Original Article

Effects of Volatile Anesthetics on Myocardial Ischemia/Reperfusion: a Meta-Analysis

Neda Aram¹, Ali Reza Abadi², Zahra Nouri¹, Ali Dabbagh¹*

Abstract

Background: Ischemia-reperfusion injury is one of the most important cellular mechanisms involved in myocardial injury; there is a possible protective role for volatile agents in myocardial cells against ischemia-reperfusion injury through inhibition of Ca²⁺ overload; in this review, the effects of volatile agents in myocardial ischemia-reperfusion were assessed using a meta-analysis methodology.

Materials and Methods: From 2007 to 2012, using the following keywords, ischemia reperfusion, volatile agent, volatile anesthetic, preconditioning, myocardial, protection, Sevoflurane, Isoflurane, and Desflurane. To select more related studies, the search was made narrower using "ischemia reperfusion" and "volatile agent" to yield in 38 articles which could be entered into study calculations, directly or indirectly, with one of the following indicators: odds ratio, standardized mean reference, relative risk and effect size.

Results: After final screening, 20 articles remaining as related to "the effects of volatile agents on myocardial ischemia/reperfusion". The study demonstrated significant decrease in myocardial ischemic region related to "exposure to volatile agents" (p<0.01); also, there was not statistically significant difference between the coverage areas of confidence intervals of 3 different drug doses: 1 MAC; 1.5 MAC and 2 MAC (p>0.05); at the same time, there was no statistically significant difference regarding the protective effects of volatile anesthetic gases on ischemic outcome (p>0.05).

Conclusion: This study demonstrated that all volatile anesthetics could lead to attenuation of myocardial infarct size; though there is no difference between different doses of volatile agents regarding their protective effects and the protective effects of volatile anesthetics are not different regarding their the main genes involved in cardio protection.

Keywords: volatile, ischemia reperfusion, ischemia reperfusion

Introduction

Anesthetic drugs have multiple effects at the molecular and sub cellular levels; volatile agents being one of the most commonly used anesthetics for more than 150 years; having their important roles in the creation of 3 different aspects of anesthesia: i.e. hypnosis, amnesia and also, some degrees of muscle relaxation (1-3).

Ischemia-reperfusion injury is one of the most important cellular mechanisms involved in myocardial injury; characterized by cellular calcium overload leading to increased contracture of the myocardium (2, 4-7). There are many studies which demonstrate the protective role of volatile agents on myocardial cells against ischemia-reperfusion injury through inhibition of Ca2+ overload (5, 6, 8-10). However, these results are not always in concordance, especially when considering clinical reports, when reviewing the results of other organs or different volatile agents (3, 7, 11-15). This study was conducted to review the effects of volatile agents on myocardial ischemia-reperfusion using meta-analysis methods.

Methods

This study was conducted using meta-analysis method, using the "Strengthening the Reporting of Observational Studies in Epidemiology" (16-18). Those clinical trials investigating the effects of volatile agent on myocardial ischemia reperfusion were included in the study. The search methods: the following data banks and search engines were used: MEDLINE (mainly though pubmed.com), Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Library. The following keywords were used: ischemia reperfusion, volatile agent, volatile anesthetic, preconditioning, myocardial, protection, sevoflurane, Isoflurane, and Desflurane.

Based on the selection criteria and the keywords, 43021 manuscripts were found in this time period with "ischemia reperfusion" keywords; then, adding "volatile agent" to the previous keywords resulted in 85 manuscripts during the study period from 2007 to 2012; their texts were in English. These 85 articles were regarded as the sample size.

Among the above 85 articles, those which had the capability to calculate, directly or indirectly, one of the following indicators remained in the study: Odds ratio, Standardized mean reference, Relative risk, Effect size.

So, after considering the above indicators, only 38 articles matched the study criteria and so, remained for further analysis.

Data collection and analysis

To extract data, we used data collection forms based on table of variables; so, throughout the reviewing process, articles were collected and their data were imported to an Excel sheet. Data pooling and analysis was done using Forest analysis method (19-23).

Heterogeneity of studies was calculated using Tau-square calculation and if it was statistically significant, random effect (DerSimonian and Laird) model was used for data pooling; data were considered homogenous if I square result was less than 50%; otherwise, it was considered as heterogeneity; per needed, subgroup analysis was done using new recording. The results were demonstrated using Forest plot (21, 24-29), Egger's regression asymmetry test with funnel plot was used for detection and prevention of publication bias (30-32). Data analysis was done using Stata software, version 11.

Results

Using the study keywords, a total of 192 studies were enrolled; among them, 85 were related to the period of 2007 to 2012. From the above 85 studies, 38 ones were homogenous studies regarding volatile agents; which entered further analysis. Classifying them to “myocardial related” and “non myocardial related” studies, ended in 20 articles remaining as related to "the effects of volatile agents on myocardial ischemia/reperfusion".

After random effect analysis of the drug effects, the study demonstrated significant decrease in myocardial ischemic region related to "exposure to volatile agents" (p<0.01); the results of the "exposure" and "control" groups are demonstrated in Figures 1 and 2, respectively. Also, their related Forest plots are demonstrated in Figures 3 and 4, respectively.

On the other hand, the drug doses had no significant effect; in other words, there was not a
Summary of studies demonstrating ischemia results in "exposure group".

<table>
<thead>
<tr>
<th>Study</th>
<th>ES</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
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<td>43.00</td>
<td>12.315</td>
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<td>33</td>
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<tr>
<td>D+L pooled ES</td>
<td>30.090</td>
<td>21.051</td>
<td>39.129</td>
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Test of $ES=0$ : $z=6.52$ $p=0.000$

Heterogeneity chi-squared = 37.75 (d.f. = 19) $p=0.006$

I-squared (variation in $ES$ attributable to heterogeneity) = 49.7%

Estimate of between-study variance Tau-squared = 203.5532

Fig. 1. Summary of studies demonstrating ischemia results in "exposure group".

Fig. 2. Summary of studies demonstrating ischemia results in "control group".

- The forest plot displays statistically significant difference between the coverage areas of confidence intervals of 3 different drug doses: 1 MAC; 1.5 MAC and 2 MAC (p value > 0.05); the genes included group 1 (PI3 kinase, Akt, and PKC); group 2 (anti-apoptosis genes), and group 3 (caveolin 3, ICAM 1 and NF). The related results and its Forest plot are demonstrated in Figures 7 and 8, respectively.

- Meanwhile, based on the gene group used for assessment of the effects, there was no statistically significant difference regarding the protective effects of volatile anesthetic gases on ischemic outcome (p value > 0.05); the genes included group 1 (PI3 kinase, Akt, and PKC); group 2 (anti-apoptosis genes), and group 3 (caveolin 3, ICAM 1 and NF). The related results and its Forest plot are demonstrated in Figures 7 and 8, respectively.
Fig. 3. Forest plot of the exposure group.

Also, the results of Egger’s regression asymmetry test with funnel plot were not statistically significant to detection and prevention of publication bias (Table 1 and Figure 9).

**Discussion**

The results of this study demonstrated that volatile agents could decrease the size of myocardial infarct; while the drug dose and the related genes are not as much important in the final outcome.

Myocardial ischemia and infarction are not only among the leading causes of perioperative mortality, but are also among the main causes of prolonged hospitalization and patient readmission to the hospital. A number of these patients undergo anesthesia; while their exposure to volatile agents is a major point of concern.

This study demonstrated that myocardial
infarct size is decreased due to exposure to any of the volatile anesthetics. Reiss et al. demonstrated the effect of Sevoflurane at clinical effects (33). However, the results of this study demonstrated that exposure to volatile agents during anesthesia, regardless of agent or dose, could lead to attenuation of myocardial ischemia-reperfusion and decreasing the myocardial infarct size.

Ischemia reperfusion injury is prevented by volatile agents due to the anesthetic preconditioning effects of these agents involving the Ca2+ homeostasis mechanisms inside myocardial mitochondria and myocardial sarcoplasmic reticulum (34). This cardioprotective effect is mediated through a number of different cellular enzymatic processes including mitogen-activated protein kinases which could be blocked by hyperglycemia (35, 36). At the same time, the protective effects of volatile agents are mediated through increase level of "nitric oxide", nuclear factor-kappa B (NF-kappaB), "protein kinase B phosphorylation" and "glycogen synthase kinase 3 beta phosphorylation", regulation of the "expression of aromatase", activation of "protein kinase C: PKC"—which leads to a number of protective mechanisms including prevention of apoptotic pathways- and also, decrease in the level of "glycogen synthase kinase 3 beta" (36-43). Some of the studies have stressed on PKC-alpha and PKC-epsilon (and not PKC-delta) in creating the protective effects of Sevoflurane (40, 42, 44) and Isoflurane (36, 39).

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**Fig. 5.** Summary of studies regarding the effect of drug dose on ischemia results.
NOTE: Weights are from random effects analysis.

Overall (I-squared = 49.7%, p = 0.006)

30.09 (21.05, 39.13) 100.00

Fig. 6. Forest plot for the effect of drug dose on ischemia results.

Fig. 7. Summary of studies regarding the effect of drug dose on ischemia results.
Fig. 8. Forest plot for the effect of drug dose on ischemia results.

Fig. 9. Funnel plot for publication bias of selected studies.

**Conclusion**

Finally, the results of this meta-analysis demonstrated that the results are as the below:

1. All volatile anesthetics could lead to attenuation of myocardial infarct size.
2. There is no difference between different doses of volatile agents regarding their protective effects.
3. The protective effects of volatile anesthetics are not different regarding their the main genes involved in cardioprotection: group 1 (PI3 kinase, Akt, and PKC); group 2 (anti-apoptosis genes) and group 3 (caveolin 3, ICAM 1 and NF); all of them make ATP-

**Table 1:** Results of Egger’s test for assessment of publication bias.

<table>
<thead>
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<th>Measurement</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td>Slope</td>
<td>1.99</td>
<td>2.99</td>
<td>0.43</td>
</tr>
<tr>
<td>Bias</td>
<td>-3.87</td>
<td>7.98</td>
<td>0.66</td>
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dependent potassium channels open.

**Acknowledgment**

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**Conflicts of Interest**

The authors declare that there are no conflicts of interest.

**References**

31. Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots