SYSTEMATIC REVIEW

Effects of Remote Ischemic Conditioning in STEMI Patients undergoing Fibrinolysis Reperfusion Therapy : A Systematic Review and Meta- Analysis

Wilbert Huang, Apridya Nurhafizah, Liana Awalia Lutfunnisa

Faculty of Medicine, Universitas Padjadjaran, Bandung, 45363 West Java, Indonesia

ABSTRACT

Introduction: Fibrinolytic therapy remains a viable reperfusion strategy in STEMI patients in locations with limited facilities. However, reperfusion injury following fibrinolysis has also led to myocardial injury. One potential intervention to prevent this injury is through remote ischemic conditioning (RIC). This study aims to evaluate the effects of RIC in reducing myocardial injury in STEMI patients undergoing fibrinolysis. **Materials and methods:** A systematic review is conducted from PubMed and CochraneLibrary. Inclusion criteria are RCTs enrolling STEMI patients on fibrinolysis therapy. Outcome measured are difference peak troponin I/ T and CKMB levels and incidence of ST resolution (STR). Data are pooled using random effects model as odds ratio and risk of biases assessed with RoB2 tool.**Results:** 4 studies with a total of 849 patients are included. Peak troponin I/ T levels are lower in the intervention in two studies. Peak CKMB level is also lower in intervention group in 2 studies while one study reported vice versa result. The results from these outcome measures however cannot be pooled due to different unit of measurements. Additionally, 2 studies demonstrate a higher incidence of STR in RIC intervention group with significant OR 1.92 (1.11 – 3.33, p = 0.02 I2 = 13%). There is no substantial risk of biases. **Conclusion:** RIC intervention resulted in a lower peak enzymatic troponin and CKMB level and also increases the incidence of STR in STEMI population on fibrinolysis. Further studies are required to evaluate the potential of RIC in reducing major clinical outcomes.
Malaysian Journal of Medicine and Health Sciences (2026) 22(SUPP1): 7-12. doi:10.47836/mjmhs.22.s1.2

Keywords: Myocardial infarct, Ischemic conditioning, Fibrinolysis, STEMI, Reperfusion

Corresponding Author:
Wilbert Huang, MD
Email: wilberthuang67@gmail.com
Tel : +6287867017830

INTRODUCTION

Acute myocardial infarction (AMI) is among the leading causes of death and disability globally and in Indonesia. In 2018, Indonesia became the second country with the highest number of deaths and disabilities due to AMI with Jakarta is the highest prevalence (1.9%) and the burden of AMI in Indonesia is steadily increasing.(1) AMI occurs in the setting of acute coronary syndrome in the form of ST segment elevation (STEMI) or non- ST segment elevation (NSTEMI) where the former one requires urgent reperfusion therapy. One of the treatments of choice for AMI is to initiate immediate revascularization with percutaneous coronary intervention (PCI). While PCI is the optimal reperfusion strategy, fibrinolytic therapy remains a viable option when PCI is limited and it has been the most commonly practiced reperfusion therapy in Indonesia. PCI and fibrinolytic therapy reduce the impact of acute myocardial infarction through reperfusion mechanisms.(2,3) Interestingly, reperfusion also has been considered as double-edged sword that can further injure ischemic myocardium through 'reperfusion injury'. Previous study reported reperfusion causes four types of injuries, myocardial stunning, no-reflux injury, reperfusion arrhythmia, and lethal reperfusion injury.(4) The first two forms can be reversed while the others cannot. Reperfusion injury can be treated with remote ischemic pre and post-conditioning (RIC) as the introduction of short ischemic cycles upon initiation of reperfusion in remote ischemic pre and post-conditioning has emerged as a promising and applicable approach clinical to reduce infarct size in acute myocardial infarct.(5) Among 64 experiments in a preclinical setting where 39 of them examined remote ischemic post-conditioning (61%) and sixteen investigated remote ischemic pre-conditioning (25%), RIC reduced infarct volume by 38.36% (CI 42.09 to 34.62%).(6) In addition to it, potential benefits of RIC on STEMI patients undergoing PCI has also been

demonstrated in several studies.(7–9) Meanwhile, data that supporting for significant effect of RIC in clinical setting especially in the setting of AMI in fibrinolytic therapy is still limited.

MATERIALS AND METHODS

Background and Aims

RIC during fibrinolytic reperfusion therapy could be an alternative solution for developing countries, such as Indonesia RIC where PCI treatment is still limited as it can reduce myocardial infarct size hence will reduce morbidity and mortality. In addition to it, RIC is easily applicable, inexpensive, and noninvasive. Additionally, no study/ meta-analysis has studied the role of RIC in STEMI patients undergoing fibrinolysis. Hence, this study aims to evaluate the effect of RIC in reducing myocardial injury in STEMI patients undergoing fibrinolytic therapy.

Design

Our systematic review is a summary of literature search conducted with a clear and systematic methodology that is critically evaluated, synthesized, minimized bias and errors. The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA consists of a 27-item checklist and a four-phase flow diagram designed to assist writers in improving systematic review and meta-analysis reporting.

Search Methods

A systematic search was performed on PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) up to August 2023 with no date restriction. Hand searching from grey literature and literature from other language database (Chinese) has also been done to acquire more studies. The search strategy was done through extraction from terms and keywords found mainly from subject headings (MeSH) and free-text terms, with the use of various endings and spellings, including, but not limited to the following keywords terms: “fibrinolytic”, “remote ischemic conditioning”, “STEMI”, and “acute myocardial infarction”. Complete search strategies are presented in supplementary file.

With the basis of the therapeutic research question in this review, we selected only RCT studies comparing patients with and without RIC in the adult population above 18 years undergoing fibrinolytic reperfusion therapy for STEMI. Studies are excluded when they are observational or animal studies, non-randomized clinical trials, review and meta-analysis studies, and conditioning intervention other than RIC. Two investigators (WH and AN) independently evaluated the pre-selected studies which comply with the inclusion criteria. Any disagreements were resolved through discussion with the other author.

Data from a total of 4 RCT studies were independently retrieved and recorded by two reviewers (WH and AN). A third reviewer (LAL) evaluated all the collected data for any inconsistency and all authors came into consensus to discuss any existing inconsistency. From all of the selected studies, the data that were extracted include: authors, year of publication, location of study, sample size (including number of intervention and control sample), important sample characteristic, average age of intervention, timing of conditioning (pre-per-post), location of conditioning, protocol of RCI, and all the available primary and secondary outcome indicator available from the studies.

Search Outcome and Audit Trials

Outcome measures being analyzed in this study include differences in peak troponin I/ T and CKMB, between intervention and control groups. Besides that, other outcomes being considered is ST resolution (at least 50% change) after fibrinolysis. Specific measurement scale is being used in each study and will be described further in this study. We used Review Manager (RevMan) version 5.4 to conduct the statistical analysis. Continuous data is being pooled by a random effects model when studies report the mean value of the outcomes and is expressed as standardized mean difference between intervention and control groups. Dichotomous outcomes (reported by incidence of events) are also pooled by random effects model and are expressed as odds ratio. Confidence interval of 95% is used and statistical significance is determined when p value is below 0.05. Random-effect model is being used in this study in consideration for potential heterogeneities between included studies. Heterogeneity is being assessed by I2 with an interpretation of I2 < 40% as not important heterogeneity, 30 – 60% as moderate heterogeneity, 50 – 90% as substantial heterogeneity, and 75 – 100% as considerable heterogeneity. Publication bias is being assessed by funnel plot.

Quality Appraisal

For any study selected for this review, it has undergone a series of risk of bias assessment using Revised Cochrane risk-of-bias tool for randomized trials protocol. The protocol included the following domains: randomization process (including allocation concealment), deviation from the intended interventions (including blinding of participants and carers), missing outcome data, measurement of the outcome, and selection of the reported result. The series of risk assessments was performed independently by two reviewers (AN and LAL) with disagreement resolved by consensus.

With respect to random sequence generation, 3 (75%) studies were judged to have unclear risk of bias, and low risk in 1 (25%) study . Allocation concealment was adequate in 1 (25%) study and unclear in 3 (75%) studies. Blinding of patients and personnel had low risk of bias in 3 (75%) studies, but in the trial by Zhang V et al, it was unclear if the patients in the intervention group

were blinded. Blinding of outcome assessment was judged to have low risk in all studies (100%). Outcome data of all patients enrolled in the studies were reported for analysis. Selective reporting of outcomes was low in 3 (75%) studies and had unclear risk in 1 (25%) study.

Data Abstraction

Initial searching from two databases (PubMed and CENTRAL) resulted in a total of 360 identified studies where 27 duplicates are removed and after screening for title, abstract, and full text articles. Additionally, hand searching from Chinese database is also conducted. Eventually, 4 studies (10-13) enrolling a total of 849 patients on fibrinolysis for STEMI are retrieved and included in this study. (Fig. 1)

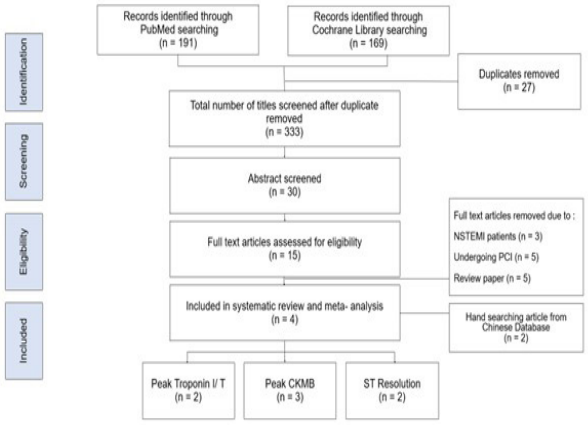

Fig 1: PRISMA study selection flow diagram

Synthesis

Summary of each selected article is presented in Table I. All 4 studies included patients with remote ischemic preconditioning protocol although one study(11) claims that to be a post conditioning study however conditioning protocol is conducted in a precondition manner based on our definition– protocol conducted before secondary insult of ischemia derived from fibrinolysis. Three studies (10–12) conducted conditioning in arms while the other in the leg(13,14) and protocols of conditioning varies from study to study. Two studies (10,13) reported peak enzyme markers of troponin I/T however is measured and reported in a different method (24h AUC and peak level), 3 studies (10,11,13) reported peak enzymatic CKMB level with one study (10) reporting in 24h AUC result, and 2 studies reported ST resolution events.

Table I: Characteristics of included studies

Journal Data							Intervention			Out-comes	Risk of Bias Assessment						
Author	*Year*	*De-sign*	*Lo-ca-tion*	*Sam-ple Size*	*Inter-ven-tion*	*Con-trol*	*Time of Condi-tioning*	*Lo-ca-tion*	*Protocol*		Random se-quence genera-tion	Allo-cation con-ceal-ment	Blinding of partici-pants and personnel	Blinding of outcome assess-ment	Incom-plete out-come data	Selec-tive re-port-ing	Other bias
Yellon DM, et al [10]	2015	RCT	UK	519	261	258	Pre-cond-tioning and peri-condi-tioning	Arm	4 cycles x 5 min ischemia and 5 min reperfusion with pres-sure cuff at 200 mmHg	24h AUC Tropo-nin T 24h AUC CKMB	Unclear	Unclear	Low	Low	Low	Low	Un-clear
Ghaf-fari S, et al [11]	2017	RCT	Iran	78	41	37	Post-condi-tioning	Arm	3 cycles x 5 min isch-emia and 5 minutes reperfusion with pres-sure cuff at >50 mmHg from SBP	Peak CKMB 24h ST resolu-tion	Low	Low	Low	Low	Low	Low	Un-clear
Zhang W, et al [12]	2009	RCT	Chi-na	180	90	90	Peri-condi-tioning	Arm	3 cycles x 5 min isch-emia and 5 minutes reperfusion	ST resolu-tion	Unclear	Unclear	Unclear	Low	Low	Un-clear	Un-clear
Shu C, et al [13]	2016	RCT	Chi-na	72	36	36	Precon-dition-ing	Leg	3 cycles x 5 min isch-emia and 5 minutes reperfusion with pres-sure cuff at > 20 mmHg from SBP	Peak tropo-nin I Peak CKMB	Unclear	Unclear	Low	Low	Low	Low	Low

RESULTS

Infarct size as estimated by troponin I and troponin T

Two studies comparing the effects of peak troponin I/T level are not able to be pooled due to different measuring scale. Nevertheless, results from the 2 studies pointed similar findings where remote ischemic conditioning is associated with a lower troponin level when compared to no intervention. Yellon et al. found that 24h AUC of troponin T after intervention resulted in a significantly lower troponin level (90.0 + 67.6 ng.h/ml) when compared to no intervention (105.9 +- 69.5 ng.h/ml) with a p value of 0.026. While study by Shu et al also shows similar result with a significantly lower troponin I level in intervention group (85.3 +- 25.97 ng/ml) when compared to no intervention (167.5 +- 63.8 ng/ml).

Infarct size as estimated by CK-MB

Three studies comparing peak CK-MB enzyme has shown variabel results where 2 studies reported significantly lower peak CK-MB level while the other study reported a higher release of CK-MB in the intervention group. Study by Ghaffari et al. showed contradicting result regarding peak CK-MB level where intervention group resulted in a higher release of CK-MB compared to control group (233 +- 212 vs 153 +- 144 ng/ml) although this result is not statistically significant (p = 0.059). However, in this study, intervention group resulted in a greater odds of ST resolution compared to the control group. While study by Yellon et al. found a significantly lower 24h AUC CK-MB level (1928 vs 2381 ng.h/ml) and study by Zhang et al. also shows a significantly lower peak CK-MB level in intervention group (160.36 vs 234.35 ng/ml).

Myocardial reperfusion as estimated by ST- segment resolution

Results from 2 studies reporting ST-segment resolution (STR) are pooled in a meta- analysis which resulted in a significant higher odds of ST resolution in intervention group (OR 1.92, CI : 1.11 – 3.33, p = 0.02) with a non-important heterogeneity level. (Fig. 2)

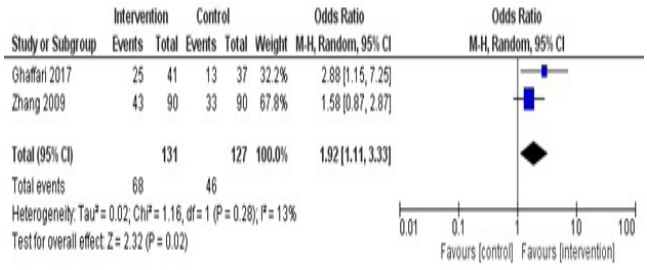

Fig 2: Difference in ST resolution of control vs RIC intervention group.

DISCUSSION

RIC is an easily feasible technique whose cardioprotective effect has been demonstrated by a number of studies as described previously. Our meta-analysis of 4 RCTs involving STEMI patients treated with fibrinolysis revealed that RIC minimizes myocardial reperfusion injury as indicated by ST-segment resolution. From analysis of the RCTs, benefits of RIC in reducing peak CKMB levels are inconclusive due to limited number of studies. However, several studies significantly show that RIC could reduce troponin levels which is also a marker of myocardial injury.

Patients with acute myocardial infarction with STR occurrence after reperfusion therapy appeared to have a better prognosis compared to patients without STR. In the last few decades, STR has been used to stratify risk in patient with STEMI. Research by Schroder et al showed that ST resolution could predict outcomes after fibrinolysis therapy in terms of risk of death and risk of heart failure. (15) ST resolution represents tissue-level reperfusion and it indicates restoration of myocardial perfusion which is described by resolution of either 50% or 70% in the ST segment seen in the electrocardiogram. Several studies used ST resolution cutoff of 50% at 90 minutes as one of the criteria for failure of epicardial reperfusion. Its use increases the accuracy of noninvasive markers for determining candidates for rescue PCI. In the other hand, complete resolution or ≥70% ST resolution 90 minutes after fibrinolysis indicates complete reperfusion at the epicardial and microvascular levels.(14) The sensitivity and specificity of STR to predict myocardial injury is considerably high which are 96% and 88%, respectively. (17) However, reperfusion following therapy has been associated with coronary microvascular dysfunction (CMD) which results in ischemia of the myocardium and endocardium. In CMD, clearance of extracellular potassium ions will be disrupted, thereby prolonging repolarization and giving rise to incidence of delayed STR.(18) One therapeutic intervention to overcome this issue may be the introduction of RIC to reverse this reperfusion injury. This meta-analysis showed that the STR rate of patients with intervention is higher than that of patients with RIC intervention. This is in accordance with another meta-analysis of acute coronary syndrome patients who received RIC which also showed an increase in STR rate in the intervention group of patients who underwent PCI where the effect of RIC on STR >50% favored RIC group than the control group with no evidence of heterogeneity.(17)

Other important biomarkers, CKMB and troponin, were

also commonly used to indicate myocardial injury. In general, a rapid decline in cardiac biomarkers after reperfusion indicates successful reperfusion. CKMB is found mainly in the cytosol and mitochondria of myocardium where it helps catalyze the formation of creatinine phosphatase and ADP from creatine and ATP. Approximately 20% of CK in the myocardium is in the form of MB, giving CKMB the sensitivity and specificity for diagnosing acute myocardial infarction. CKMB will rise within 4-6 hours after cardiac necrosis and remain for 24-48 h. The relationship between CKMB levels and infarct size has been widely studied and is significantly correlated.(19,20) Assessment of CK-MB peak and total CK-MB AUC are approaches to determine infarct size. Hence, it is also valuable in evaluating reperfusion therapy. In our study, we found no significant differences in peak CK-MB between the RIC and control groups. However, this result can be explained by a lack of statistical power due to the small number of studies included in the analysis.

Currently, troponin is the most important cardiac protein used in the diagnosis of AMI. It is synthesized in myocytes and is one of the main components of heart muscle. Furthermore, it works by regulating the interaction between actin and myosin. TnI and TnT are known as specific cardiac troponins. Troponins are released from myocyte and can be detected in the bloodstream after 2-4 hours from the onset of acute myocardial damage and reach its peak level after 24 hours. Its level will remain high for 2-3 weeks.(19,20) Beside as diagnostic marker, serial evaluation of TnT is also useful for early assessment of reperfusion therapy. In the other hand, reperfusion injury can also result in the release of troponin from cardiomyocyte. The mechanism behind this is thought to be associated with microembolization of plaque and side-branch occlusion. In general, patients with good reperfusion would show a lesser AUC for cardiac biomarkers compared to patients with failed reperfusion. In this meta-analysis, all studies reporting troponin results showed lower troponin levels in the RIC group compared to the differences found were statistically significant. Many previous exploratory studies and meta-analyses have reported similar results regarding RIC role in significant reductions of cardiac biomarker in various cardiovascular intervention including PCI and CABG.(21—23)

RIC increases the ischemic tolerance of a tissue through a short repetitive occlusion effect. The mechanism for the formation of the cardioprotective effect of RIC is believed to be mainly through the activation of ATP-sensitive potassium channels which will prevent the opening of the mitochondrial permeability transition pore (mPTP). Furthermore, it will modulate the release of various inflammatory mediators in ischemia-reperfusion injury. Through this mechanism, RIC offers a cardioprotective effect to increase the ability of myocardium to withstand ischemic effects of reperfusion.(24) The mechanisms underlying this cardioprotective effect of RIC have been well studied in animal models.

CONCLUSION

In conclusion, RIC intervention resulted in a lower peak enzymatic troponin and CKMB level and also increases the incidence of STR in STEMI population on fibrinolysis. Hence, RIC can be an important intervention to reduce reperfusion injury in patients undergoing fibrinolytic therapy. Several limitations in this meta-analysis are the scarce number of studies addressing this topic hence the result has not been able to be applied in daily clinical practice. Besides that, the small number of subjects also reduced the statistical power of this study. The small effect size from the meta-analysis also limit the representation of our result hence, the result of this study should be interpretated as a stepping stone for conducting further studies. Currently there are 2 studies, namely the ERIC-LYSIS and RIC-AFRICA trials which will examine the same topic in this paper and it is in hope that the 2 future studies will describe a better evidence regarding the use of RIC in fibrinolytic therapy. Future studies studying the long-term outcome of RIC on STEMI patients receiving fibrinolytic therapy are also needed to generate a better evidence based application in daily clinical practice.

ACKNOWLEDGEMENT

We acknowledge the committee of ACSA 2023 in helping the process of publication.

REFERENCES

1. Hussain MA, Mamun A Al, Peters SAE, Woodward M, Huxley RR. The burden of cardiovascular disease attributable to major modifiable risk factors in Indonesia. J Epidemiol. 2016;26(10):515–21. DOI: 10.2188/jea.JE20150178
2. Hausenloy DJ, Ntsekhe M, Yellon DM. A future for remote ischaemic conditioning in high-risk patients. Basic Res Cardiol. 2020;115(3):1–4. DOI : 10.1007/s00395-020-0794-2
3. Task A, Members F, Byrne RA, Ireland C, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;00:1–107. DOI : 10.1093/eurheartj/ehad191
4. He J, Liu D, Zhao L, Zhou D, Rong J, Zhang L, et al. Myocardial ischemia/reperfusion injury: Mechanisms of injury and implications for management (Review). Exp Ther Med. 2022 Jun;23(6):430. DOI : 10.3892/etm.2022.11357
5. Hausenloy DJ, Kharbanda RK, Мшller UK, Ramlall M, Aarше J, Butler R, et al. Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. Lancet.

2019 Oct;394(10207):1415–24. DOI : 10.1016/S0140-6736(19)32039-2
6. Torres-Querol C, Quintana-Luque M, Arque G, Purroy F. Preclinical evidence of remote ischemic conditioning in ischemic stroke, a metanalysis update. Sci Rep. 2021;11(1):23706. DOI : 10.1038/s41598-021-03003-6
7. Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. Basic Res Cardiol. 2015 Mar;110(2):11. DOI : 10.1007/s00395-015-0467-8
8. Sandven I, Eritsland J, Abdelnoor M. Remote Ischemic Conditioning in Patients with Acute Coronary Syndromes: A Systematic Review with Meta-Analysis and Trial Sequential Analysis. Clin Epidemiol. 2020;12:595–605. DOI : 10.2147/CLEP.S249785
9. Lou B, Cui Y, Gao H, Chen M. Meta-analysis of the effects of ischemic postconditioning on structural pathology in ST-segment elevation acute myocardial infarction. Oncotarget. 2018 Jan;9(8):8089–99. DOI : 10.18632/oncotarget.23450
10. Yellon DM, Ackbarkhan AK, Balgobin V, Bulluck H, Deelchand A, Dhuny MR, et al. Remote ischemic conditioning reduces myocardial infarct size in STEMI patients treated by thrombolysis. J Am Coll Cardiol. 2015;65(25):2764–5. DOI : 10.1016/j.jacc.2015.02.082
11. Ghaffari S, Pourafkari L, Manzouri S, Nader ND. Wirksamkeit der indirekten ischɅmischen Postkonditionierung wɅhrend Thrombolyse bei STEMI. Herz. 2018;43(2):161–8. DOI : 10.1007/s00059-017-4550-9
12. Shu Chengfu, Yan Xiaohong, Tan Zhiling, Shi Yufang, Yu Chuankun FW. Efficacy of remote ischemic postconditioning combined with Edaravone for patients with myocardial ischemia-reperfusion after acute myocardial infarction. Journal of Chongqing Medical University. 2016;41(no.9):937–40. DOI : 10.3389/fneur.2021.716316
13. Zhang W, Hou B. The protective effects of non-wound legs ischemic postconditioning on patients with ischemia/reperfusion myocardial injury. China Medical Herald. 2009; 6: 13-5. DOI : 10.2174/1877381801002010138
14. Schrцder R. Prognostic impact of early ST-segment resolution in acute ST-elevation myocardial infarction. Circulation. 2004;110(21):506–10. DOI : 10.1161/01.CIR.0000147778.05979.E6
15. De Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. J Am Coll Cardiol. 2001;38(5):1283–94. DOI : 10.1016/s0735-1097(01)01550-9
16. Dong Q, Wen X, Chang G, Xia R, Wang S, Yang Y, et al. ST-segment resolution as a marker for severe myocardial fibrosis in ST-segment elevation myocardial infarction. BMC Cardiovasc Disord. 2021 Sep;21(1):455. DOI : 10.1186/s12872-021-02269-y
17. Lemkes JS, Janssens GN, Van Royen N. ST-resolution and spontaneous reperfusion in patients with transient ST-segment elevation myocardial infarction. Eur Heart J. 2019;40(29):2465. DOI : 10.1093/eurheartj/ehz333
18. Elbadawi A, Ha LD, Abuzaid AS, Crimi G, Azzouz MS. Meta-Analysis of Randomized Trials on Remote Ischemic Conditioning During Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction. American Journal of Cardiology. 2017;119(6):832–8. DOI : 10.1016/j.amjcard.2016.11.036
19. Aydin S, Ugur K, Aydin S, Sahin İ, Yardim M. Biomarkers in acute myocardial infarction: Current perspectives. Vasc Health Risk Manag. 2019;15:1–10. DOI : 10.2147/VHRM.S166157
20. Hallйn J. Troponin for the estimation of infarct size: What have we learned? Cardiology. 2012;121(3):204–12. DOI : 10.1159/000337113
21. Le Page S, Bejan-Angoulvant T, Angoulvant D, Prunier F. Remote ischemic conditioning and cardioprotection: a systematic review and meta-analysis of randomized clinical trials. Basic Res Cardiol. 2015;110(2). DOI : 10.1007/s00395-015-0467-8
22. Yetgin T, Manintveld OC, Boersma E, Kappetein AP, van Geuns RJ, Zijlstra F, et al. Remote Ischemic Conditioning in Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting. Circ J. 2012;76(10):2392–404. DOI : 10.1253/circj.cj-12-0518
23. Healy DA, Carroll PJ, Clarke Moloney M, Tang TY, Grace PA, Kiernan TJ, et al. Systematic review and meta-analysis of remote ischaemic preconditioning in percutaneous coronary intervention. IJC Metab Endocr. 2013;1:13–9. DOI : 10.1016/j.ijcme.2013.10.002
24. Ge ZD, Ionova IA, Vladic N, Pravdic D, Hirata N, Vásquez-Vivar J, et al. Cardiac-specific overexpression of GTP cyclohydrolase 1 restores ischaemic preconditioning during hyperglycaemia. Cardiovasc Res. 2011;91(2):340–9. DOI : 10.1093/cvr/cvr079