Heparin monitoring during cardiopulmonary bypass

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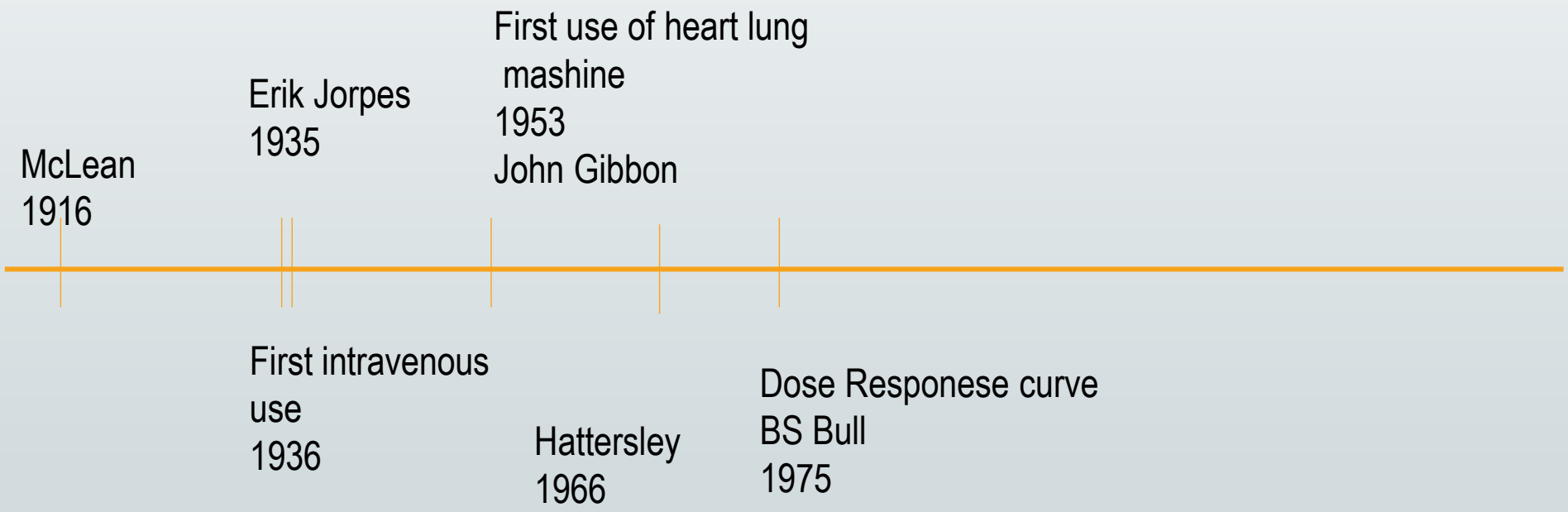
THORACIC CENTERS IN SWEDEN

- Umeå
- **Uppsala**
- Stockholm
- Örebro
- Linköping
- Göteborg
- Karlskrona
- Lund

5500 procedures/year

HEPARIN AND ACT



Heparin therapy during extracorporeal circulation

I. Problems inherent in existing heparin protocols

Five heparin protocols, representative of about 30 presently used throughout the country, were analyzed. The adequacy of anticoagulation during and the precision of protamine neutralization at the conclusion of extracorporeal circulation were studied. In each of 50 patients, the half life of heparin and the sensitivity to heparin were measured. Knowledge of the patient's age, height, weight, or surface area was of no help in predicting heparin kinetics. The study group consisted of the 2 patients with the longest and the 2 patients with the shortest heparin half lives, as well as the 2 patients who showed the greatest sensitivity to heparin and the 2 who showed the least. By computer simulation, each was managed according to the five protocols and by a monitoring procedure. The protocols failed to provide safe anticoagulation or precise protamine neutralization, whereas the simplified monitoring approach was uniformly successful.

Brian S. Bull, M.D.,* Ralph A. Korpman, M.D.,* Wilfred M. Huse, M.D.,** and Bernard D. Briggs, M.D.,*** *Loma Linda, Calif.*

"WITH AN ACT IN EXCESS OF 300 SECONDS, BLOOD IN THE EXTRACORPOREAL CIRCUIT NEVER TENDS TO FORM EVEN SMALL CLOTS"

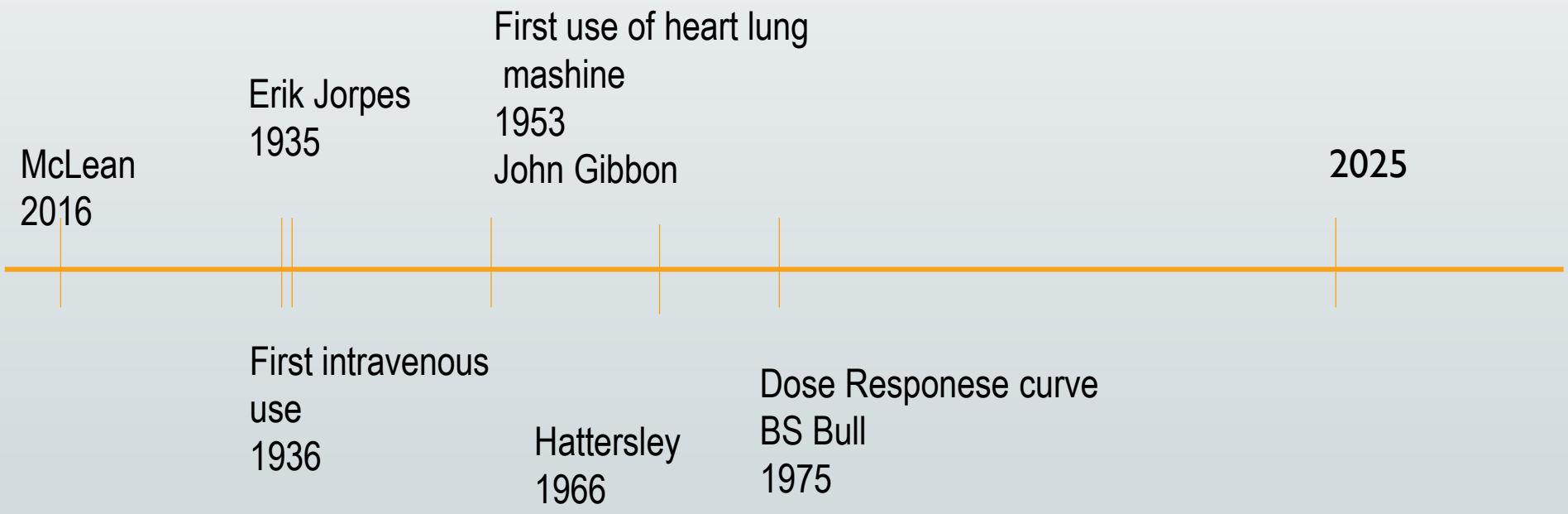
Heparin therapy during extracorporeal circulation

II. The use of a dose-response curve to individualize heparin and protamine dosage

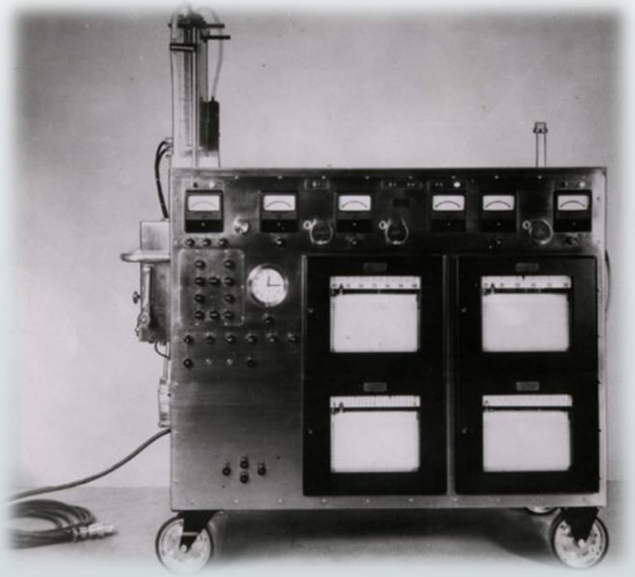
Because the administration of heparin and protamine according to a set protocol will fail to anticoagulate safely or neutralize appropriately a significant number of patients, a method of monitoring heparin therapy during cardiopulmonary bypass is presented. A dose response curve relating heparin dosage to its effect on the activated coagulation time (ACT) can be determined with sufficient accuracy for clinical purposes from three ACT's. Preparation of such a curve makes it possible to maintain anticoagulation in a safe range during bypass and minimizes the number of monitoring tests of coagulation required. At the conclusion of bypass, this curve can be used to predict the precise amount of protamine needed for neutralization. Freed from the confusing effects of hyperheparinemia or protamine excess, the physician can diagnose and treat postoperative bleeding problems much more readily.

Brian S. Bull, M.D.,* Wilfred M. Huse, M.D.,** Floyd S. Brauer, M.D.,*** and Ralph A. Korpman, M.D.,* *Loma Linda, Calif.*

HEPARIN AND ACT



CARDIOPULMONARY BYPASS



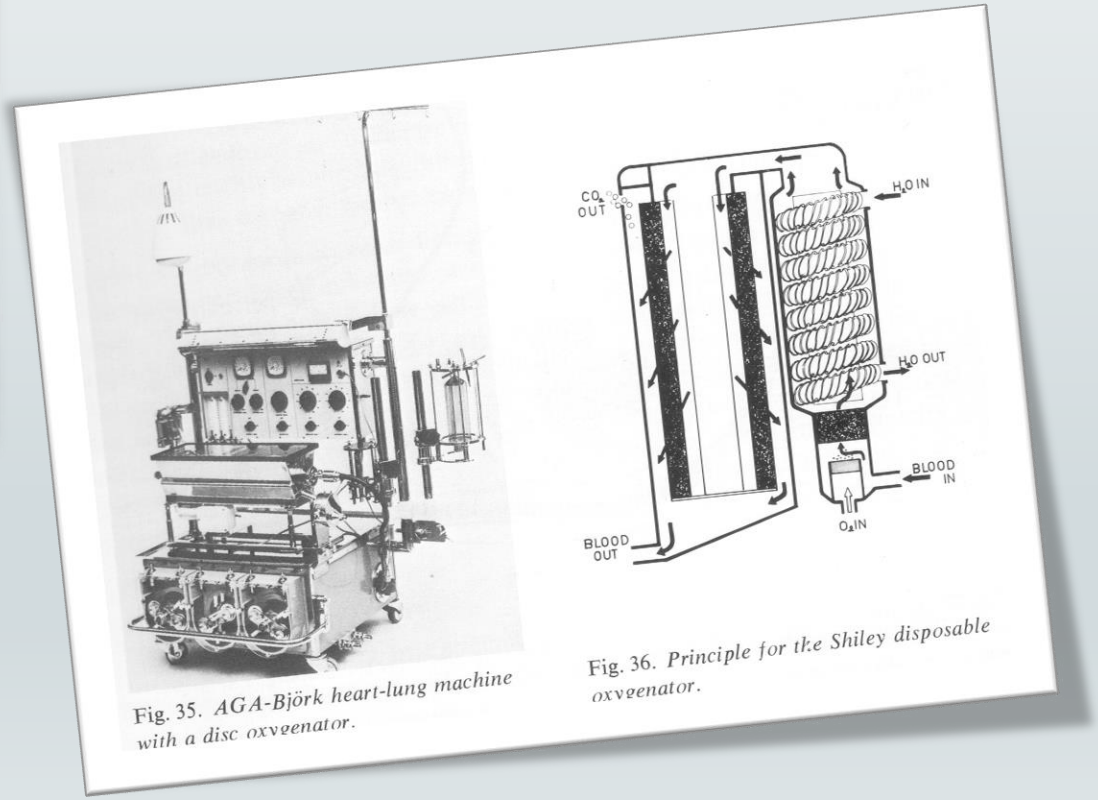
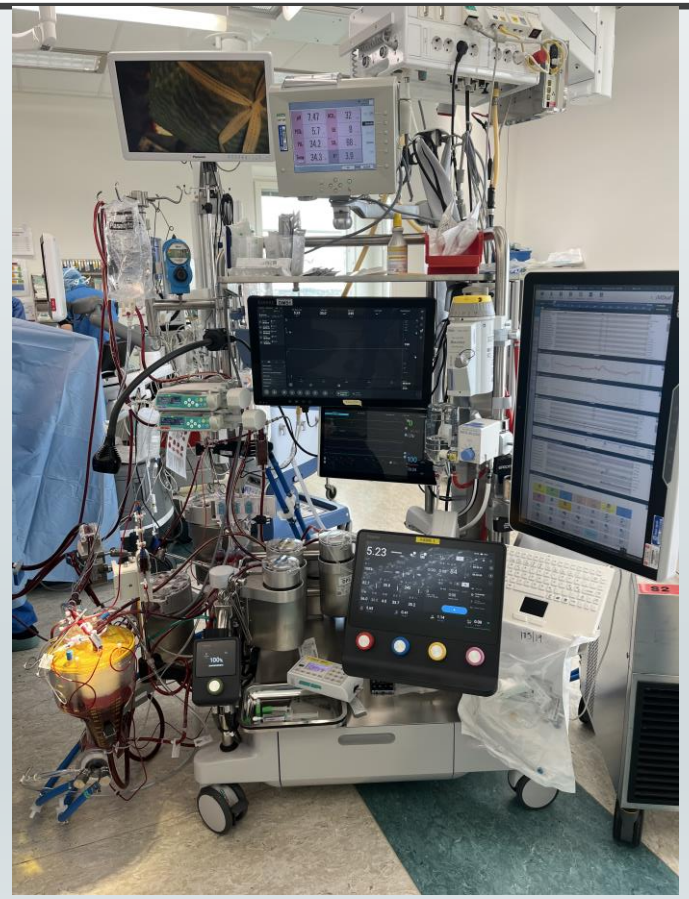


Fig. 35. *AGA-Björk heart-lung machine with a disc oxygenator.*

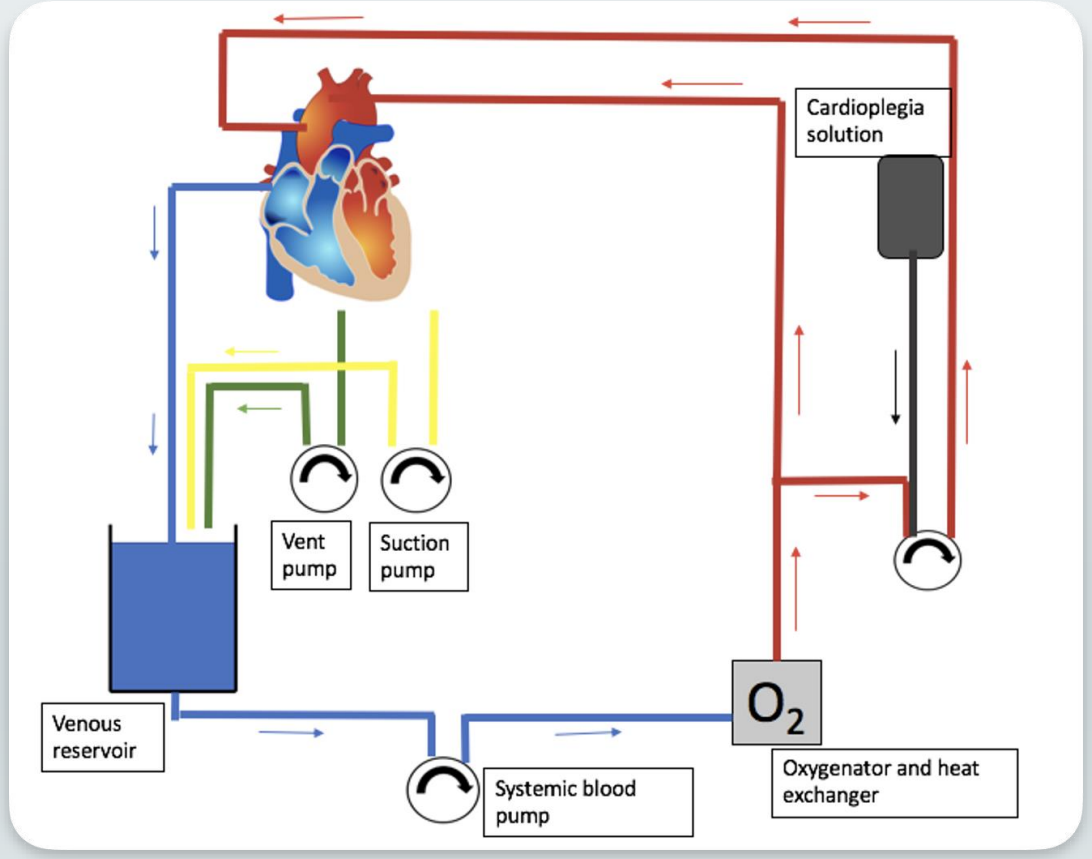
Fig. 36. *Principle for the Shiley disposable oxygenator.*

CARDIOPULMONARY BYPASS

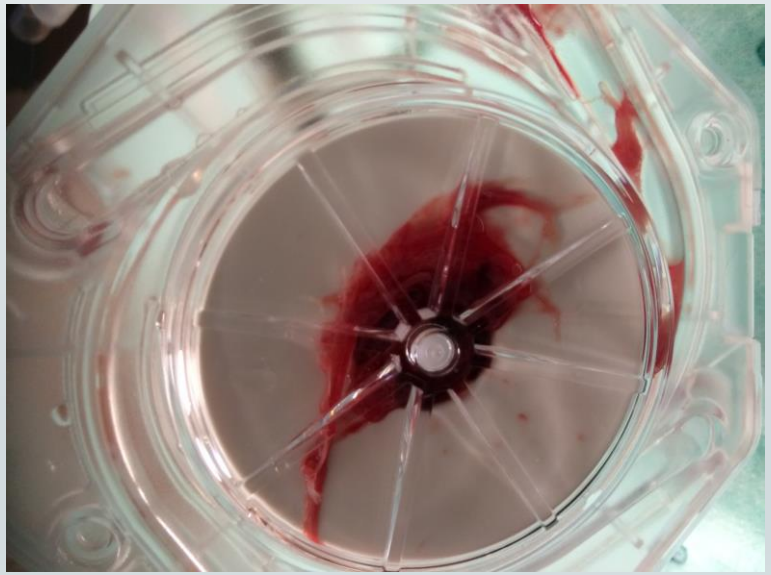


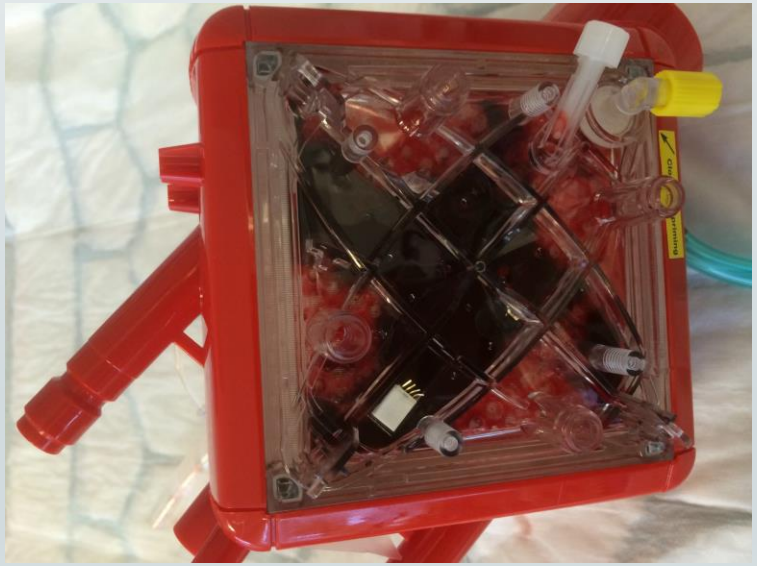
Gunilla Kjellberg Werfen 2025-10-16

CARDIOPULMONARY BYPASS



“Few drugs are so relatively harmless in large doses and possibly life threatening in small doses as heparin in this context”.





DEVICES

i-stat

Hemochron Signature Elite

HMS Plus

GUIDELINES – HEPARIN AND ACT

Individualized heparin and protamine management should be considered to reduce postoperative coagulation abnormalities and bleeding complications in cardiac surgery with CPB.	IIa	B	[479, 480]
It is recommended that ACT checks be performed at regular intervals based on institutional protocols and that heparin doses be administrated accordingly, especially in the absence of individual heparin dosing services.	I	C	-

2024 EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery

HEPARIN DOSING

300-600 units of heparin/kg

300-600 s ACT

Aiming for ACT>480 sec when using open systems and cardiotomy suction

HEPARIN

- Dose dependent
- Individual response
- Heparin resistance

HEPARIN CONCENTRATION

Cureus. 2024 Feb 13;16(2):e54144. doi: 10.7759/cureus.54144

Comparison of Blood Concentration and Weight-Based Heparin and Protamine Dosing Strategies for Cardiopulmonary Bypass: A Systematic Review and Meta-Analysis

Gavin Raner [1], Yirui Hu [2], Cody Trowbridge [3], Li Zhang [4], John Logan [5], Xianren Wu [4], Xiaopeng Zhang [4,✉]

HEPARIN CONCENTRATION

• Despotis et al 1995	RCT	127/127	fewer platelet interventions
• Hofman et al 2013	RCT	29/24	reduce thrombin generation
• Kjellberg et al 2019	RCT	19/20	no impact bleeding
• Slight et al 2008	RCT	18/20	no diff in blood loss, hemost activation
• Nuttall et al 2022	RCT	91/90	did not reduce blood loss or transf req
• Koster et al 2002	RCT	100/100	reduction of thrombin generation
•			

HEPARIN CONCENTRATION

- "Protamine and heparin overdoses were associated with significantly reduced platelet counts and dysfunction"
- Individualized heparin response could be a safer way for protamine titration than weight based
- Reduced target protamine-to-heparin dose ratio.
- Due to characteristics of heparin elimination, additional postoperative protamin can be beneficial

2019 SURVEY

550 respondents worldwide

How is the the adequate degree of anticoagulation for initiation of CPB determined?

- ACT level 85%
- ACT and heparin concentration 13%
- Other 12%

How is ACT maintained during CPB?

- Additional doses to target an ACT level 88%
- Additional doses to target heparin concentration7%
- Other

Anesthesia & Analgesia 129(2):p e41-e44, August 2019

WHAT CAN BE DONE TO MINIMIZE COAGULATION IMPACT DURING CPB

Optimizing the cirquit	MiECC	Tip to tip coated cirquit	Shed blood separation to reduce inflammatory response
Use of cell-salvage systems	Ultra filtration	Normothermia	Context-dependent and may vary based on surgical procedure and cpb system used

FACTORS AFFECTING ACT

Heparin	Hemodilution	Hypothermia	Platelet count	Aprotinin	Protamine in excess
• Individual response • AT level	• prolongs ACT but only in presens of heparin	• Inhibition of FXa	• < 20 x 10^3 /µL	• celine based ACT measurements	• ratio <1:1 to reduce bleeding

HEPARIN RESISTANCE

- Hypoalbuminemia
- Hereditary deficiency
- Active endocarditis
- LMWH treatment

HEPARIN RESISTANCE - TREATMENT

When starting surgery, AT supplementation is recommended in patients with AT deficiency to improve heparin sensitivity.	I	A	[326-328]

2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP

PROTAMINE - GUIDELINES

A protamine-to-heparin ratio < 1.0 is recommended to avoid overdosing of protamine.	I	B	[489, 492]

2024 EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery

Protamine administration is recommended in a protamine-to-heparin dosing ratio[d] <1.0 to avoid overdosing and reduce bleeding complications.	I	B	[313, 314, 316-318]

2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP

Cardiotomy suction should be discontinued with the start of the administration of protamine.	IIa	C	[489]

2024 EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery

PROTAMINE

Minimum protamine dose required to neutralize heparin in cardiac surgery: a single-centre, prospective, observational cohort study

Ravi Taneja [1] [2], Daniel J Szoke [3], Zachary Hynes [3], Philip M Jones [3] [4]

Can J Anaesth 2023 Feb;70(2):219-227

PROTAMIN

- Observational
- 28 patients
- Protamin infusion at rate of 25 mg·min^{-1}.
- 150, 200, 250, and 300 mg
- ACT, anti-IIa and -Xa activity

PROTAMINE

Eight out of 25 (32%) patients showed complete neutralization of anti-IIa and -Xa activity at the first sampling point (150 mg protamine; protamine:heparin ratio, 0.3 [0.1])

A protamine:heparin ratio of 0.5 (0.2) was sufficient for heparin neutralization in > 90% of patients.

METHODS PROTAMINE DOSING

Protamine Dosing for Heparin Reversal after Cardiopulmonary Bypass: A Double-blinded Prospective Randomized Control Trial Comparing Two Strategies

Pankaj Jain [1], Alejandra Silva-De Las Salas [1], Kabir Bedi [2], Joseph Lamelas [3], Richard H Epstein [1], Michael Fabbro 2nd [4]

Anesthesiology 2025 Jan 1;142(1):98-106.

METHOD

”A calculated initial heparin dose greater than or equal to **27,500 U** were randomized to receive, after cardiopulmonary bypass, protamine as a **fixed dose (250 mg) or a ratio-based dose (1 mg:100 U heparin).”**

”The primary outcome was the act**ivated clotting time** after initial protamine administration, assessed by Student's t test. Secondary outcomes included **total protamine, the need for additional protamine, and the cumulative 24-h chest tube output.”**

RESULTS

”There were 62 and 63 patients in the fixed- and ratio-based dose groups, respectively.

The **mean postprotamine activated clotting time was not different between groups** (-2.0 s; 95% CI, -7.2 to 3.3 s; P = 0.47).

Less total protamine per case was administered in the fixed-dose group

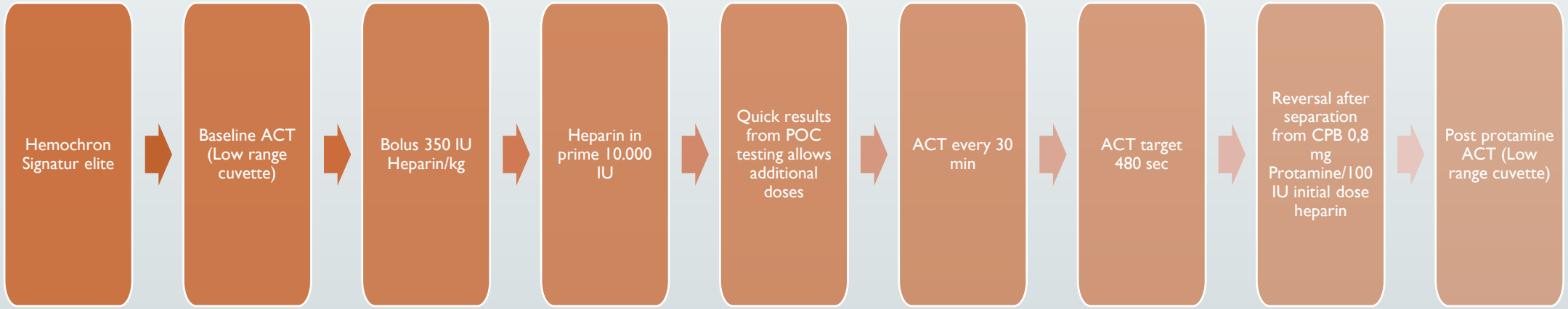
There was no difference in the cumulative 24-h chest tube output (difference, -77 ml; 95% CI, 220 to 65 ml; P = 0.28).”

PROTOCOL AT UPPSALA AKADEMISKA HOSPITAL

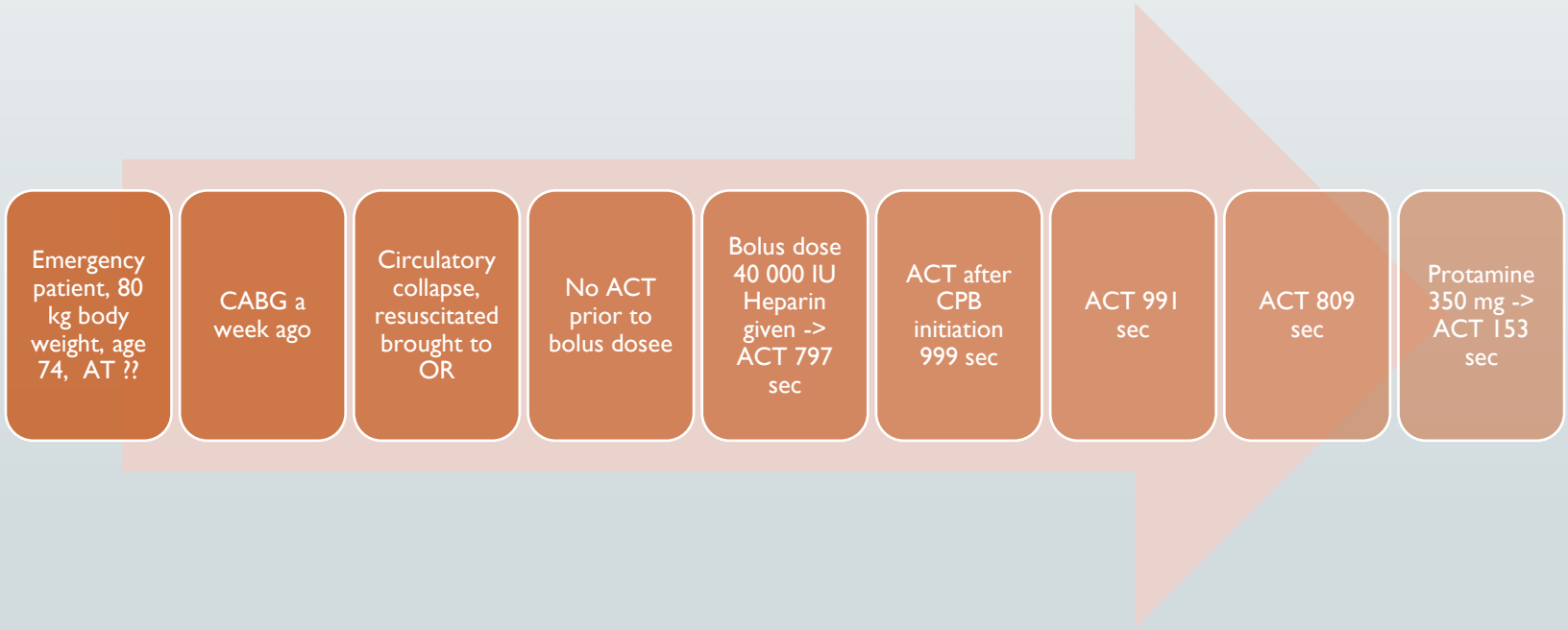
Previolusly: Hepcon HMS,

- Low compliance
- Hight costs (service, Cartridges)
- Uncertain delivery of matereial

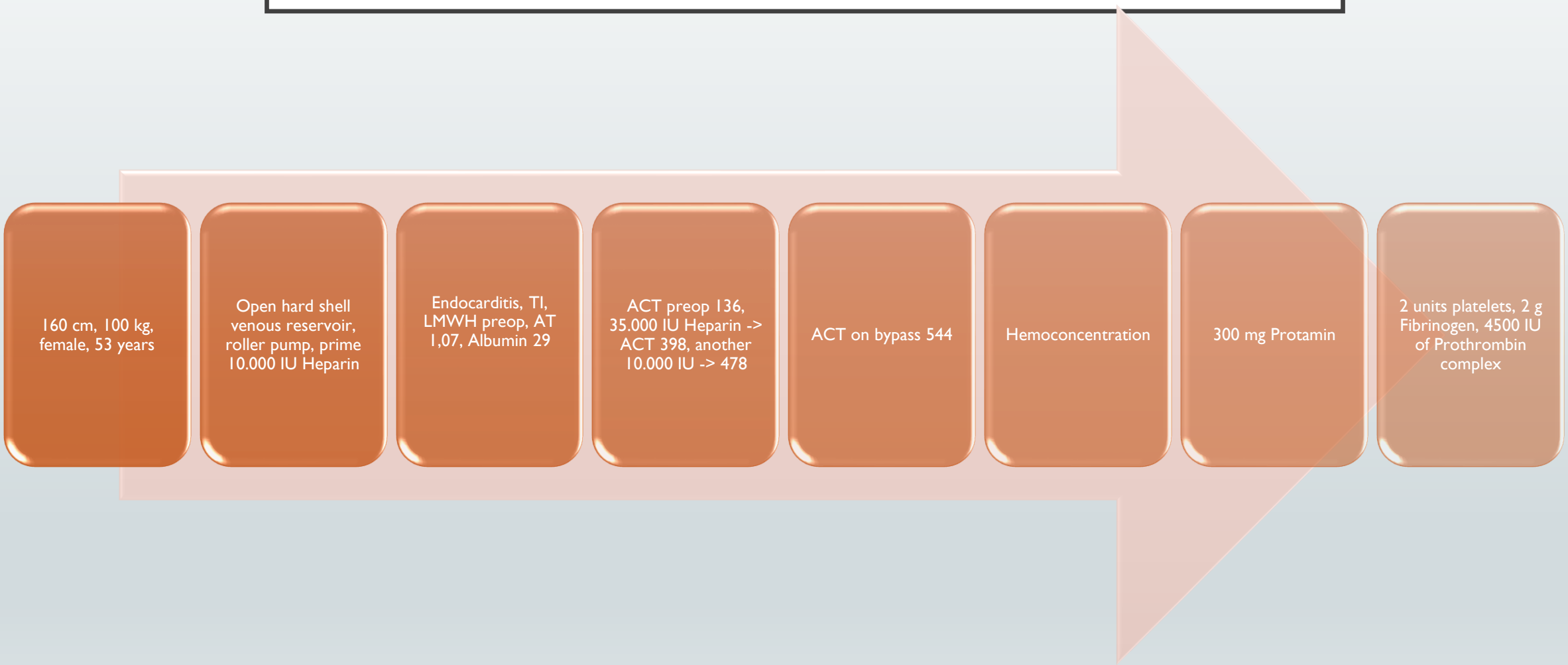
PROTOCOL AT UPPSALA AKADEMISKA HOSPITAL



CASE 1


Emergency patient, 80 kg body weight, age 74, AT ??
CABG a week ago
Circulatory collapse, resuscitated brought to OR
No ACT prior to bolus dosee
Bolus dose 40 000 IU Heparin given -> ACT 797 sec
ACT after CPB initiation 999 sec
ACT 991 sec
ACT 809 sec
Protamine 350 mg -> ACT 153 sec

CASE 2


160 cm, 100 kg, female, 53 years
Open hard shell venous reservoir, roller pump, prime 10.000 IU Heparin
Endocarditis, TI, LMWH preop, AT 1,07, Albumin 29
ACT preop 136, 35.000 IU Heparin -> ACT 398, another 10.000 IU -> 478
ACT on bypass 544
Hemoconcentration
300 mg Protamin
2 units platelets, 2 g Fibrinogen, 4500 IU of Prothrombin complex