

**Vasküler Cerrahide İskemik Önkoşullama**

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## Sunum Akışı

- Vasküler cerrahide sorunlar ve profil
- Vasküler cerrahide risk azaltma yöntemleri
- İskemik koşullama
- Vasküler cerrahide iskemik koşullama ile ilgili çalışmalar
- Olumsuz sonuçların olası nedenleri

- ✓ 65 yaş
- ✓ Arteriyel sorunlar
- ✓ Majör vasküler cerrahi



### Klinik risk faktörleri

- Anjina pektoris
- Geçirilmiş MI
- Kalp yetmezliği
- Serebrovasküler hastalıklar
- Renal yetmezlik
- Diabetes mellitus

Table 1. Relative Contribution of 29 Procedures to Adverse Events and Excess Length of Stay in Vascular surgery, ACS-NSQIP 2005-2006

Procedure	No. of Procedures (% of Total)	Adverse Event Rate (%)	Proportion of All Adverse Events (%)	Average Excess Length of Stay for Adverse Event (Days)	Proportion of All Excess Length of Stay (%)
1. Lower extremity bypass graft	3614 (22.5)	29.6	29.1	7.8	24.2
2. Abdominal aortic reconstruction	2955 (18.4)	23.8	19.7	10.2	21.6
3. Lower extremity amputation	1710 (10.6)	32.6	15.7	9.7	16.2
4. Carotid endarterectomy	4156 (25.8)	6.6	7.7	7.1	5.8
5. Thoracic aortic reconstruction	217 (2.0)	47.0	4.2	14.1	6.3
6. Lower extremity thrombectomy	358 (2.2)	41.3	4.2	8.7	3.9
7. Lower extremity aneurysm repair	445 (2.8)	24.3	3.0	7.7	2.5
8. Lower extremity thromboendarterectomy	442 (2.7)	21.9	2.7	10.6	3.1
9. Arteriovenous anastomosis	634 (3.9)	11.5	2.0	4.4	1.0
10. Intra-abdominal artery bypass graft	123 (0.8)	44.7	1.5	17.6	2.9
11. Thrombectomy of graft	203 (1.3)	24.1	1.4	6.7	1.0
12. Toe or foot amputation	181 (1.1)	26.0	1.3	13.4	1.9
13. Excision of infected graft in extremity	183 (1.1)	22.4	1.2	7.7	0.9
14. Intra-abdominal artery thromboendarterectomy	139 (0.9)	23.0	0.9	5.5	0.5
15. Repair of interruption of inferior vena cava	45 (0.3)	62.2	0.8	24.5	2.1
16. Carotid or vertebral artery bypass graft	127 (0.8)	18.9	0.7	9.2	0.7
17. Upper extremity thrombectomy	75 (0.5)	32.0	0.7	8.2	0.6
18. Excision of infected graft in abdomen	35 (0.2)	57.1	0.6	9.7	0.6
19. Lower extremity fasciotomy	36 (0.2)	52.8	0.5	6.1	0.3
20. Iliac artery aneurysm repair	36 (0.2)	36.1	0.4	23.5	0.9
21. Intra-abdominal artery thrombectomy	23 (0.1)	59.1	0.4	40.5	1.6
22. Upper extremity bypass graft	69 (0.4)	17.4	0.3	2.7	0.1
23. Carotid or subclavian artery aneurysm repair	48 (0.3)	22.9	0.3	7.0	0.3
24. Splenic or mesenteric artery aneurysm repair	51 (0.3)	19.6	0.3	1.9	0.1
25. Axillary or brachial artery aneurysm repair	32 (0.2)	21.9	0.2	34.6	0.7
26. Upper extremity amputation	22 (0.1)	18.2	0.1	15.0	0.2
27. Radial or ulnar artery aneurysm repair	9 (0.1)	22.2	0.1	7.0	0.04
28. Carotid or innominate artery thrombectomy	21 (0.1)	9.5	0.1	6.5	0.04
29. Upper extremity thromboendarterectomy	8 (0.1)	12.5	0.03	1.0	0.003

Schilling PL, Surgical Innovation 2010

**Table 1. Risk of MI and Cardiac Death Within 30 Days After Surgery<sup>1</sup>**

Low Risk <1%	Intermediate Risk 1%-5%	High Risk >5%
Breast	Abdominal	Aortic/major vascular
Dental	Carotid	Peripheral vascular
Endocrine	Peripheral arterial angioplasty	
Eye	Endovascular aneurysm repair	
Gynecology	Head and neck	
Reconstructive	Hip and spine	
Orthopedic—minor	Transplant—lung/kidney/liver	
Urology—minor	Urology—major	

**Per-op komplikasyonlar**

- MI
- Serebrovasküler olaylar
- Renal yetmezlik
- Ölüm

Schiefermuller, Angiology, 2013  
Healy DA, Vasc Endovascular Surg, 2015

## Komplikasyonların Nedenleri

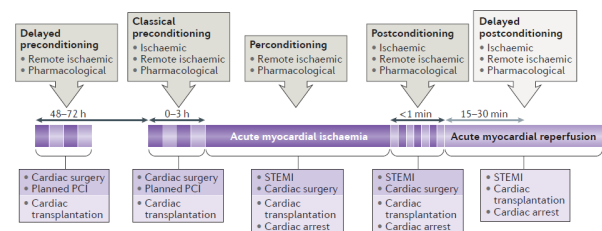
- Plak rüptürü
- Hemodinamik instabilite
- Suprarenal veya jukstarenal klemp
- Reperfüzyon
- Miyokardın oksijen gereksiniminin artması
- Hiperkoagülasyon
- Nöroendokrin değişiklikler
- Anestezi etkisi

## Korunma Yöntemleri

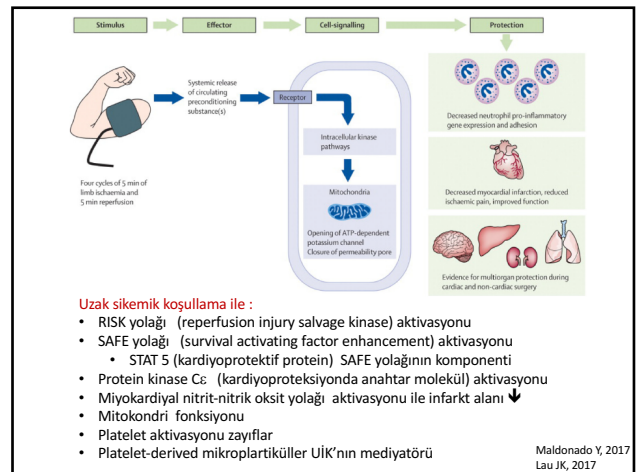
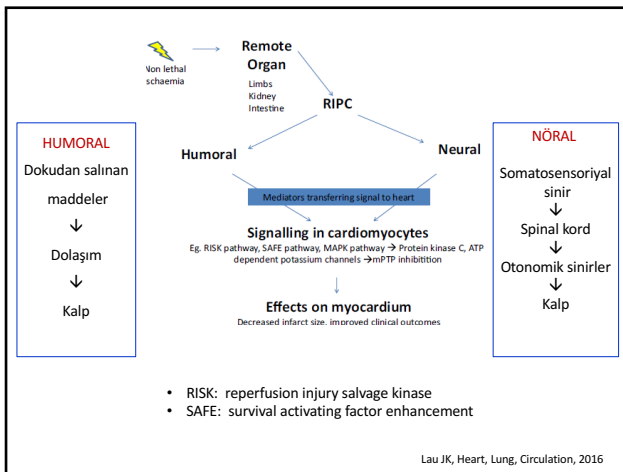
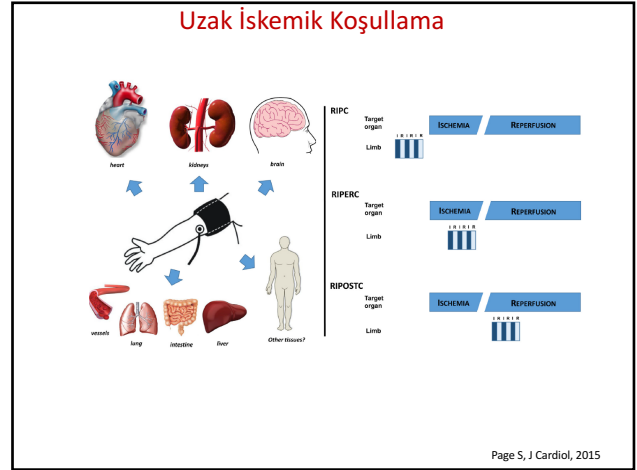
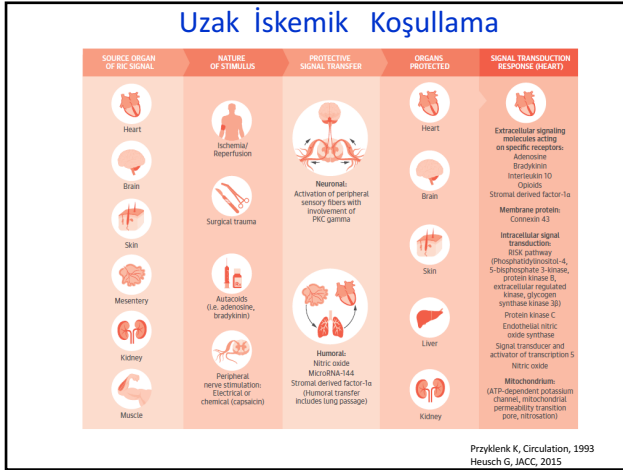
# İskemik Koşullama

**Ortak Etyolojik Mekanizma**  
**İskemi / Reperfüzyon Hasarı**

## İskemik Koşullama



Murry CE, Circulation, 1986  
Hausenloy DJ. Nat Rev Cardiol, 2016



**Table 1** Potential circulating mediators of RIPC.

Mediator	Species	Effect in RIPC	References
Adenosine	Rabbits	Adenosine in dialysate from rabbits treated with RIPC involved in protection of cardiomyocytes against simulated IR injury. Adenosine also reduced infarct size after cardiac IR injury. The adenosine A1 receptor appears to be involved in RIPC.	[20,23]
Aldehyde dehydrogenase-2	Humans and rabbits	RIPC associated attenuation of endothelial dysfunction after IR injury to the forearm not seen with genetic polymorphism of ALDH-2 gene or with Disulfiram (ALDH-2 inhibitor). ALDH-2 inhibitor abolished RIPC induced cardioprotection against IR injury.	[29]
Apolipoprotein A1	Rats	Upregulated by RIPC and administration mimicked RIPC cardioprotection. Human HDL administered to mice reduced myocardial infarction size.	[28]
Nitrite	Mice	Upregulated by RIPC and administration mimicked RIPC cardioprotection. Dependent on eNOS and myoglobin to reduce nitrite to NO.	[37]
Stromal cell derived factor-1 $\alpha$	Rats	RIPC increased levels in rat plasma with cardioprotection blocked by SDF-1 $\alpha$ receptor antagonist and mimicked by SDF-1 $\alpha$ administration.	[27]
Exosomes	Humans and rats	Plasma exosomes (containing CD63, CD81 and HSP-70) increased by RIPC and confer protection against cardiac IR injury in recipient rats.	[32]
MicroRNA-144	Humans and mice	RIPC increased plasma microRNA-144. An antagonist of microRNA-144 and administration of microRNA-144 abolished and mimicked, respectively, RIPC induced cardioprotection.	[34]

Lau JK, Heart, Lung, Circulation, 2017

**Uzak İskemik Koşullama (UİK) ve İskemik Koşullama (İK)****Benzerlikler**

- Protein kinase C $\epsilon$  integral komponent
- HSP-70  $\downarrow$  (inflamatuar sitokin salınımı ve immün yanıt stimülasyonu)
- K-ATP kanalı açılışı

**Farklılıklar**

- SAFE yoluğu UİK'da daha önemli
  - STAT5 SAFE yoluğunun önemli komponenti
- Bcl-2 UİK ile  $\rightarrow$  (hücre devamlılığını teşvik eden faktör)
- IL-8, IL-1b, TNF- $\alpha$  UİK ile  $\uparrow$  (sistemik inflamasyon modülasyonu)

**Uzak İskemik Önkoşullamanın Koruyuculuğunu Etkileyen Faktörler**

- Antitrombin III kompleksi
- Immunglobulin M
- Kompleman C1r
- Platelet inhibisyonu
- Aşırı koşullama (*hyperconditioning*)
- Medikasyonlar
  - Ganglion blokörleri (Hekzametonyum, Trimetafan)
  - Atropin
  - Antidiyabetikler
  - Statinler
  - ACE inhibitörleri
- Vagotomi
- Propofol

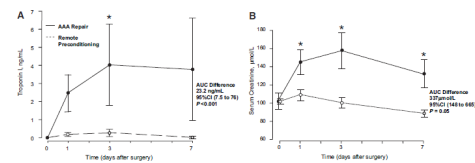
**Remote Ischemic Preconditioning Reduces Myocardial and Renal Injury After Elective Abdominal Aortic Aneurysm Repair**

Ziad A. Ali, MRCP, DPhil; Chris J. Callaghan, MRCS; Eric Lim, MRCS; Ayyaz A. Ali, MRCS;

**TABLE 3.** Major Adverse Outcomes After Open AAA Repair

	Remote Preconditioning	Conventional AAA Repair	P
Sample size	41	41	
In-hospital			
Myocardial injury, no. (%)	5 (12)	16 (39)	0.005
Myocardial infarction, no. (%)	2 (5)	11 (27)	0.006
Renal impairment, no. (%)	3 (7)	12 (30)	0.009
In-hospital death, no. (%)	2 (5)	3 (7)	0.37

- Abdominal Aort Anevrizma Cerrahisi
- 82 Olgu: 41UİK / 41 konvansiyonel
- Common iliak arter klempsi
- 2 kez 10 dk klemp/10 dk reperfüzyon
- GA+ Epidural analjezi



Circulation. 2007;116(4)

Remote Ischemic Preconditioning for Renal and Cardiac Protection During Endovascular Aneurysm Repair:

Stewart R. Walsh, MSc, FRCS<sup>1</sup>; Jonathan R. Boyle, MD, FRCS<sup>1</sup>; Tjun Y. Tang, MRCS<sup>1</sup>;

- EVAR: 40 AAA Hasta, GA
• 18 Hasta UIK: bir kez, her iki alt ekstremite, turnike, 10 dk
• 22 Hasta Kontrol
• Üriner biyobelirteç: retinol binding protein, kreatinin

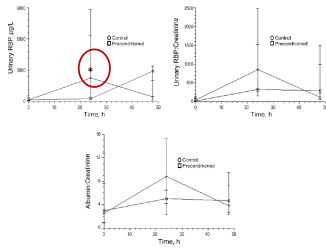


Figure 2 • Comparisons of (A) urinary RBP levels, (B) urinary RBP:creatinine ratio, and (C) urinary albumin:creatinine ratio. Data are presented as the median (point) and interquartile range (bars).

J Endovasc Ther. 2008;16:680-689

Limb Remote Ischemic Preconditioning for Intestinal and Pulmonary Protection during Elective Open Infraarenal Abdominal Aortic Aneurysm Repair

- 62 Hasta, açık infraarenal AAA
• Üst ekstremite 3 döngü 5 dk I/R ile UIK
• Epidural + GA
• Akciğer ve intestinal hasar
• I-FABP, endotoksin, DAO
• a/A oranı, A-aDO2, RI
• İnflamatuvar yanıt

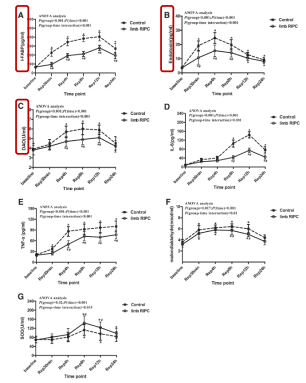


Table 3: Hemodynamic Data and the Variables Reflecting Lung Function. Columns include Control, Baseline, 30min after, 45-After, 60-After, 120-After, 24h-After, and P-value.

Fig 3. Diagrams of intestinal injury and variables reflecting oxidative stress and inflammatory response at various time points.

Cui Li, M.D., Yun-Sheng Li, M.D., Mao Xu, M.D., Shi-Hong Wen, M.D., Xi Yao, M.D., Yan Wu, M.D., Anesthesiology 2013; 118:842-52

Remote Ischemic Preconditioning for Renal Protection During Elective Open Infraarenal Abdominal Aortic Aneurysm Repair: Randomized Controlled Trial

Stewart R. Walsh, MSc, FRCS<sup>1</sup>, Umar Sadat, MRCS<sup>1</sup>

- UIK: sağ ve sol common iliac arter, 1 kez, 10 dk klemp
• Üriner retinol binding protein (RBP) renal tubuler hasar belirteci

Table 4: Comparison of Clinical Outcomes Between Groups in the Open Aneurysm Trial. Columns: Variable, Preconditioned Group (n=22), Control Group (n=18), P.

Table 3: Renal Outcome Data. Columns: Baseline, 3 hours, 24 hours, 48 hours for Preconditioned and Control groups.

Vascular and Endovascular Surgery 44(5): 2010

A Multi-Center Pilot Randomized Controlled Trial of Remote Ischemic Preconditioning in Major Vascular Surgery

S. R. Walsh, MSc<sup>1</sup>, On behalf of The Preconditioning Study Group

- Çok merkezli (3 hastane), prospektif
• Elektif major vasküler cerrahi
• AAA, EVAR, CE, alt eks. revas.
• UIK: üst eks. 4 döngü 5 dk I/R
• GA, RA, GA+RA
• 188 hasta - 99/99
• Klinik sonuç?

Table 4: Serum Troponin Values within the First 72 Hours Postoperatively. Columns: Control, RBC, P.

Table 1. Definitions of Components of the Composite Primary Outcome.

Table with 3 columns: Outcome, Definition, and P-value. Lists various clinical events like Myocardial infarction, Stroke, etc.

Table 3. Primary and Secondary Outcomes.\*

Table with 4 columns: Outcome, Control (n=99), RBC (n=99), P. Lists composite and secondary outcomes.

Vascular and Endovascular Surgery 2015, Vol. 49(8) 220-227



### Remote Preconditioning and Vascular Surgery: Challenges in Translation

#### Vasküler cerrahide UİK kavramının kanıtlanması ??

- Vasküler cerrahi hastalarındaki ileri ateroskleroz
  - Klodikasyon ve anjina ile koşullama
- Çalışmalardaki örneklem sayısı düşüklüğü ve heterojenite
- İskemik koşullama mekanizmasının çözülmesi
- Propofol kullanımı
  - UİK mekanizması ile etkileşim içinde
- İskemik hasar çok büyük ise koşullama ile sağlanan koruma kaybolabilir (Murry)
  - Vasküler girişimler sınıflandırılırsa yararı anlaşılabilir
- Vasküler cerrahiden önceki uygulamalarda yararlı olabilir
  - Anjioplasti, kontrast maddeli görüntüleme yöntemleri
- Böbrek hasarında yararlı olabilir

Journal of Cardiovascular Pharmacology and Therapeutics 2012; 27(3): 216-220  
Donagh A. Healy, PhD<sup>1</sup> and Stewart R. Walsh, MSc, MCh<sup>2</sup>

### Effects of ischaemic conditioning on major clinical outcomes in people undergoing invasive procedures: systematic review and meta-analysis

Loebis Sukkar,<sup>1,2</sup> Daming Hong,<sup>1,2</sup> Mui Geet Wong,<sup>1,2</sup> Suniti Boshui,<sup>1,2</sup> Kris Rogers,<sup>1,2</sup> Václav Perkoč,<sup>1</sup> Michael Walsh,<sup>1,2</sup> Victoria W. F. Coombes,<sup>1,2</sup> Graham S.Hills,<sup>1,2</sup> Martin Gallagher,<sup>1,2</sup> Meg Jardine<sup>1,2</sup>

Table 1 | Summary of included trials by setting\*

Setting	No of trials	No of participants	Placebo controlled trials (%)	Studies examining pre-conditioning (%)	Remote ischaemia reperfusion stimulus (%)
Adult cardiac surgery <sup>††</sup>	34	7230	65	91	71
Paediatric cardiac surgery <sup>***</sup>	9	823	89	44	56
Vascular surgery <sup>†††</sup>	7	425	43	100	86
Pericardiac coronary intervention	21	3875	43	48	67
Transplantation <sup>††††</sup>	7	487	71	71	57
Resection surgery <sup>§§§</sup>	8	689	0	100	13
Secondary stroke prevention <sup>†††††</sup>	3	411	67	100	100

11 000 hasta  
424 exitus

Setting	Use of volatile anaesthetic agent <sup>§</sup> (%)	Median (IQR) follow-up time (months) <sup>¶</sup>	Median (IQR) age of participants (years)	Mean (SD) age of participants (years)	Participants with diabetes (%)	Mortality <sup>††</sup>	Cardiac <sup>†††</sup>	Renal <sup>§§</sup>	Clinical outcome reported <sup>**</sup> (%)
Adult cardiac surgery <sup>††</sup>	67	1 (0.25-3)	62 (8.8)	27	73	59	43	22	
Paediatric cardiac surgery <sup>***</sup>	100	1 (0.5-1)	4 (2.3)	NR	100	11	11	22	
Vascular surgery <sup>†††</sup>	67	1 (0.25-1)	71 (37)	16	86	100	86		
Pericardiac coronary intervention	NA	6 (0-12)	63 (6.9)	32	62	57	48		
Transplantation <sup>††††</sup>	75	12 (3-21)	49 (4.9)	7	57	14	0		
Resection surgery <sup>§§§</sup>	67	3 (3-3)	55 (4.9)	12	100	13	25		
Secondary stroke prevention <sup>†††††</sup>	NA	6 (3-10)	67 (7.4)	25	33	33	0		

- Akut renal hasar ↓
- Mortalite →
- MI →
- Aritmi →

BMJ 2016;355:e999

### Vasküler Cerrahide Uzak İskemik Koşullama

- Güvenilir
- Zararsız
- Ucuz
- Kolay uygulanabilir
- Potansiyel vaat ediyor
- UİK mekanizmasının anlaşılması
  - Karışıklık oluşturan faktörlerin eliminasyonu
  - UİK'nın standardizasyonu
  - ile yeni bulgulara gereksinim var

24. Ulusal Rangnyaesi  
Göğüs Kalp Damar Anestezi ve Yoğun Bakım Derneği  
3-6 MAYIS 2018 | HADISON BLUE RESORT, ÇEŞME

Teşekkür Ederim