)}{Slope\ of\ the\ patient}$$

The difference is given by:

$$[H[difference = [H]desired - [H]current$$

OR:

$$[H]difference = \frac{(ACTcurrent - ACTbh)}{Slope\ of\ the\ patient} - \frac{(ACTdesired - ACTbh)}{Slope\ of\ the\ patient}$$

which simplifies to:

$$[H]difference \times Slope\ of\ the\ patient = (\text{ACTDesired} - \text{ACTBH}) - (\text{ACTCurrent} - \text{ACTBH})$$

∴ A.4. $[H]difference = \frac{(\text{ACTdesired} - \text{ACTcurrent})}{Slope\ of\ the\ patient}$

If the actual slope for an individual patient was 81.23 seconds.IU^{-1}.mL, and the current ACT was measured as 320 seconds and the estimated blood volume was 5040 mL then to increase the ACT to 360, the calculation would be as follows:

$$Heparin\ Dose = [H]difference \times EBV$$

OR in this case,

$$Heparin\ Dose = \frac{(360 - 320)}{81.29} \times 5040$$

OR

2480 IU’s

Heparin Infusion

Estes has calculated the half-life of the anticoagulant effect for heparin in healthy men to be about 1.5 hours. However, this estimate is dose-dependent and varies with the assay method employed for its measurement. In the doses used for catheter ablation, this is a reasonable starting point.

If we assume the rate of elimination of heparin to be constant over short periods of time, and half the amount of heparin is no longer active after 1.5 hours, then we can say that half the dose of heparin will be gone in 90 minutes:

$$\frac{1}{2} \times [H] \cong \frac{3}{2}\ hours$$

If we multiplying both sides by 2/3, the amount of activity lost in one hour can be estimated.

Therefore roughly one-third the initial dose lost in the first hour. It would be reasonable to start an infusion at a rate equivalent to one-third the initial loading dose per hour, adjusting the rate thereafter to account for changes in the ACT.

Estimating the ACT for a given initial heparin dose in an individual patient when their HDR is known

We know that

$$Slope = \frac{(ACTah - ACTbh)}{([H]ah - [H]bh)} \qquad \text{(Equation A.1.)}$$

$$\therefore (ACTah - ACTbh) = Slope \times ([H]ah - [H]bh)$$

Given a pre-heparin concentration of zero, this becomes

A.5. $ACTah = Patient\ Slope\ \times [H]ah + \ ACTbh$

If 1 mg/Kg is given, the heparin dose will give a heparin concentration of:

$\frac{1\times \text{Weight in Kg}}{EBV}$ as mg/mL

As 1mg of heparin is equivalent to 100 Units;

$[H]AH \ = \frac{(100 * \text{WtKg})}{EBV}$ Units/mL

∴ From equation A.5. $ACTah = \frac{(Patient\ Slope \times 100 \times WtKg)}{EBV} + \ ACTbh$

e.g. if weight is 113 Kg, Slope is 59.08, EBV is 6838 mL , and ACT_{BH} is 126

$$ACTah = \frac{(59.08 \times 100 \times 59.08)}{6838} + \ 126$$

OR

ACT_{ah} = 223 seconds

References

1. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962 Feb;51(2): 224-232.
2. Estes J.W. Clinical Pharmacokinetics of Heparin. Clinical Pharmacokinetics, 1980;5:204–220.

Appendix B. TEG results

1. Cases showing the heparin effect

Patient 20

Time	Test	TEG_ACT	R-Time	K-Time	alpha	A10	MA	LY30	ID
2024-03-07 15:56:21	CK	144	20.9	2.8	58.3	57.8			
2024-03-07 15:56:21	CRT		1.0	1.3	72.1	60.7	55.9		
2024-03-07 15:56:21	CKH		13.5	5.8	38	55.9			
2024-03-07 15:56:21	CFF					21.3			
2024-03-07 15:59:11	CK	87.9	9.1	1.5	68.4	62.9			
2024-03-07 15:59:11	CRT		0.4	1.3	75.4	62.8	63.2		
2024-03-07 15:59:11	CKH		7.1	1.6	69.5	62.4			
2024-03-07 15:59:11	CFF					21.9			

CK R > 9.1 and CK K > 2.1 - consider anticoagulants, haemophilia, factor deficiency.
CKR-CKH > 3 **but restored by additional protamine**
Suggest Fresh Frozen Plasma, Protamine

Patient 21 Protamine predicted 798mg –> protamine given 500 mg
CKR 26.9 CKH 18.3 → difference > 3 minutes → more protamine needed

Time	Test	TEG_ACT	R-Time	K-Time	alpha	A10	MA	LY30	ID
2024-03-07 14:48:15	CK	134.7	26.9	10.9	38.0	23			
2024-03-07 14:48:15	CRT		0.9	1.0	75.3	66.1			
2024-03-07 14:48:15	CKH		18.3	4.6	42	57.9			
2024-03-07 14:48:15	CFF					35.7			

Patient 30 Protamine predicted 331 –> protamine given 300 mg

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	125.3	11.5	3.3	52.1		43.1	
CRT		0.8	2.5	63.6	37.5	45.8	
CKH		7.2	1.8	69.0		47.8	
CFF						13.2	

Low Fibrinogen and possible low platelets
Suggest Cryoprecipitate 10 Units or fibrinogen 2G
CKR-CKH > 3minutes – suggest protamine

Patient 31 (Heparin effect)

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	125.3	11.5	3.3	52.1		43.1	
CRT		0.8	2.5	63.6	37.5	45.8	0.0
CKH		7.2	1.8	69.0		47.8	
CFF					12.6	13.2	

Low Fibrinogen and possible low platelets Suggest Cryoprecipitate 10 Units or fibrinogen 2G
R is prolonged, indicating delayed clot formation Suggest giving FFP
CK R > 9 minutes. Suspect decrease in coagulation factors CK R and CKH both prolonged with CKR-CKH > 3 minutes (4.3 minutes) there is a coagulation defect due to heparin. Suggest more protamine.
CK R > 9.1 and CK K > 2.1 - consider anticoagulants, haemophilia, factor deficiency.
Suggest Fresh Frozen Plasma
CK MA < 52 and CK alpha < 63 - suggesting weak clot
Consider anticoagulants, haemophilia, factor deficiency.
Suggest Cryoprecipitate 10, 20 or 30 Units) or fibrinogen (2, 3 or 4G)

Patient 44 Protamine predicted 261 –> protamine given 260 mg

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	97.3	15.6	4.2	36.9		53.8	
CRT		0.5	1.8	72.1	48.5	56.1	0.2
CKH		9.1	2.2	36.9		57.3	
CFF						19.5	

Patient 45

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	97.3	8.6	2.8	54.4		44.6	
CRT		0.5	2.8	63.6	36.3	44.5	
CKH		6.5	1.9	67.9		47.9	
CFF					13.5	14.3	

Low Fibrinogen and possible low platelets
Suggest Cryoprecipitate 10 Units or fibrinogen 2G
CK MA < 52 and CK alpha < 63 - suggesting weak clot
Consider anticoagulants, haemophilia, factor deficiency.
Suggest Cryoprecipitate 10, 20 or 30 Units) or fibrinogen (2, 3 or 4G
CK R / CKH R ratio > 1.25 Indicates Heparin effect Additional protamine is indicated

2. Cases where heparin is not significant

Patient 6 (Platelet defect)

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	116	7.4	1.5	69.4		57.0	
CRT		0.7	2.2	71.5	43.2	51.3	
CKH		7.6	1.6	67.2		56.3	
CFF					17.6	17.7	

Platelet function is abnormal or numbers decreased If CFF MA < 25 mm give 2 units pooled platelets

Patient 14

Time	Test	TEG_ACT	R-Time	K-Time	alpha	A10	MA	LY30	ID
2024-03-07 15:31:27	CK	181.5	19.2						
2024-03-07 15:31:27	CRT		1.4	2.2	66.4	47.4	41.6		
2024-03-07 15:31:27	CKH		19.2						
2024-03-07 15:31:27	CFF						12		
2024-03-07 15:34:36	CK	125.3	18	1.4	72.1	53.8			
2024-03-07 15:34:36	CRT		0.8	1.8	71.8	58.0	44.2	0	
2024-03-07 15:34:36	CKH		18	2.9	55	51.0			

CK R > 9 minutes Suspect decrease in coagulation factors
CK R and CKH both prolonged to the same extent
There is a coagulation defect, but NOT due to heparin
R is prolonged, indicating delayed clot formation
Suggest FFP 2-4 units or Prothrombinex 25-50u/kg

Patient 15

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	125	6.6	2.4	62.7		46.6	
CRT		0.8	3.2	56.1		44.7	
CKH		6.7	2.1	66.5		47.3	
CFF					9.4	10.2	

Low Fibrinogen and possible low platelets
Suggest Cryoprecipitate 10 Units or fibrinogen 2G
CK MA < 52 and CK alpha < 63 - suggesting weak clot Consider anticoagulants, haemophilia, factor deficiency. Suggest Cryoprecipitate 10, 20 or 30 Units) or fibrinogen (2, 3 or 4G)

Patient 28

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	116	6.2	2.3	56.7		51.4	
CRT		0.7	2.8	64.6	41.4	49.1	
CKH		6.2	1.6	69.7		52.8	
CFF					15.7	16.4	

Platelet function is abnormal or numbers decreased
If CFF MA < 25 mm give 2 units pooled platelets
CK MA < 52 and CK alpha < 63 - suggesting weak clot
Consider anticoagulants, haemophilia, factor deficiency. Suggest Cryoprecipitate 10, 20 or 30 Units) or fibrinogen (2, 3 or 4G)

Patient 21 Normal TEG

Test	TEG-ACT (seconds)	R Time minutes	K Time (minutes)	alpha (degrees)	A10 (mm)	MA (mm)	LY30 (%)
CK	106.6	6.4	1.2	72.7		62.8	
CRT		0.6	1.4	72.2	56.3	61.8	0.1
CKH		7.3	1.6	68.2		60.9	
CFF						21.6	