Long-term Results of One Cycle of Remote Ischemic Preconditioning Applied Before Elective Percutaneous Coronary Intervention

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ABSTRACT

Introduction: Myocardial injury after percutaneous coronary intervention (PCI) is seen frequently. Ischemia/reperfusion injury, side branch occlusion and distal embolization of atherothrombotic debris are the main causes of myocardial injury. Remote ischemic preconditioning (RIPC) is a promising technique for protection from ischemia/reperfusion injury, but sufficient data of long-term clinical outcomes is not available. In this study we planned to investigate the effect of one cycle of RIPC on major cardiovascular events one year after elective PCI.

Patients and Methods: 102 patients, undergoing elective PCI, with normal baseline cTroponin-I (cTn-I) values, were randomized equally into two groups. Five minutes of ischemic preconditioning was applied before the intervention to the preconditioning group, by inflating blood pressure cuff up-to 200 mmHg on non-dominant arm. After 1 year, the clinical outcomes of these patients (angina, heart failure, death, myocardial infarction, repeat revascularization) were questioned.

Results: From a total of 102 patients, 90 could be reached after an year. The mean duration of follow-up was 432 vs. 423.5 days (p= 0.793). Post-PCI 16th hour cTn-I was insignificantly lower in the preconditioning arm (0.079 μg/L vs. 0.069 μg/L, p= 0.074). The incidence of cTn-I elevation 5 fold above the URL (> 0.115 μg/L) was lower in the preconditioning group; however, it was also insignificant (24.4% vs. 13.3%, p= 0.301). Death, MI or repeat revascularization rates did not differ between the groups.

Conclusion: One cycle of RIPC had no effect on major cardiovascular events (MACE) after elective PCI.

Key Words: Remote ischemic preconditioning; percutaneous coronary intervention

Elektif Perkütan Koroner Girişim Öncesi Uygulanan Uzaktan İskemik Ön Koşullanmanın Uzun Dönem Sonuçları

ÖZET

Giriş: Perkütan koroner girişim sonrası miyokart hasarı sıklıkla görülmektedir. Miyokart hasarı iskemi/reperfüzyon hasarına, yan dal tıkanmasına ve aterotrombotik debrisi distal embolizasyonuna bağlı gelişmektedir. Uzaktan iskemik ön koşullanma iskemi reperfüzyon hasarından korunmada ümit verici tekniklerdendir ancak uzun dönem sonuçları ile ilgili yeterli veri henüz bulunmamaktadır. Biz bu çalışmada perkütan koroner girişim öncesi uygulanan tek sefer uzaktan ön koşullanmanın bir yıl sonunda majör kardiyovasküler olaylar üzerine etkisini araştırmayı planladık.

Hastalar ve Yöntem: Elektif perkütan koroner girişim planlanan 102 hasta çalışmaya alındı ve hastalar iki gruba randomize edildi. Ön koşullanma grubundaki hastalara girişimden önce, kan basıncı manşonu 5 dakika boyunca 200 mmHg'da şişirilerek ön koşullanma uygulandı. İşlem öncesi ve sonrası cTroponin-I değerlerine bakıldı. Birinci yıl sonunda hastaların klinik durumları sorgulandı (angina, kalp yetersizliği, ölüm, miyokart infarktüsü, tekrar revaskülarizasyon).

Bulgular: Yüz iki hastanın 90'ına ulaşılabildi. Ortalama takip süresi 432 vs. 423.5 gün (p= 0.793). Ön koşullanma grubunda koroner girişim sonrası 16. saat cTroponin-I değeri kontrol grubuna göre daha düşük bulundu ancak istatistiksel anlamlılık saptanmadı (0.079 μg/L vs. 0.069 μg/L, p= 0.074). cTroponin-I beş kat arttığı hasta oranı da ön koşullanma grubunda daha azdı ancak bu fark da istatistiksel olarak anlamlı saptanmadı (24.4% vs. 13.3%, p= 0.301). Ölüm, miyokart infarktüsü ve tekrar revaskülarizasyon açısından gruplar arasında fark saptanmadı.

Sonuç: Tek sefer uzaktan iskemik ön koşullanmanın elektif perkütan koroner girişim sonrası majör kardiyovasküler olaylar üzerine etkisi saptanmamıştır.

Anahtar Kelimeler: İskemik ön koşullanma; perkütan koroner girişim

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INTRODUCTION

Myocardial injury after percutaneous coronary intervention (PCI) is observed frequently. Although the prognostic importance of troponin elevation after PCI is under debate , there are studies reporting that even minor elevations are significant[1,4]. Ischemic pre- or post-conditioning to protect the myocardium from ischemia/reperfusion injury has been investigated in various trials. Remote ischemic preconditioning (RIPC) before elective PCI has been demonstrated as beneficial in protecting the heart from post-PCI myocardial injury; but sufficient data about its effect on major cardiovascular events (MACE) is not available[5-7]. In remote ischemic preconditioning (RIPC), brief episodes of sublethal ischemia, followed by reperfusion, is applied to decrease myocardial injury. However, the best timing and protocol has not been determined yet. In one study, it has been demonstrated that one cycle of RIPC is also effective in reducing post-PCI myocardial injury, whereas in our study with a similar study population, we could not demonstrate cardioprotection with one cycle of RIPC[7-8]. Most of the studies about RIPC evaluated myocardial injury by post-PCI cardiac enzyme elevation, there are a few studies with clinical end-points. The long-term effects of RIPC has been investigated in CRISP stent trial and they were able to show a decrease in MACE ratio[9]. Our aim in this study was to evaluate the long-term effects of one cycle RIPC on major cardiovascular events.

PATIENTS and METHODS

We conducted a study previously to assess the effect of one cycle of RIPC after elective PCI, on myocardial injury. This study was a single center randomized study and was approved by the local ethical committee and was registered to clinicaltrials.gov. The details and results of this study were published recently[8]. Patients with stable angina pectoris and undergoing elective PCI were randomized into two groups. The exclusion criteria were presence of 1) acute coronary syndrome, 2) left main disease, 3) baseline cardiac troponin-I (cTn-I) elevation (> 0.023 ng/mL), 4) hemodynamically instability 5) renal failure (a glomerular filtration rate (GFR) below or equals a threshold value of 60 mL/min/1.73 m^2), 6) glibenclamide or nicorandil usage 7) contraindication to cuff inflation in upper extremities (lymphoedema, fistula) 8) suspicion of pregnancy. Patients who did not give written informed consent were not enrolled to the study.

The follow-up data of the patients were gathered from outpatient clinic files or by phone call. Eventually, 90 of the 102 patients could be reached. Recurrent angina, stent restenosis, thrombosis, revascularization of any lesion, heart failure symptoms, myocardial infarction, death and cerebrovascular incidents were recorded.

Statistical Methods

IBM SPSS version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, IBM Corp) was used to perform the statistical analysis. Continous variables (heart rate, systolic and diastolic blood pressure, etc.) were summarized as mean, standard deviation, minimum, maximum, median and were compared by use of Student's t test or Mann-Whitney U test when appropriate. Categorical data (target vessel, lesion type etc.) were expressed as numbers, percentages and were compared by use of chi square test. A value of $p< 0.05$ was accepted significant.

RESULTS

Ninety of the 102 patients could be reached. Forty-five patients in each group were analyzed.

Table 1 lists the demographic data of the patients. There were no significant differences between the groups in terms of risk factors. The lesion type, target vessel, stenosis severity and Approoach score did not differ also between the groups (Table 2). Likewise, there were no procedural differences between the two groups regarding the procedural data such as predilatation, postdilatation and total dilatation durations and counts (Table 2).

Post-PCI 16th hour cTn-I values and the cTn-I change (difference between 16th hour and baseline cTn-I values) were also compared in these 90 patients. There were no significant differences between the control group and the preconditioning group (0.079 vs. 0.069, p= 0.074 and 0.073 vs. 0.06, p= 0.051 consecutively).

The incidence of patients with troponin above the upper reference limit (URL) (> 0.023 μg/L) was insignificantly lower in the preconditioning group. (77.7% vs. 66.6%, p= 0.101). The incidence of cTn-I elevation 5 fold above the URL (> 0.115 μg/L) was lower in the preconditioning group; however, it was also insignificant (24.4% vs. 13.3%, p= 0.301).

Table 3 presents the follow-up data. The mean duration of follow-up was 432 (404.8-459.7) days in the control group and 423.5 (406.2-441) days in the preconditioning group (p= 0.793). MACE ratio, death, MI, revascularization, angina, heart failure also did not differ between the groups. One patient in each group died from subacute stent thrombosis/MI. One patient in the preconditiong group died from acute cerebrovascular incident.

DISCUSSION

The present study demonstrated that one cycle of RIPC just before elective PCI had no effect on long-term cardiac events.

Periprocedural myocardial injury is observed frequently after elective PCI. With the ongoing developments in interventional techniques and stent technology, major complications like death and extensive myocardial infarctions have decreased. Although the prognostic importance of troponin elevation after PCI is under debate, guidelines recommended troponin measurement to detect myocardial injury [1-3, 10-12]. Particularly, pre-procedural troponin elevation is linked to poorer prognosis; besides there are studies indicating even minor troponin elevations after PCI have worse prognosis [4,13].

Table 1. Demographic and clinical data of the patients

Variable	Controls (n= 45)	Preconditioning (n= 45)	p
Demographics			
Age, years	60.7 (38-79)	57.4 (39-76)	0.126
Male/Female	37/8	34/11	0.438
Risk factors			
Hypertension, n (%)	37 (82.2%)	42 (93.3%)	0.102
Hyperlipidemia, n (%)	38 (84.4 %)	40 (88.9%)	0.534
Family history, n (%)	7 (15.6%)	12 (26.7%)	0.194
Smoker, n (%)	33 (73.4%)	30 (66.7%)	0.490
Diabetes mellitus, n (%)	13 (28.9%)	15 (33.3%)	0.649
BMI, kg/m^2	28.4 (26.8-29.9)	28.83 (27.5-30.2)	0.626
Clinical features			
LVEF (%)	58 (55.3-60.9)	58.3 (56-59)	0.869
GFR, mL/min/1.73 m^2	92.6 (86.7-98.5)	90.2 (85.1-95.3)	0.529
CCS 2/3 n/n	29 (64.4%)	19 (42.2%)	0.035
Previous MI, n (%)	9 (20%)	10 (2.2%)	0.796
Previous CABG-O, n (%)	3 (6.7%)	2 (4.4%)	1
Last 24 hour angina, n (%)	6 (13.3%)	3 (6.7%)	0.485
Medications, n (%)			
β-blockers	43 (95.6%)	43 (95.6%)	1
ACEI/ARB	33 (73.3%)	36 (80%)	0.454
Ca-channel blocker	9 (20%)	10 (22.2%)	0.796
Statins	32 (71.1%)	34 (75.6%)	0.633

ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, BMI: Body mass index, CCS: Canadian Cardiology Society, CABG-O: Coronary artery bypass graft operation, GFR: Glomerular filtration rate, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction.

Side branch occlusion, atherosclerotic debris embolization and ischemia/reperfusion injury are the main reasons for PCI-related myocardial injury. Various adjunctive pharmacological agents and methods have been tried to reduce ischemia reperfusion injury but none of them have been proven[14-16]. Remote ischemic preconditioning is an easy, cheap, and practical method. The basics underlying remote ischemic preconditioning is that brief sublethal episodes of ischemia followed by reperfusion in another organ can reduce the hazardous effects of the subsequent ischemia. The whole process of ischemic preconditioning has not been understood yet. Neural pathways, cellular mechanisms and circulating mediators such as adenosine, aldehyde dehydrogenase-2, apolipoprotein A1, nitrite, stromal cell derived factor-1æi, have a role in the potential mechanisms of RIPC[17-21]. The earlier animal studies confer a more evident beneficial effect, whereas clinical studies have conflicting results. Recently published trials of RIPC in CABG surgery could not reveal effective myocardial protection, whereas in the acute myocardial infarction setting, the application of remote ischemic conditioning before primary PCI reduced the infact size[22-24].

A majority of the studies investigating the effect of RIPC before elective PCI, used three cycles of five minutes ischemia/reperfusion and the results were mostly favorable. CRISP stent trial was the first and largest study demonstrating that three cycles of RIPC were successful in reducing myocardial injury[5]. Nevertheless not all of the studies supported this conclusion. Prasad et al. used a different protocol with 3 minutes of RIPC instead of 5 minutes[25]. They implied that shorter time of RIPC could be an insufficient stimulant, resulting neutral outcome. Differently, Zografos et al., demonstrated reduced type 4a MI after elective PCI with one cycle of RIPC, whereas in our study we could not demonstrate a significant reduction[7,8]. Six year clinical outcomes of the patients enrolled in CRISP trial were

Table 2. Angiographic and procedural data of the patients

Variable	Controls (n= 45)	Preconditioning (n= 45)	p
Angiographic parameters			
Target vessel, n (%)			0.515
LAD	13 (28.89%)	16 (35.56%)	
LCx	5 (11.11%)	8 (17.78%)	
RCA	18 (40.00%)	16 (35.56%)	
Combined/other	9 (20.00%)	5 (11.11%)	
Lesion AHA/ACC, n (%)			0.955
Type A	8 (17.78%)	9 (20.00%)	
Type B	21 (46.67 %)	21 (46.67%)	
Type C	16 (35.56%)	15 (33.33%)	
Approach score	27.57 (23.45-31.71)	25.07 (21.3-28.81)	0.455
Stenosis severity	82.3 (79.51-85.1)	82 (79.1-84.7)	0.842
TIMI flow 0-2, n (%)	33 (73.33%)	38 (84.44%)	0.194
Procedural data			
Heart rate, beats/min	77.5 (74.2-76)	74.22 (71.4-77.05)	0.134
Systolic blood pressure, mmHg	138.7 (134.3-143.1)	141 (135-147)	0.548
Diastolic blood pressure, mmHg	77.7 (75.3-80)	75.38 (73-78)	0.356
Procedural angina, n (%)	23 (51.11%)	22 (48.89%)	0.833
Procedural ST deviation, n (%)	15 (33.33%)	10 (22.22%)	0.238
Bifurcation procedure, n (%)	3 (6.67%)	4 (8.89%)	0.693
DES/BMS/Balloon, n/n/n	40/5/0	43/0/2	0.007
Stent length, mm	27.1 (23-31.16)	26.14 (22.7-29.7)	0.973
Stent number (n)	1.31 (1.16-1.47)	1.16 (1.01-1.3)	0.185
Stent diameter, mm	2.87 (2.75-3)	2.81 (2.7-2.92)	0.614
Total dilatation time, s	76 (59.02-93)	80.17 (68-92.36)	0.686
Predilatation, n (%)	19 (42.22%)	20 (44.44%)	0.832
Postdilatation, n (%)	28 (62.22%)	29 (64.44%)	0.827
Predilatation time, s	34.25 (17.91-50.6)	22.2 (17.15-27.2)	0.443
Postdilatation time, s	45.07 (34-56.16)	47.6 (38.4-56.85)	0.436
Total dilatation count (n)	3.66 (2.85-4.50)	3.62 (3.05-4.20)	0.472
Post-PCI results			
TIMI flow 2/3	0/45	2/43	0.093
cTn-I values			
Bazal cTn-I	0.006 (0.004-0.009)	0.009 (0.007-0.011)	0.139
cTn-I rise, median, µg/L (16^{th} hour-baseline)	0.073 (0.051-0.094)	0.060 (0.029-0.092)	0.051
cTn-I 16.h, median, µg/L	0.079 (0.058-0.100)	0.069 (0.036-0.101)	0.074
cTn-I > 5 x URL, n (%)	11 (24.4%)	6 (13.3%)	0.301
cTn-I > URL, n (%)	35 (77.7%)	30 (66.6%)	0.101

BMS: Bare metal stent, cTn-I: Cardiac troponin-I, DES: Drug eluting stent, LAD: Left anterior descending artery, LCx: Left circumflex artery, RCA: Right coronary artery, PCI: Percutaneous coronary intervention, TIMI: Thrombolysis in myocardial infarction, URL: Upper reference limit.

Table 3. Follow-up data of the patients

Variable	Controls (n= 45)	Preconditioning (n= 45)	p
Follow-up duration	432.2 (404.8-459.7)	423.5 (406.2-441)	0.793
Angina	10 (22.2%)	10 (22.2%)	1
Revascularization	6 (13.3%)	5 (11.1%)	0.748
Heart failure	0	2 (4.4%)	0.494
Death	1 (2.2%)	2 (4.4%)	0.553
MI	2 (4.4%)	1 (2.22)	0.553
Stent restenosis/Thrombosis	1/2	2/1	1
MACE, (%)	2 (4.4%)	2 (4.4%)	1
Any event	10 (22.2%)	10 (22.2%)	1

MACE: Major cardiovascular events, MI: Myocardial infarction.

also published and the results were coherent with the CRISP trial with lower MACE in the RIPC group[5,9]. Miyoshi et al. recently published a study comparing the effects of RIPC and nicorandil; although postprocedural myocardial injury was lesser than the control group in either treatment group, the results were not statistically significant[26]. Several meta-analysis have been published so far, despite the beneficial effects demonstrated in these articles, the insufficient data about the long-term outcomes prevented the translation into daily clinical practice[27].

In the present study we could not demonstrate any difference between the control group and the RIPC group, in terms of one year clinical outcomes. The study population, method of RIPC, follow-up period and size of the study, are the main potential factors that might cause lack of effect on clinical outcomes. We have recently published the effect of one cycle of RIPC on post-PCI myocardial injury in the same patient population. Failure to achieve significant reduction in myocardial injury with one cycle of RIPC might also be the reason of lack of benefit in the long-term; we might not reach the acquired treshold of preconditioning. The treshold and the effect of RIPC can be affected by numerous factors such as, age, sex, comedications, and comorbidities, but the study was not powerful enough to analyse all the possible confounding factors[28-30]. The size of the study could also explain the neutral results; it could be underpowered to demonstrate the moderate differences in post-PCI myocardial injury, leading to a type II error. Another possible reason is the follow-up period is just about 1 year. In this period, lower rates of MACE have occurred, with longer time of follow-up; the difference in adverse events might be meaningful.

In conclusion, one cycle of RIPC did not have an effect on long-term- outcomes after elective PCI. Remote ischemic preconditioning is a promising technique; however, still the opitmal protocol and the patients who will have the most benefit have not been determined. Further multicenter studies with large populations targeting high risk patients are needed to overcome these limitations and to evaluate the effects of confounding factors.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MY, GT, FMU, UÖ, MA, HYG
Analysis/Interpretation: MY, GT, FMU, UÖ, MA, HYG
Data Acquisition: MY, GT, FMU, UÖ
Writting: MY, GT, MA, HYG
Critical Revision: MY, GT, FMU, MA, HYG
Final Approval: All of authors

REFERENCES

1. Christensen MK, Huang H, Torp-Pedersen C, Trydal T, Ravkilde J. Incidence and impact on prognosis of peri-procedural myocardial infarction in 2760 elective patients with stable angina pectoris in a historical prospective follow-up study. BMC Cardiovasc Disord 2016;16:140.

2. Ndrepepa G, Colleran R, Braun S, Cassese S, Hieber J, Fusaro M, et al. High-sensitivity troponin T and mortality after elective percutaneous coronary intervention. J Am Coll Cardiol 2016;68:2259-68.

3. Ferreira RM, de Souza ESNA, Salis LH, da Silva RR, Maia PD, Horta LF, et al. Troponin I elevation and all-cause mortality after elective percutaneous coronary interventions. Cardiovasc Revasc Med 2017;18:255-60.

4. Selvanayagam JB, Porto I, Channon K, Petersen SE, Francis JM, Neubauer S, et al. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. Circulation 2005;111:1027-32.

5. Hoole SP, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, et al. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. Circulation 2009;119:820-7.

6. Luo SJ, Zhou YJ, Shi DM, Ge HL, Wang JL, Liu RF. Remote ischemic preconditioning reduces myocardial injury in patients undergoing coronary stent implantation. Can J Cardiol 2013;29:1084-9.
7. Zografos TA, Katritsis GD, Tsiafoutis I, Bourboulis N, Katsivas A, Katritsis DG. Effect of one-cycle remote ischemic preconditioning to reduce myocardial injury during percutaneous coronary intervention. Am J Cardiol 2014;113:2013-7.
8. Yilmaztepe MA, Taylan G, Aktoz M, Gurlertop HY, Aksoy Y, Ozcelik F, et al. The impact of a single episode of remote ischemic preconditioning on myocardial injury after elective percutaneous coronary intervention. Postepy Kardiol Interwencyjnej 2017;13:39-46.
9. Davies WR, Brown AJ, Watson W, McCormick LM, West NE, Dutka DP, et al. Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: the CRISP stent trial long-term follow-up. Circ Cardiovasc Interv 2013;6:246-51.
10. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Glob Heart 2012;7:275-95.
11. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). Catheter Cardiovasc Interv 2014;83:27-36.
12. Liou K, Jepson N, Kellar P, Ng B, Isbister J, Giles R, et al. Prognostic significance of peri-procedural myocardial infarction in the era of high sensitivity troponin: a validation of the joint ACCF/AHA/ESC/WHF universal definition of type 4a myocardial infarction with high sensitivity troponin T. Heart Lung Circ 2015;24:673-81.
13. Zanchin T, Raber L, Koskinas KC, Piccolo R, Juni P, Pilgrim T, et al. Preprocedural high-sensitivity cardiac troponin T and clinical outcomes in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention. Circ Cardiovasc Interv 2016;9.
14. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, et al. Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015;373:1021-31.
15. Upadhaya S, Madala S, Baniya R, Subedi SK, Saginala K, Bachuwa G. Impact of cyclosporine A use in the prevention of reperfusion injury in acute myocardial infarction: A meta-analysis. Cardiol J 2017;24:43-50.
16. Ekelof SV, Halladin NL, Jensen SE, Zaremba T, Aaroe J, Kjaergaard B, et al. Effects of intracoronary melatonin on ischemia-reperfusion injury in ST-elevation myocardial infarction. Heart Vessels 2016;31:88-95.
17. Contractor H, Lie HR, Cunnington C, Li J, Støttrup NB, Manlhiot C, et al. Adenosine receptor activation in the "trigger" limb of remote preconditioning mediates human endothelial conditioning and release of circulating cardioprotective factor(s). JACC Basic Transl Sci 2016;1:461-71.
18. Ormerod JO, Evans JD, Contractor H, Beretta M, Arif S, Fernandez BO, et al. Human second window pre-conditioning and post-conditioning by nitrite is influenced by a common polymorphism in mitochondrial aldehyde dehydrogenase. JACC Basic Transl Sci 2017;2:13-21.
19. Lau JK, Pennings GJ, Yong A, Kritharides L. Cardiac remote ischaemic preconditioning: mechanistic and clinical considerations. Heart lung Circ 2017;26:545-53.
20. Anttila V, Haapanen H, Yannopoulos F, Herajarvi J, Anttila T, Juvonen T. Review of remote ischemic preconditioning: from laboratory studies to clinical trials. Scand Cardiovasc J 2016;50:355-61.
21. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. J Am Coll Cardiol 2015;65:177-95.
22. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. Remote ischemic preconditioning and outcomes of cardiac surgery. N Engl J Med 2015;373:1408-17.
23. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, et al. A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med 2015;373:1397-407.
24. White SK, Frohlich GM, Sado DM, Maestrini V, Fontana M, Treibel TA, et al. Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 2015;8:178-88.
25. Prasad A, Gossl M, Hoyt J, Lennon RJ, Polk L, Simari R, et al. Remote ischemic preconditioning immediately before percutaneous coronary intervention does not impact myocardial necrosis, inflammatory response, and circulating endothelial progenitor cell counts: a single center randomized sham controlled trial. Catheter Cardiovasc Interv 2013;81:930-6.
26. Miyoshi T, Ejiri K, Kohno K, Nakahama M, Doi M, Munemasa M, et al. Effect of remote ischemia or nicorandil on myocardial injury following percutaneous coronary intervention in patients with stable coronary artery disease: A randomized controlled trial. Int J Cardiol 2017;236:36-42.
27. Pei H, Wu Y, Wei Y, Yang Y, Teng S, Zhang H. Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. PLoS One 2014;9:e115500.
28. Whittington HJ, Harding I, Stephenson CI, Bell R, Hausenloy DJ, Mocanu MM, et al. Cardioprotection in the aging, diabetic heart: the loss of protective Akt signalling. Cardiovasc Res 2013;99:694-704.
29. Tsang A, Hausenloy DJ, Mocanu MM, Carr RD, Yellon DM. Preconditioning the diabetic heart: the importance of Akt phosphorylation. Diabetes 2005;54:2360-4.
30. Xu X, Zhou Y, Luo S, Zhang W, Zhao Y, Yu M, et al. Effect of remote ischemic preconditioning in the elderly patients with coronary artery disease with diabetes mellitus undergoing elective drug-eluting stent implantation. Angiology 2014;65:660-6.