T. C.
MALTEPE ÜNİVERSİTESİ

KPB Uygulamalarında Antikoagülasyon

Zeliha Özer
Maltepe Üniversitesi Tıp Fakültesi
Anesteziyoloji ve Reanimasyon AD

HEPARİN

1916

KPB

1953

History

- The first successful open heart procedure on a human using bypass machine was performed by John Gibbon on May 6, 1953 in Philadelphia. The operation was correction of an ASD on an 18 year-old girl.

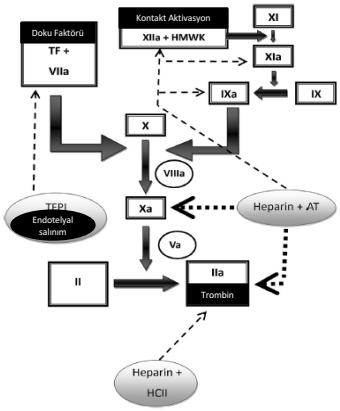
KPB

Tromboz

Post operatif kanama

Heparin

Protamin



CLINICAL PRACTICE GUIDELINES

The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical Practice Guidelines*—Anticoagulation During Cardiopulmonary Bypass

Linda Shore-Lesserson, MD, Robert A. Baker, PhD, CCP, Victor A. Ferraris, MD, PhD, Philip E. Greilich, MD, David Fitzgerald, MPH, CCP, Philip Roman, MD, MPH, and John W. Hammon, MD

Department of Anesthesiology, Zucker School of Medicine at Hofstra Northwell, Hempstead, New York; Cardiac Surgery Research and Perfusion, Flinders University and Flinders Medical Center, Adelaide, South Australia, Australia; Division of Cardiovascular and Thoracic Surgery, University of Kentucky, Lexington, Kentucky; Department of Anesthesiology and Pain Management, University of Texas-Southwestern Medical Center, Dallas, Texas; Division of Cardiovascular Perfusion, Medical University of South Carolina, Charleston, South Carolina; Department of Anesthesiology, Saint Anthony Hospital, Lakewood, Colorado; and Department of Cardiothoracic Surgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina

- KPB başlangıç ve devamında heparinin dozu ve monitorizasyonu
- Heparinin kontrendikasyonları ve alternatifleri
- Antikoagülasyonun geri döndürülmesi

HEPARİN DOZU VE HEDEFLENEN ACT DÜZEYİ NE OLMALIDIR?

- Yeterli antikoagülasyonu sağlamak için hastanın kilosuna göre heparin yapılması uygundur !!

YETERLİ ANTİKOAGÜLASYON?

KİLOYA GÖRE HEPARİN?

- KPB sırasında ACT 480 sn üzerinde olmalıdır!
- Ortalama bir değerdir.
- 400sn'nin üzerindeki değerler terapotik kabul edilmektedir!
- Heparin 300IU/kg!

ISI, PROTEAZ İNHİBİTÖRLERİ, HEMODİLÜSYON, AKTİVATÖR TÜRÜ

ACT DEĞERLERİNİ ETKİLER!

JECT. 2005;37:265–271
The Journal of The American Society of Extra-Corporeal Technology

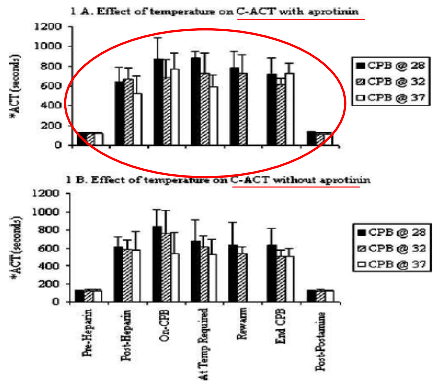
The Effect of Temperature and Aprotinin During Cardiopulmonary Bypass on Three Different Methods of Activated Clotting Time Measurement

Celite-ACT
Kaolin-ACT
Max-ACT

David Machin, BSc (Hons), ACP;* Philip Devine, MSc†

*Perfusion Department, Theatres, and †Medical Statistician, Glenfield Hospital, Leicester, United Kingdom

Abstract: The activated clotting time (ACT) is used frequently for monitoring blood anticoagulant response with heparin before, during, and after cardiopulmonary bypass (CPB). Many cardiac procedures involving CPB require reduction of the patient's blood temperature and use of the serine protease inhibitor, aprotinin. Three different methods of ACT measurement were compared to show the effects of different CPB temperatures and the presence of aprotinin. A total of 42 patients were included in the study: 14 received CPB at 28°C, 14 received CPB at 32°C, and 14 normothermic (37°C) CPB. Within each temperature group, seven received aprotinin. The ACT in each group of patients was measured by a celite activator (C-ACT), a kaolin activator (K-ACT), and a celite, kaolin and glass activator (MAX-ACT). All three methods of ACT measurement showed significant increases ($p < .05$) in clotting times at hypothermic CPB compared with normothermic groups. During heparinization the C-ACT was significantly increased ($p < .05$) in the presence of aprotinin. Comparability between the 3 ACT measurement methods showed a very high correlation between C-ACT and K-ACT clotting times ($R^2 = .8962$), and slightly lower correlation between MAX-ACT and C-ACT ($R^2 = .7780$), and MAX-ACT and K-ACT ($R^2 = .7827$). All ACT measurements are affected by changes in blood temperature. The C-ACT measurement is prolonged with aprotinin, whereas the MAX-ACT and K-ACT method of measurement in the presence of aprotinin are not significantly altered. It appears that the MAX-ACT produces lower values and may necessitate additional heparin therapy for ACT target values considered safe during CPB. Further study is required from these additional findings. **Keywords:** temperature, MAX-ACT, aprotinin, cardiopulmonary bypass. *JECT.* 2005;37:265–271



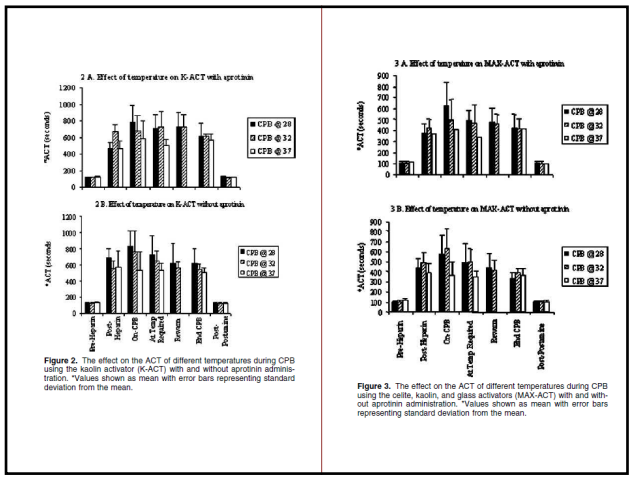
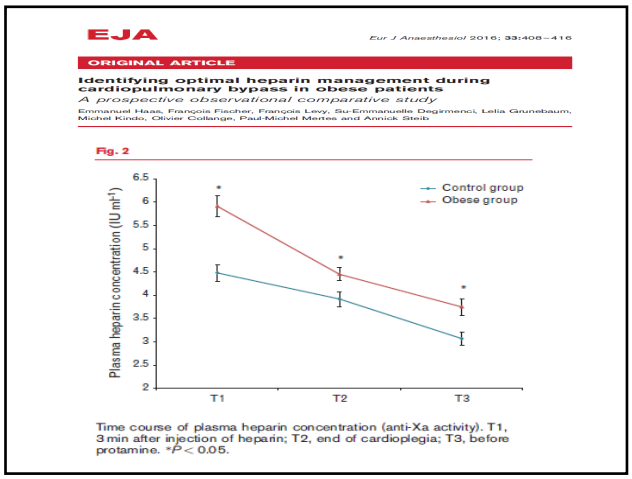


Figure 2. The effect on the ACT of different temperatures during CPB using the kaolin activator (K-ACT) with and without aprotinin administration. *Values shown as mean with error bars representing standard deviation from the mean.

Figure 3. The effect on the ACT of different temperatures during CPB using the celite, kaolin, and glass activators (MAX-ACT) with and without aprotinin administration. *Values shown as mean with error bars representing standard deviation from the mean.


EJA
Eur J Anaesthesiol 2016; 33:408–416
ORIGINAL ARTICLE

Identifying optimal heparin management during cardiopulmonary bypass in obese patients
A prospective observational comparative study

Emmanuel Haas, François Fischer, François Levy, Su-Emmanuelle Degirmenci, Lelia Grunebaum, Michel Kindo, Olivier Collange, Paul-Michel Mertes and Annick Steib

Fig. 2

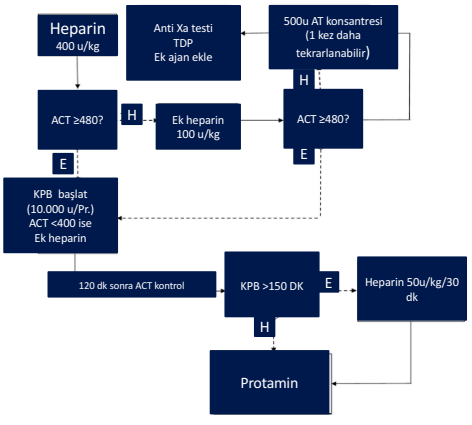
Time course of plasma heparin concentration (anti-Xa activity). T1, 3 min after injection of heparin; T2, end of cardioplegia; T3, before protamine. *$P < 0.05$.

500 U/kg Heparin ↷ ACT<480 sn

HEPARİN RESİSTANSI

Düşük AT düzeyleri (<%60)

Trombositoz
Platelet Faktör 4 (PF4) yüksekliği
F VIII yüksekliği
Daha önce heparin uygulaması
DIC
Endokardit
KC fonksiyon bozukluğu
Yaş>65



Heparin Geri Salınımı

- Yüksek doz heparin kullanımı neden olabilir.
- Heparin molekülleri yağ dokusu ve plazma proteinlerine sekestre olup, sonrasında kanda belirebilir.
- KPB sonrası 6 st.süresince düşük doz protamin inf. (25mg/st.) yapılması düşünülebilir.

Heparinin kontrendikasyonları ve alternatifleri

Temel Kontrendikasyonlar

HİT (Heparin İlişkili Trombositopeni)
Heparin Hipersensitivitesi

HiT??

Heparinin tetiklediği immün bir yanıt sonucu, trombositlerin antikor aracılı aktivasyonu ve buna bağlı tüketimi ile oluşan, trombositopeni ve tromboz ile karakterize edinsel bir sendromdur.

Heparin verilmesinden sonraki 5-14 gün içinde trombosit sayısında %50'nin üzerinde azalma veya trombotik bir olay gelişimi

HiT'DEN ŞÜPHELENMELİYİZ !

Tanı

ELISA (Antikor belirlenmesi)

Yıkanmış trombosit aktivasyon testleri

- **Serotonin salınım testi**
- **Heparin ilişkili trombosit aktivasyon testi**

Trombosit agregasyon testi

HİT + ➡ NE YAPMALIYIZ ?

- HİT (+) olan hastalar yüksek komplikasyon ve mortalite riski taşırlar!
- Elektif kardiyak operasyonlar ertelenmelidir!
- Acil durumlarda heparin alternatifleri kullanılmalıdır!

Heparin Alternatifleri

Direk trombin inhibitörleri
- Argatroban
- Lepirüdin
- Dabigatran (p.o)
- Bivalüridin

Faktör Xa inhibitörleri
- Danaparoid
- Fondaparinuks
- Rivaroksaban (p.o)
- Apiksaban (p.o)

Heparin Alternatifleri

Değişkenler	Argatroban	Lepirudin	Bivalirudin	Danaparoid	Fondaparinux
Yapı	Sentetik, L-arginin türevi	Hirudinin rekombinant formu	Sentetik Peptit	Glikozaminoglukan karışımı	Sentetik Pentasakkarid
Aktivite	Direkt trombin inhibitörü	Antitrombin	Antitrombin	Anti-faktör Xa	Anti-faktör Xa
Atılım	Hepatobiliyer	Böbrek	Enzimatik (%80), böbrek	Böbrek	Böbrek
Yarılanma ömrü	40-50 dakika	80 dakika	25 dakika	18-24 saat	17-20 saat
Tedavi monitorizasyonu	aPTT x1.5-3 (tedavi öncesi)	aPTT x1.5-2 (tedavi öncesi)	aPTT x1.5-2.5 (tedavi öncesi)	Anti faktör Xa düzeyi 0.5-0.8 Ü/ml	Anti faktör Xa düzeyi
HİT'deki dozu	Başlangıç dozu 2 µg/kg/dk İV, bilirubin>1.5mg/dl, kalp yetersizliği, kardiyak cerrahi sonrası, anazarka ödem; 0.5-1.2 ↔g/kg/dk	0,2 mg/kg İV bolus (sadece uzuv veya hayati tehdit varsa), maksimal başlangıç infüzyon hızı 0,1 mg/kg/saat	Başlangıç infüzyon hızı 0.15mg/kg/saat İV	Bolus: 2,250 ünite İV, infüzyon, 400 ünite/saat 4 saat sonra, 300 unite/saat 4 saat sonra, 200 ünite/saat İV devamlı infüzyon, ardından anti-Xa düzeyi ile ayarlanır.	<50kg: 5 mg/gün 50-100kg: 7.5 mg/gün, >100 kg: 10 mg/ gün SC.
Doz Ayarlaması	Karaciğer yetersizliği	Böbrek yetersizliği	Böbrek yetersizliği	Böbrek yetersizliği, vücut ağırlığı	Böbrek yetersizliği

Assessment of hemostatic activation during cardiopulmonary bypass for coronary artery bypass grafting with bivalirudin: Results of a pilot study

Andreas Koster, MD,[a] Ruhi Yeter, MD,[b] Semih Buz, MD,[b] Hermann Kuppe, MD,[a] Roland Hetzer, MD,[b] A. Michael Lincoff, MD,[c] Cornelius M. Dyke, MD,[d] Nicholas G. Smedira, MD,[e] and Bruce Spiess, MD[f]

Objective: Bivalirudin has been successfully used as a replacement for heparin during on-pump coronary artery bypass grafting. This study was conducted to assess the effects of the currently suggested protocol for bivalirudin on hemostatic activation during cardiopulmonary bypass with and without cardiotomy suction.

Methods: Ten patients scheduled for coronary artery bypass grafting were enrolled. Bivalirudin was given with a bolus of 50 mg in the priming solution and 1.0 mg/kg for the patient, followed by an infusion of 2.5 mg · kg^{-1} · h^{-1} until 15 minutes

Effectiveness of *Bivalirudin* as a Replacement for *Heparin* During Cardiopulmonary Bypass in Patients Undergoing Coronary Artery Bypass Grafting

Andreas Koster, MD, Bruce Spiess, MD, Derek P. Chew, MBBS, MPH, Thomas Krabatsch, MD, Luc Tambeur, MD, Abe DeAnda, MD, Roland Hetzer, MD, Hermann Kuppe, MD, Nicholas G. Smedira, MD, and A. Michael Lincoff, MD

We investigated the use of bivalirudin as an anticoagulant therapy during cardiopulmonary bypass in 20 patients who underwent coronary artery bypass grafting. Primary end points consisted of clinical outcome data, whereas secondary end points focused on blood loss, transfusions, pharmacokinetics, and monitoring. Our data provide the first evidence of clinical feasibility of anticoagulation with bivalirudin during cardiopulmonary bypass.

(Am J Cardiol 2004;93:356–359)

From the Departments of Anesthesia and Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum, Berlin, Germany; Departments of

Bivalirudin (Angiomax, The Medicines Company, Parsippany, New Jersey) is a short-acting (half-life approximately 25 minutes) bivalent reversible direct thrombin inhibitor. This agent has been demonstrated to be more effective with less associated

Surgery for Acquired Cardiovascular Disease

ACD

A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: The EVOLUTION-ON study

Cornelius M. Dyke, MD, Nicholas G. Smedira, MD, Andreas Koster, MD, Solomon Aronson, MD, Harry L. McCarthy II, CCP, Ronald Kirshner, MD, A. Michael Lincoff, MD, and Bruce D. Spiess, MD

See related editorial on page 515 and related article on page 686.

Objectives: Unfractionated heparin and its antidote, protamine sulfate, allow for rapid and reversible anticoagulation during cardiac surgery with cardiopulmonary bypass, yet limitations exist, including a variable dose-response, dependence on a cofactor for anticoagulant effect, and antigenic potential. This trial was performed to evaluate the safety and efficacy of bivalirudin as an alternative to heparin with protamine reversal in on-pump cardiac surgery.

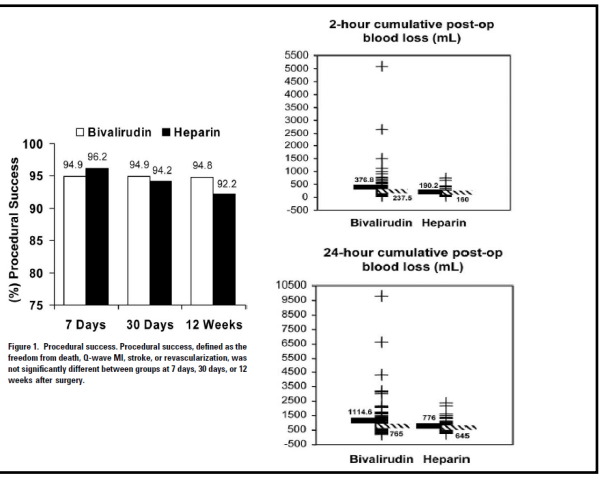


Figure 1. Procedural success. Procedural success, defined as the freedom from death, Q-wave MI, stroke, or revascularization, was not significantly different between groups at 7 days, 30 days, or 12 weeks after surgery.

CARDIOVASCULAR

Bivalirudin During Cardiopulmonary Bypass in Patients With Previous or Acute Heparin-Induced Thrombocytopenia and Heparin Antibodies: Results of the CHOOSE-ON Trial

Andreas Koster, MD, Cornelius M. Dyke, MD, Gabriel Aldea, MD, Nicholas G. Smedira, MD, Harry L. McCarthy II, CCP, Solomon Aronson, MD, Roland Hetzer, MD, Edwin Avery, MD, Bruce Spiess, MD, and A. Michael Lincoff, MD

Departments of Anesthesia and Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum Berlin, Germany; Department of Cardiovascular and Thoracic Surgery, Gaston Memorial Hospital, Gastonia, North Carolina; Department of Cardiac Surgery, Washington State University, Seattle, Washington; Departments of Cardiothoracic Surgery and Cardiovascular Medicine,

Staz olan alanlarda trombüs riski!
Aspirasyon ile sistemik koagülasyon-inflamasyonun tetiklenmesi

Bivalirudin as an Alternative to Heparin for Anticoagulation in Infants and Children

Marcia L. Buck, PharmD

Departments of Pharmacy Services and Pediatrics, University of Virginia Children's Hospital, Charlottesville, Virginia

Cardiopulmonary bypass				
Argueta-Morales et al[8]	2 (not specified)	1 mg/kg, 2.5 mg/kg/hr (50 mg added to CPB circuit)	ACT > 400 sec	None
Almond et al[9]	1 (5-yr)	0.15 mg/kg, 0.25 mg/kg/hr (50 mg add to the CPB circuit)	ACT 200-500 sec	Bleeding at the time of CPB separation requiring blood products and factor VI
Gates et al[10]	1 (5 mo)	0.5-1 mg/kg (2.5 mg/kg/hr, 50 mg/kg bivalirudin added for every 400 mL CPB prime)	ACT > 400 sec	None
Dragomer et al[11]	1 (17 mo)	0.5-1 mg/kg (2.5 mg/kg/hr, no bivalirudin added to the CPB circuit)	ACT > 400 sec	Minimal bleeding

The use of argatroban as an anticoagulant for cardiopulmonary bypass in cardiac operations

European Journal of Haematology ISSN 0902-4441

CASE REPORT

Argatroban for anticoagulation during cardiac surgery

Monte E. Martin, Goetz H. Kloecker, Damian A. Laber

Division of Hematology and Medical Oncology, Department of Medicine, University of Louisville and J.G. Brown Cancer Center, University of Louisville, Louisville, KY, USA

Argatroban Anticoagulation for Cardiac Surgery with Cardiopulmonary Bypass in an Infant with Double Outlet Right Ventricle and a History of Heparin-induced Thrombocytopenia

Michael L. Ciccolo, MD,*† Jonathan Bernstein, MD,‡ Juan C. Collazos, MD,§¶ Ruben J. Acherman, MD,§¶ Humberto Restrepo, MD, MPH,§¶ James M. Winters, CCP,** Justin Krueger, CCP,** and William N. Evans, MD§¶

*Cardiothoracic Surgery, Cardiovascular Surgical Associates, †Department of Cardiology and Pediatrics, ‡University of Nevada School of Medicine, §Pediatric Hematology and Oncology, Childrens Center for Cancer and Blood Disease, ¶Children's Heart Center, and **Clinical Technician Associates, Las Vegas, Nev, USA

J Anesth (2013) 27:951–955
DOI 10.1007/s00540-013-162

CLINICAL REPOR

Geri döndürülemeyen ACT

MASİF KANAMA

-

-

-

HASTA KAYBEDİLMİŞ

Non-recovery … thrombocytop… using argatro…

Yoshinori Tanigawa · …
Koichi Matsumoto · …
Arisu Torikai · Yoshi…

Received: 25 March 2012 /

Abstract Argatroban wa… ACT, although the correct dose ing cardiopulmonary bypass (CPB) in a patient with hep- …has not yet been established. There is no neutralizer of arin-induced thrombocytopenia (HIT) type II undergoing … argatroban, such as protamine sulfate against heparin

Alternatif Yaklaşımlar

- Plazmaferez yapılmasının ardından heparin uygulanması
  PF4-Heparin antikorlarında azalma
- İntravenöz antitrombositer tedavi (Glikoprotein IIb/IIIa ant., prostaglandin analogları)
  Trombosit aktivasyonunda azalma
- LMWH (?)

Antikoagülasyonun geri döndürülmesi

- Geleneksel yöntem
  Heparin kadar Protamin!

Titrasyon Yöntemi?
Viskoelastik ölçümler?
→ ACT, TEG

Protamin/Heparin oranı ≤ 2.6 olmalı!
≥2.6

Trombosit fonksiyonları inhibe olur
ACT uzar
Kanama riski artar

CARDIOVASCULAR ANESTHESIA
SECTION EDITOR
KENNETH J. TUMAN

SOCIETY OF CARDIOVASCULAR ANESTHESIOLOGISTS

Protamine Reversal of Heparin Affects Platelet Aggregation and Activated Clotting Time After Cardiopulmonary Bypass

Toshiaki Mochizuki, MD, Peter J. Olson, MD, Fania Szlam, MMS, James G. Ramsay, MD, and Jerrold H. Levy, MD

Department of Anesthesiology, Emory University School of Medicin
Critical Care, The Emory Clinic, Atlanta, Georgia

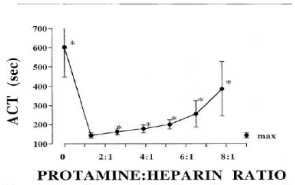
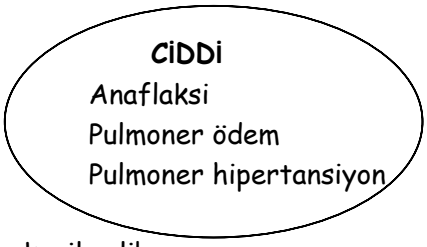


Figure 1. Effects of incremental ratios of protamine on reversal of heparin from blood samples obtained after cardiopulmonary bypass. Activated clotting time (ACT) values are expressed as mean ±

(5). Reliance on the ACT as the sole measure of reversal of heparin effect may be unreliable because it can be affected by many disorders of coagulation (6). Thus, an increased ACT after protamine administration may be due to excess protamine (rather than inadequate protamine) or coagulation issues unrelated to residual heparin.

The protamine dose or ratio that prolongs an ACT

Protamine bağlı komplikasyonlar



Protamin kesilmeli!

KPB tekrar başlatılmalı!

SON SÖZ

Heparin alamayan hastalarda KPB için ideal bir antikoagülasyon stratejisi bulunmamaktadır!

Bivaluridin en güvenli alternatif gibi durmaktadır!

Heparin ve protamin altın standart olarak kalmaya devam etmektedir!