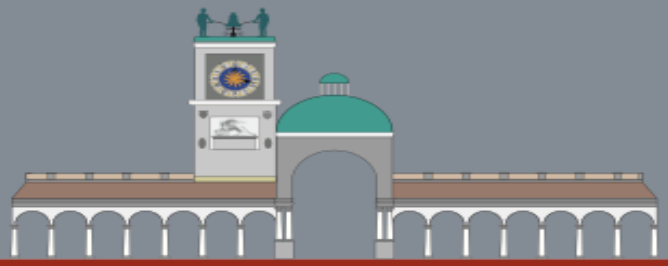

FIRST ANNOUNCEMENT

BEYOND THE SLIDES 2015

1st UDINE ECMO WORKSHOP

DECEMBER 18-19, 2015 - AUDITORIUM HYPO ALPE ADRIA - TAVAGNACCO (UD)

HIT in ECMO: a challenging complication

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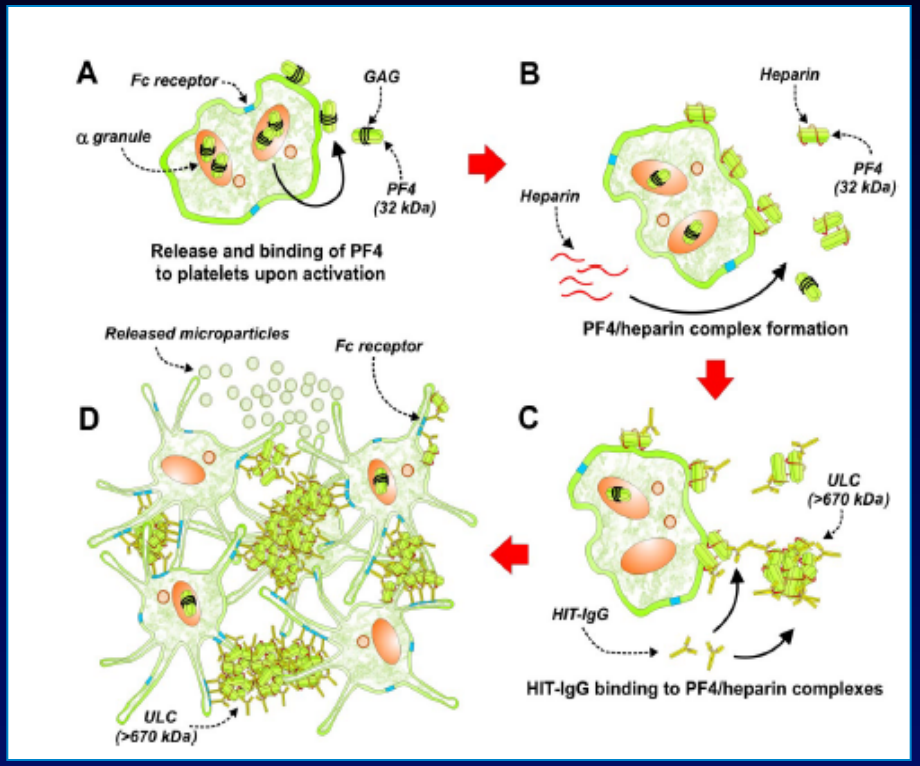
HIT-T DEFINITION

Heparin-Induced Thrombocytopenia Type II

- Immunological origin (central role of Ig G immunoglobulin class)
- Life-threatening prothrombotic side effect: mortality reaches 45 % in case of arterial thrombosis (V4:A1)
- Drop in platelet between day 5-7 after the start of heparin
- Often no severe thrombocytopenia (median platelet count nadir 60000/uL) (misleading, HIT underestimation)
- The striking dichotomy of a heparin induced platelet count decrease, but rise in the level of fibrinogen captures the essence of HIT: heparin simultaneously promotes and treats the thrombosis
- When immune system and coagulation concur to… THROMBIN GENERATION



Kelton JG. Blood 2008; 112(7)

HIT in ECMO, why a challenging issue?

- Difficult diagnosis in postoperative cardiac surgery and ECMO patients
- Management of alternative anticoagulants (DTI) during ECMO
- Management of anticoagulation during CPB to convert ECMO to long-term VAD or to perform heart transplantation
- Treatment of hemorrhagic complications of alternative anticoagulants
- Anticoagulation in the postoperative period

Diagnosis in postoperative cardiac surgery and ECMO patients

- Clinical evaluation
  - *4T score*: confounders (consumption, IABP, CRRT) in CCH/ECMO
  - Cannulae/catheters trigger thrombus independently of HIT

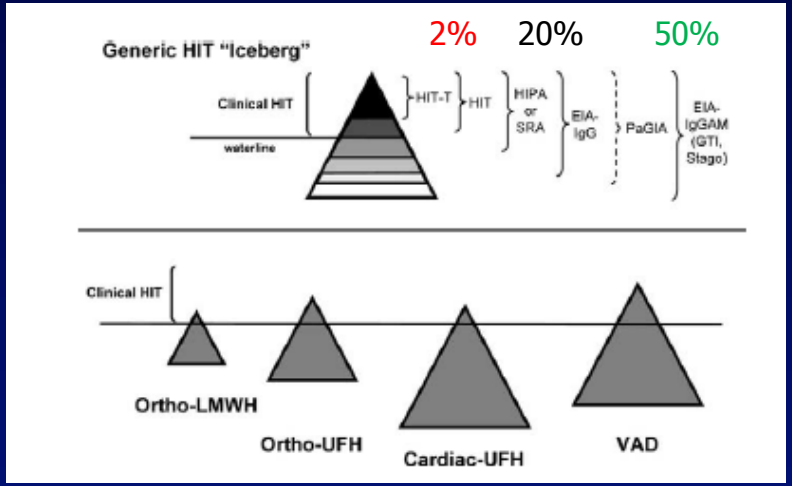
4T's	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20 x 10^9/L	Platelet count fall 30-50% or platelet nadir 10-19 x 10^9/L	Platelet count fall < 30% or platelet nadir < 10 x 10^9/L
Timing of platelet count fall	Clear onset between days 5-14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None
oTher causes of thrombocytopenia	None apparent	Possible	Definite

High probability: 6-8 points; intermediate probability: 4-5 points; low probability: ≤3 points.

- PF4/heparin antibodies

EIA (ELISA) GAM: high sensitivity/low specificity

- The ***"iceberg model":*** Only in 10% of patients with HIT suspicion, a real HIT has been demonstrated!!



- Functional assays: Serotonin-release assay, HIPA test (higher specificity for biologically active HIT antibodies, BUT not widespread)

J Thromb Haemost 2006;4:759-65 Chest 2005;127:35-45 Blood 2008; 112(7) Warkentin TE. Hematology 2011

Alternative anticoagulants during ECMO
Direct Thrombin Inhibitors

Argatroban vs Bivalirudin

Advantages of DTIs:

- Ability to inhibit thrombin rapidly
- Simple monitoring with aPTT
- Short half-life (in case of bleeding or need for surgery)

Drawbacks:

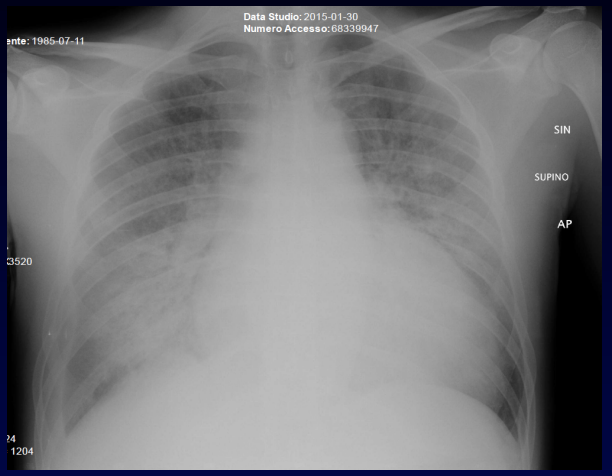
- Drug accumulation in case of renal failure (bivalirudin), hepatic failure (argatroban)
- Difficult monitoring in some circumstances
- **No antidote!**

➢**Heparin-coated ECMO** circuit with bivalirudin anticoagulation: if the immune reaction continues unabated is **still discussed**

Case report

- A 29 yr old male was admitted suffering from congestive heart failure due to suspected post-influenza myocarditis

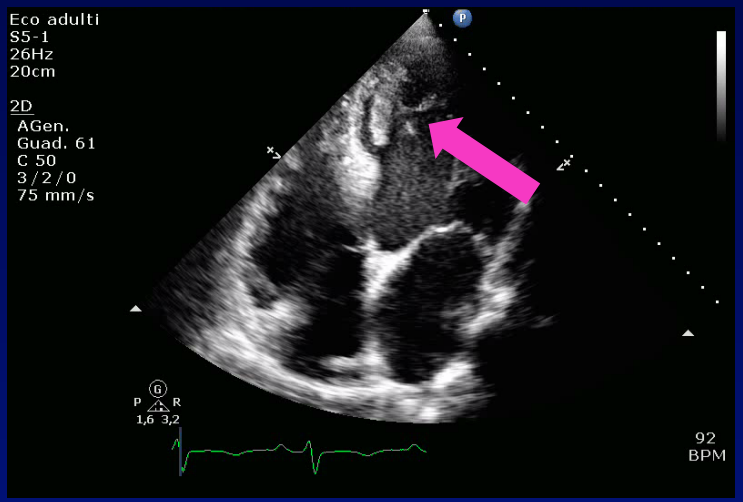
  Medical history: Berger disease



- LVEF 15%, high wall thickness, restrictive LV filling pattern , PAPs 60 mmHg

- T 38°C, WBC 17000/uL, PCR 76 mg/dL, Hb 12,6 g/dL, Cr 2,65 mg/dL, Na+ 127 mMol/L, INR 2.05, ALT 580,
- BNP 2253, cTnI 66, BP 160/115 mmHg
- Dobutamine, furosemide, azitromicin, ceftriaxone, oseltamivir, NPS

- 4 days after admission: Two large apical thrombus in the left ventricle. Continuous infusion of Unfractioned Heparin started



- Heparin resistance

Case report

Refractory FV

LV thrombus

Start UFH

VA ECMO

IABP

ELISA IgG OD 1,269

4T score:5

ELISA Ig GAM POS

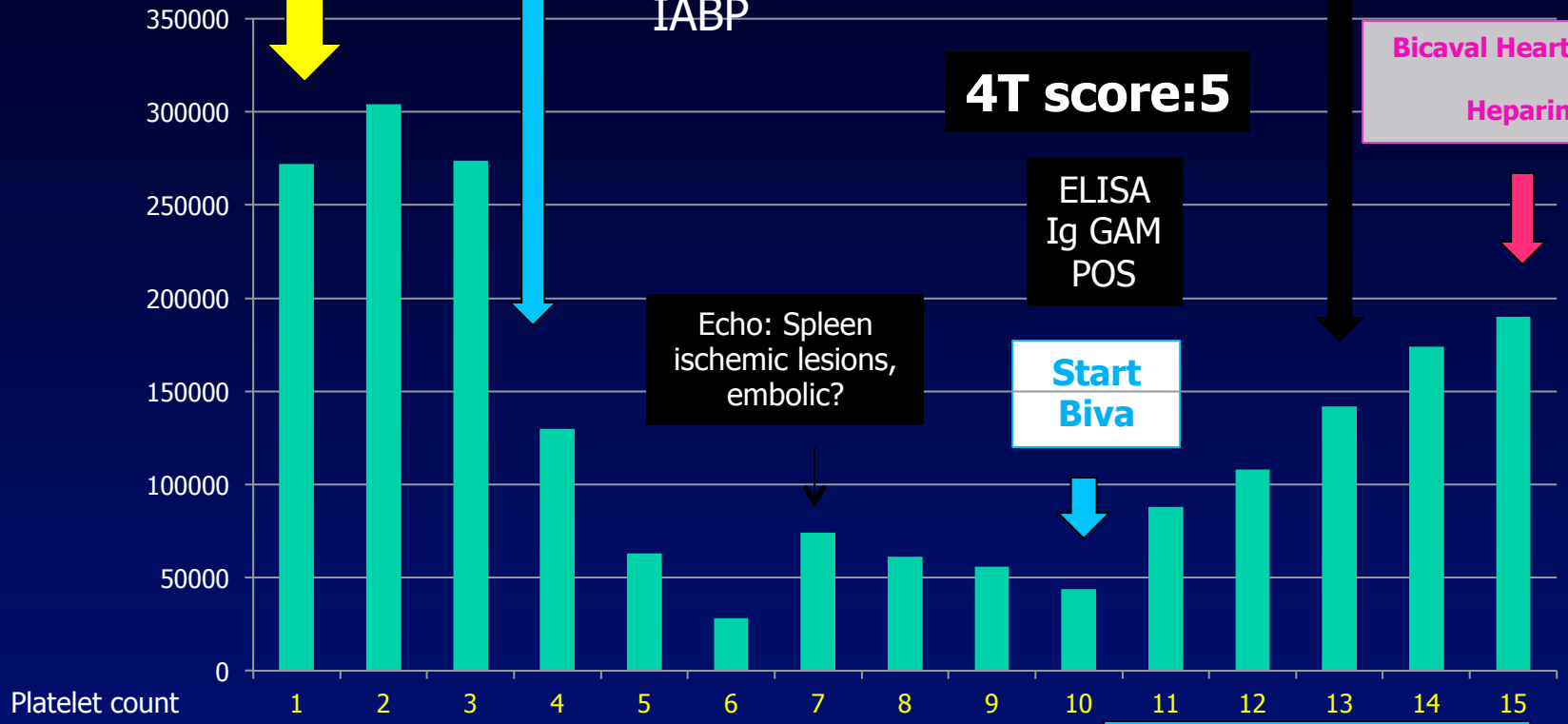
Echo: Spleen ischemic lesions, embolic?

Start Biva

Bicaval Heart Transplantation

Heparin+ tirofiban

SUBACUTE HIT



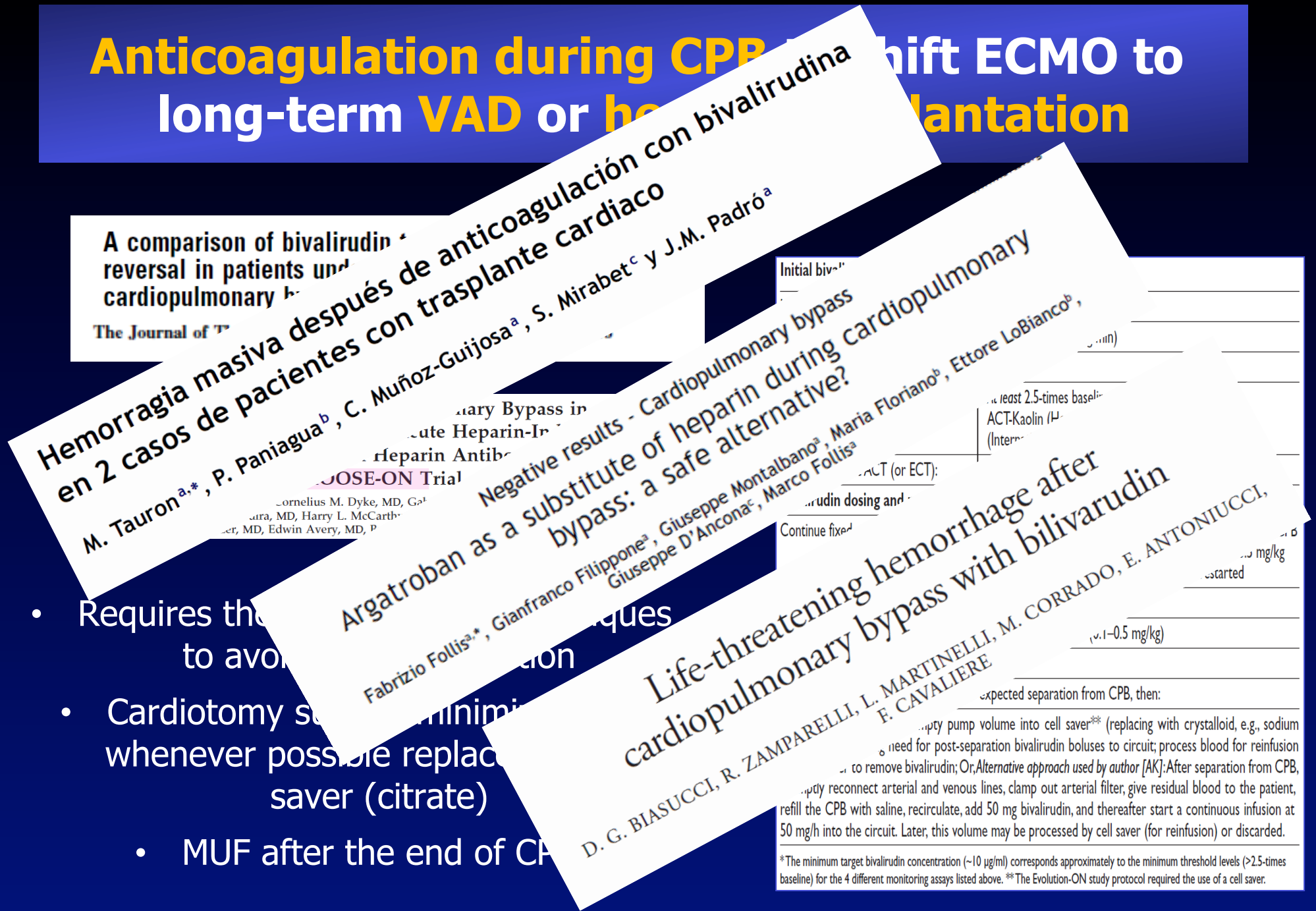
Unfractioned heparin

Bivalirudin

0.03-0.085 mg/kg/h per aPTTr target 2.00 e ACT 180"

Anticoagulation during CPB … hift ECMO to long-term VAD or he… lantation

- Requires the … to avo… …ques
  - Cardiotomy s… …minimi… whenever possible replac… saver (citrate)
    - MUF after the end of CP…



Anticoagulation during CPB to shift ECMO to long-term VAD or heart transplantation

Brief report

Management of anticoagulation in patients with subacute heparin-induced thrombocytopenia scheduled for heart transplantation

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[1]Institut für Immunologie und Transfusionsmedizin, Ernst-Moritz-Arndt Universität, Greifswald; and [2]Klinik und Poliklinik für Herz-, Thorax- und herznahe Gefäßchirurgie, Klinikum der Universität Regensburg, Regensburg, Germany

Anticoagulation management of patients with recent heparin-induced thrombocytopenia (HIT) requiring cardiopulmonary bypass (CPB) surgery is a serious challenge, and especially difficult in patients requiring urgent heart transplantation. As nonheparin anticoagulants during CPB bear a high risk of major bleeding, these patients are at risk of being taken off the transplant list. Short-term use of unfractionated heparin (UFH) for CPB, with restriction of UFH to the surgery itself, is safe and effective in patients with a history of HIT who test negative for antiplatelet factor 4 (PF4)/heparin antibodies. We present evidence that it is safe to expand the concept of UFH reexposure to patients with subacute HIT (ie, those patients with recent HIT in whom the platelet count has recovered but in whom anti-PF4/heparin IgG antibodies remain detectable) requiring heart transplantation, if they test negative by a sensitive functional assay using washed platelets. This can be lifesaving in patients with end-stage heart failure. (Blood. 2008;112: 4024-4027)

Introduction

Management of patients with recent heparin-induced thrombocytopenia (HIT) requiring cardiopulmonary bypass (CPB) surgery is a serious challenge for the consulting hematologist. In particular, the choice of adequate anticoagulation management during CPB is problematic. The situation is especially difficult in patients requiring heart transplantation, as the timing of surgery usually cannot be planned in advance, whereas the use of alternative anticoagulants during CPB requires special monitoring and preparation[1,2] and bears a significantly enhanced bleeding risk.[3] A major conceptual breakthrough was the recognition that use of unfractionated heparin (UFH) for CPB in patients with a history of HIT is safe and

Results and discussion

Case 1

A 55-year-old male patient with severe dilated cardiomyopathy (DCM) and cardiogenic shock was scheduled for high urgency heart transplantation. At day 9 of UFH treatment, HIT developed (platelet count fall from 135×10^9/L to 28×10^9/L; anti-PF4/heparin IgG [optical density (OD) = 1.1] and positive HIPA; 4T score[7] = 5). After switch of anticoagulation to argatroban (aPTT 50-60 seconds) platelet counts recovered rapidly. When a donor

BLOOD, 15 NOVEMBER 2008 • VOLUME 112, NUMBER 10

Subacute HIT

CPB with UFH

Functional assay using washed platelets:

HIPA test NEGATIVE

Anticoagulation during CPB to shift ECMO to long-term VAD or cardiac transplant

Subacute HIT and functional assays not available

Anticoagulation during Cardiopulmonary Bypass in Patients with Heparin-induced Thrombocytopenia Type II and Renal Impairment Using Heparin and the Platelet Glycoprotein IIb–IIIa Antagonist Tirofiban

Andreas Koster, M.D., Marian Kukucka, M.D.,* Friedhelm Bach, M.D.,† Oliver Meyer, M.D.,‡ Thomas Fischer, M.D.,* Fritz Mertzlufft, M.D.,§ Matthias Loebe, M.D.,‖ Roland Hetzer, M.D.,# Hermann Kuppe, M.D.***

Anesthesiology, V 94, No 2, Feb 2001

Protocol:

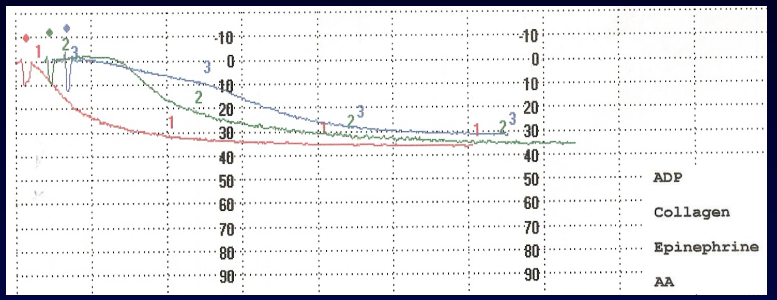
- Bolus of tirofiban 10µg/kg 10 minutes before cannulation
- Bolus of 400 UI/kg heparin 5 minutes after tirofiban bolus
- Tirofiban infusion 0.15 µg/kg/min until 1 hour before weaning from CPB
- Protamine administration, Platelet transfusion according to bleeding and platelet aggregometry

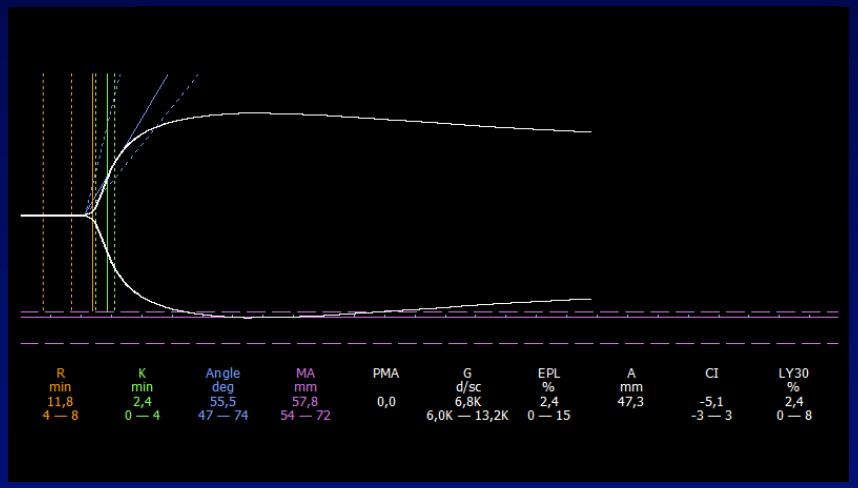
Results: Postoperative blood loss 110-520 mL, no reexploration, no clinical thrombosis or embolism, no D-dimer

Case report

Intraoperative coagulation management during ECMO removal and heart transplantation

- Preoperative bivalirudin infusion until 1 hour before skin incision
- Bolus of tirofiban 10 µg/kg 10 minutes before cannulation
- Bolus of heparin according to HMS (300 UI/kg), 15 minutes after tirofiban bolus
- Tirofiban infusion 0.15 µg/kg/min until 1 hour before weaning from CPB
- Ultrafiltration during CPB to clear bivalirudin
- ACT every 15 minutes
- Stop tirofiban 1 hour before CPB weaning
- Protamine administration after CPB weaning, according to HMS analysis
- 2 Platelet concentrates transfusion according to bleeding and platelet light transmission aggregometry
- Fibrinogen concentrate 1 g +2 RBC packages
- Postoperative bleeding 600 mL/24h
- Platelets after surgery
- Platelets in POD 1-4: 190000-180000/µL





Case report

POD 1-5: fondaparinux 2,5-5 mg according to Creatinine Clearance (37-51 ml/min)

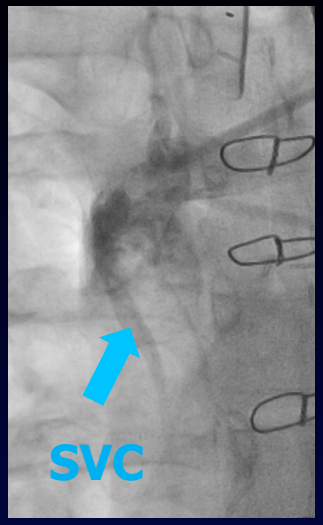
POD 6: Cardiac tamponade. Reexploration

POD 7: fondaparinux re-start

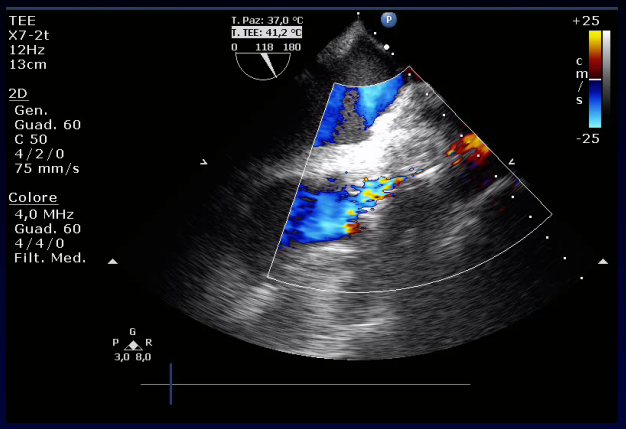
POD 11: Superior caval syndrome: face and neck edema; PLT 226000/uL

SVC thrombosis

Bivalirudin 0.03-0.1 mg/kg/h, target aPTTr 2.5



Phlebography



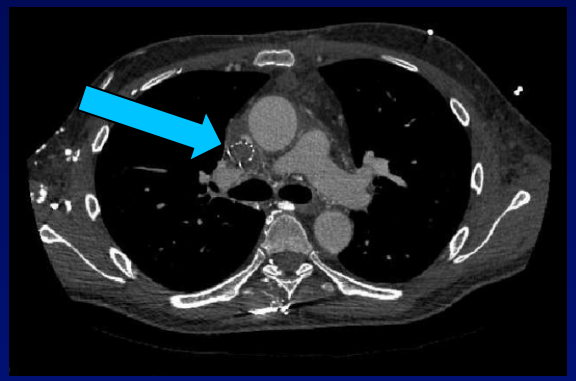
TEE
Bicaval view

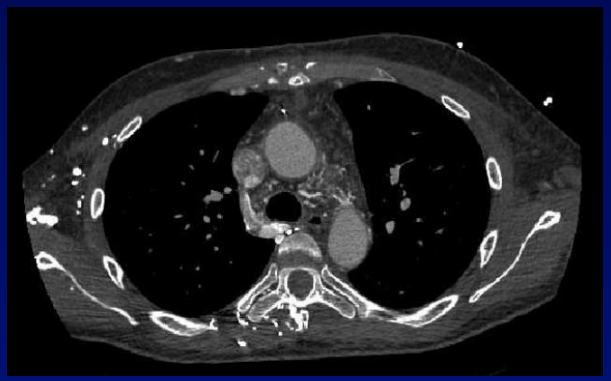
POD 14: Stent SVC, bivalirudin and VKA

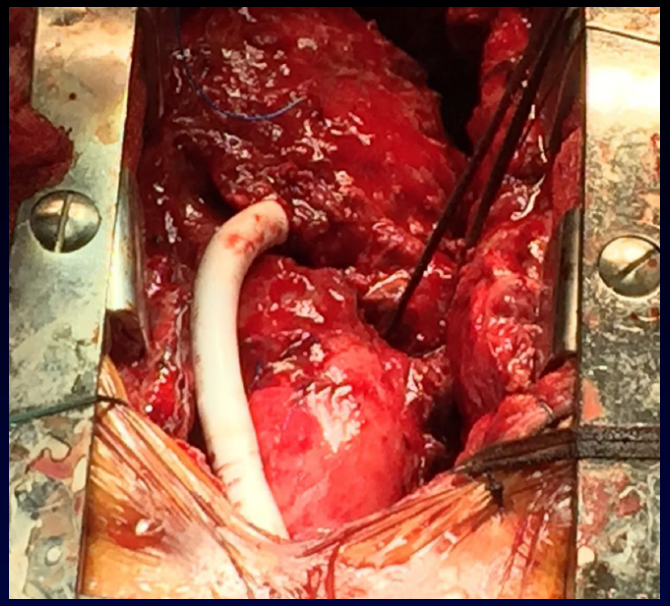
POD 27: stenosis intrastent ,

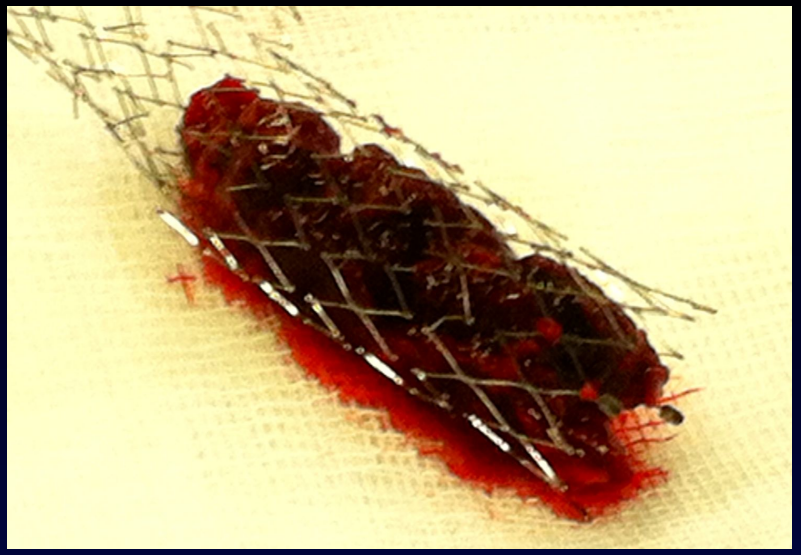
Ab antiPF4/heparin positive

Normal Platelet count









POD 33:

Stent removal, thrombectomy of SVC and enlargement by means of a plasty with Hemopatch

Temporary bypass between left innominate vein and right atrium with Goretex prosthesis

No CPB

Bivalirudin 1.75 mg/kg/h, ACT target 300”

3 RBC packages

Anticoagulation in the postoperative period

- Discontinue heparin and anticoagulate with warfarin can worse clinical picture and thrombosis (severe reduction in the natural anticoagulant protein C)
- Postpone warfarin therapy until there has been substantial resolution of the thrombocytopenia (platelet count rise at least a stable level of 150000/uL)
- Maintain a at least 5 days DTI/warfarin overlap
- Maintain anticoagulant therapy (VKA) for at least 3 months (recommended duration of anticoagulation in VTE) in HIT-T
- Maintain anticoagulation for at least 4 weeks in HIT without thrombosis (high risk of thrombosis extends for 2 to 4 weeks after the treatment of HIT is initiated)

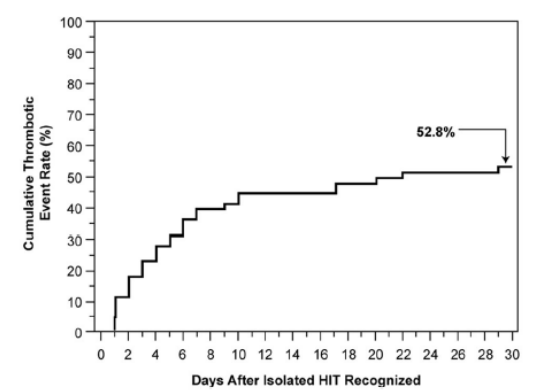


Figure 7. Cumulative frequency of thrombosis in HIT patients presenting with isolated thrombocytopenia. Approximately 50% of HIT patients initially recognized with isolated thrombocytopenia developed objective evidence for thrombosis during the subsequent 30-day period. Reprinted from Warkentin and Kelton[89] with permission.

Probability of thrombosis in case of presence of PF4-heparin antibodies and thrombocytopenia

CHEST / 141 / 2 / FEBRUARY, 2012 SUPPLEMENT

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Treatment and Prevention of Heparin-Induced Thrombocytopenia

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Case report

Postoperative period:

- VKA, Bivalirudin, ASA
- VKA+ DAPT (ASA, Clopidogrel) after bivalirudin stop
- VKA for 3 months from last heparin exposure. D-dimers monitoring (DVT)
- Ab anti PF4/heparin negative after 50 days from heparin stop
- 12 months of DAPT
- Discharged on 76 days after admission

Conclusions

- HIT is an insidious and potentially deadly complication
- Multidisciplinary management (CPB, etc)
- Risk of underestimate, but also…
- Risk of overdiagnosis (discuss with lab staff)
- Don’t underestimate the risk of thrombosis in postoperative period (pro-thrombotic period *per se*) especially until antibodies become negative