Author's response to reviews

Title: Repeated epinephrine doses during prolonged cardiopulmonary resuscitation have limited effects on myocardial blood flow. A randomized porcine study

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Author's response to reviews:

Reviewer # 1

Answer to Lars Wiklund November 18 2014, Thank you for your thoughtful review and remarks.

In the Reviewer report I just would like to comment that the set up with only 1 minute of untreated ventricular fibrillation (VF) is as Prof Wiklund mentions a short period. Nevertheless this is a common situation when a cardiac arrest occurs in cath-lab. Clinically we start CPR and if the situation has not been solved in a few minutes we switch to mechanical chest compressions, assess vital parameters and continue with the PCI. The aim of the study design is to reflect this specific setting/situation. Thus we find the VF time appropriate which is stated in the manuscript. I hope this is an acceptable explanation.

Reviewer question # 1: The animals were randomized as previously described (26, 27)”. Please describe this procedure also in this work.

Answer question # 1: We can see that the sentence can cause misunderstanding. The references in the manuscript refer to one animal study by Morten Pytte and Co-workers (ref#26) where they have used Epinephrine (EPI) 0.02mg/kg, and Giuseppe Ristagno and Co-workers used 0.03 mg/kg in their study (ref#27). Thus the references refer to the chosen dosages used in these studies. The part “were randomized to” in this sentence has been deleted for clarification.

Reviewer question # 2: The randomization results in groups called EPI 0.02 and 0.03 mg/kg/dose. In contrast to this, in the Tables the groups are presented as
“Adr 0.02 mg/kg” and “Adr 0.03 mg/kg”. The authors have to decide about a common nomenclature.

Answer question # 2: The manuscript, tables and figures has been changed to EPI.

Reviewer question # 3: The coronary perfusion pressure was presented as a maximum pressure during diastole, often it is the mean pressure during the same period.

Answer question # 3: We have calculated CPP as the difference of the intra aortic arterial end-diastolic blood pressure and right atrial end-diastolic blood pressure just as Otlewski proposed (ref#28). When CPP was depicted it was at the maximum CPP which was caused by the effect of administered Adrenaline (EPI). The CPP value was a median of values during 10 seconds of the short lasting peak.

Reviewer question # 4: In statistics: “The ANOVA-test was used to compare multiple median comparisons”. How do you compare comparisons? Also: Was the data collected normally distributed? You use parametric testing.

Answer question # 4: We are sorry for the mistake... The sentence should state: “... was used to compare multiple median values”. The manuscript has been changed accordingly. The values were not normally distributed. Hence we have made a correction and instead of using the ANOVA-test we have used Kruskal – Wallis test which is more appropriate when the data is not normal distributed. Manuscript has been clarified and p – values has been changed in table 3.

Reviewer question # 5: In Figs a * signifies “p<0.05”. Compared to what? Needs a definition.

Answer question # 5: It is the comparison between the control group and EPI-groups. This has been clarified in figure legends.

Minor essential revisions: The discussion is on the whole good but rambling. If it could be somewhat more structured it would be easier to read.

Answer Minor essential revisions: We have tried to address the rambling that the reviewer has concerns about and modified the discussion to some extent.

Reviewer # 2

Answer to Meng – Hua Cheng November 27 2014, Thank you for your thoughtful review and remarks.

Reviewer question # 1: The authors should tell us how the VF was induced using a 9 V direct current, such as stimulating electrical pulse wide, frequency and stimulation time. Is the VF persisted at 5, 8, 11 and 14 minutes after VF-induction and before each defibrillation performed.
Answers question # 1: The use of a simple commercial 9 V direct current battery is a common way to induce a ventricular fibrillation (VF) in Cardiac arrest animal studies.

Reviewer question # 2: How was the VF induced?

Answers question # 2: Ventricular fibrillation was induced with one cable connected to one pole on the battery and to that cable a needle was connected. This needle was inserted in the skin of the pig. The other pole was connected to another cable which was connected to a cardiac needle. This needle was then inserted just caudal of processus Xiphoideus and moved to the pericardial/epicardial structure where VF commenced instantaneously. Thus we have not used a pacemaker cable which also is a common method to induce a VF.

Some correction has been made to the method section, which we hope will clarify this.

Reviewer question # 3: How long was the stimulation time?

Answers question # 3: The stimulation time was between 5 – 10 seconds which has been added to the manuscript.

Reviewer question # 4: Did the ventricular VF persist at 5, 8, 11 and 14 minutes after VF-induction and before each defibrillation?

Answers question # 4: Yes the VF persisted during the whole period of 16 minutes. Defibrillation attempts were not performed when the rhythm was asystole or pulseless electrical activity. However all animals had VF when the first defibrillation was performed.