Author’s response to reviews

Title: Evaluation of Coronary Blood Flow during Cardiac Arrest with Circulation Maintained through Mechanical Chest Compressions in a Porcine Model

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Author’s response to reviews: see over
Dear Sir/Madam
We are resubmitting the original article entitled “Evaluation of Coronary Blood Flow Velocity during Cardiac Arrest with Circulation Maintained through Mechanical Chest Compressions in a Porcine Model”. (MS: 1563319414558372)
We wish to thank the editor for the excellent review performed of our submission which has clearly improved the manuscript. We have implemented most of the suggestions of the reviewers and these can be easily seen by highlighted text.
We have also made separate point-by-point responses to all of the reviewer’s questions below on the following pages and hope that both they and the editor are satisfied with our answers.

Sincerely,

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Responses to Reviewer 1

1) How was the average peak velocity obtained - an average of 3 or 5? - please comment i Methods.

Answer: The average peak velocity was calculated as mean over each 2 min period. How long periods for each 2 min has been added in the results and methods sections.

2) The conclusion that during cardiac arrest with ongoing mechanical chest compressions, coronary blood flow can be normalized is speculative. Comparing the model in rest (baseline) with mechanical chest compression is difficult. Please provide the data on heart rate at rest and during chest compressions (probably 100 compressions/bpm). Probably there is a significant difference in heart rate. This may alter both the flow frequency and velocity (as you measure). It will strengthen the study to increase the baseline heart rate to the same level as during chest compressions to have a "clean" comparison.

Answer: We agree that baseline heart rate at should be added and we have done so. During VF there is of course no real heart rate but compressions are delivered at 100 compressions/minute. This has been added to the article. Actually, the heart rate at baseline was 97 ± 16 beats per minute which is in the same range as the compression rate for LUCAS.

Regarding changing the heart rate to increase coronary flow velocity (average peak velocity) at baseline, this is an interesting option where we in other earlier experiments wanted to use a pacemaker lead to increase heart rate and thus increase coronary blood flow (we thought). However, we found that Average peak velocity (APV) stayed the same between 70 beats per minute and up to 130 bpm. The simple answer why affecting heart rate did not change APV was that coronary blood flow does not increase in this range because no additional work is performed by the heart (Cardiac output stays the same etc.). We have not tested for Isoprenaline, but we did not want to pollute the experiment by adding this drug. Luckily the baseline heart rate was so close to the delivered compression rate that no adjustment was needed.

3) Please correct the analysis for heart rate.

Answer: The baseline heart rate was so close to the delivered compression rate that no adjustment was needed.

4) Was the heart rate at a fixed rate during mechanical compressions? Provide table 1 with baseline heart rate and compression heart rate.

Answer: The chest compressions were delivered at a fixed rate of 100 bpm during VF. The baseline heart rate and compressions per minute have been added to table 1.

5) The conclusion "....may even generate a slight tendency towards reactive
hyperemia....." is also speculative. The difference in APV from baseline to the fx. 0-2 min APV and so on - might be the increasing heart rate and increased adrenaline levels and not a reactive hyperemic response.

**Answer:** We agree, we have made it more clear that this is speculative and have also added the possibility of increased adrenaline levels.

6) Furthermore it would strengthen the study to have a "control group" with manual chest compression and an comparison to the mechanical group by blinded analysis.

**Answer:** We agree that manual compressions would have been an interesting control group. However, manual compressions in general are very prone to bias depending on who is providing them which reduces repeatability. From a practical standpoint it is more difficult to maintain a stable position of the flow wire in the LAD during the course of manual compressions and constant changes of chest compressions providers. This is our experience from other experiments when we have had to resuscitate pigs with a flow wire in the LAD. Based on empirical patient cases in the cath lab on humans we have frequently noticed essentially normalized coronary blood flow (TIMI 3 flow). Therefore we wanted to actually measure (quantify) the coronary flow by APV in this single group of pigs that were induced with VF. It was from that perspective that we elected not to use a control group with manual compressions.

7) In the Methods section coronary flow velocity was measured and evaluated by "time periods which were visually free from noise and had typical Doppler-curve like shape" - please provide data on how many sec/minutes that was analyzed in each time frame (0-2, 2-4 and so on)? It might have a large impact on data (especially late in compression time) and as the authors mention in limitation section "During ongoing mechanical chest compressions when evaluating coronary flow with APV, the measured curves were prone to movement artifacts...."

**Answer:** Has been to the results section

8) Finally it would be preferable to have the "area under curve (time velocity integral)" for the flow profiles of coronary flow velocity because the peak value says nothing about the amount of blood and is a surrogate for coronary flow.

**Answer:** We agree that to measure the area under curve would have been an alternative but our console does not measure this entity unfortunately. Furthermore, even the area under the curve is not absolutely certain in terms of amount of blood that passes through the vessel. Ideally, measurements of the actual blood volume that passes through the LAD would have been preferred, but this would then entail an open chest experiment with Doppler/ultrasounds transducers around the LAD which would have been able to give us both the diameter and the velocity at the same time. This would of course make the experiment nearly impossible to succeed.

**Minor Essential Revisions:**
1) The title should include Velocity. "Evaluation of Coronary Blood flow Velocity...."

Answer: We agree and have changed the title

2) Abstract: Line 4: quantitatively instead of actually

Answer: We agree and have revised accordingly.

3) Abstract: the abbreviation APV is used several times in the abstract and manuscript for average peak velocity, Intracoronary blood flow and mean coronary flow - please decide and use consistent. The most correct term seems to be "average peak coronary flow velocity".

Answer: We agree and have revised

4) Background: second last line please provide sentence with "...the left descending artery during...." instead of "...coronary arteries...".

Answer: We agree and have revised

5) Methods, Experimental protocol: The sentence "Continuous measurements of ECG, body...." contains ECG 2 times.

Answer: Has been revised

6) Methods, Experimental protocol: Line 1: Please spell out LAD first time.

Answer: Has been revised

7) Methods, Measurements: AP and CVP has already been defined.

Answer: Has been revised

8) Methods, Measurements: Line 6: Coronary flow velocity, APV.... Is APV still a abbreviation for average peak velocity?

Answer: Yes, and we have revised to make this clear

Responses to Reviewer 2
1) Methods, ventilator settings and instrumentation, last paragraph.
Please explain the term “arbitrary units” for measuring coronary flow. The measurement of average peak velocity (APV) should be further described, is it the average of a number of peak velocities? Calculation of APV should be further described.
Answer: We agree and have added an explanation for arbitrary units and also further described APV.

2) Methods, experimental protocol.
I would appreciate more detailed information regarding the ventilator settings during the intervention.
- Was ventilation discontinued during the period of ventricular fibrillation?

Answer: Yes, immediately when VF was confirmed ventilation was stopped added in the text.

- During mechanical chest compressions?

Answer: During chest compressions the ventilation was one breath for each ten compressions. This has been added in the text.

- After restoring spontaneously circulation? Was 100 % oxygen administered?

Answer: Yes. This has been added in the text.

3) Methods, measurements, Figure 1.
The Doppler signal at baseline is fine, diastolic flow and no artefacts. During mechanical chest compressions the ECG signal is hard to see, does not look like ventricular fibrillation, more like movements artefacts from the mechanical compression device.

Answer: All pigs had VF during chest compressions, the ECG in Figure 1 is as the reviewer mentions, disturbed by chest compressions artifacts, but ECG was also registered on another monitor and from defi-pads confirming VF, thus the Doppler machine was not the primary ECG lead. We can include printouts of a clear VF on separate leads if necessary but we feel this would take up too much space.

4) My concern is the Doppler curve under mechanical chest compressions. How can the reader be convinced that the Doppler signals is not due to motion artefacts from chest compressions and does in fact represent coronary flow in the LAD. Please comment on the very high initial peak velocity during chest compressions compared to baseline. Please comment on the phase of compression in which the flow appears. This is important for evaluating the use of your method, especially in regard of peak velocities as a marker for coronary flow.
Answer: We believe this to be clear with the new figure 1.

We avoided performing too many angiograms during chest compression since contrast injection would impact the APV measurements. We did however, check all animals at baseline and 2-3 times during VF with contrast injections as well if there was indications that flow was impacted as happened in the pig with wedged catheter. However when contrast injections were performed APV was impacted with a large risen in APV. During the VF phase without compressions, APV was very low as expected. Then almost immediately following initiation of chest compressions APV rises and exceeds levels at baseline. This is very similar to the reactive hyperemia seen following a short occlusion of a coronary artery. We have added figure 1 to illustrate our point.

5) Furthermore: Much emphasis is put on the correlation on TIMI flow and APV in these models. From the methods section it can be appreciated that a guiding catheter was in place (or even wedged) during the VF phase. Were no angiograms performed and if there were, did the authors find any correlation between the finding and the APV or CPP?

Answer: We avoided performing too many angiograms during chest compression since contrast injection would impact the measurements too much, however when done the TIMI flow was at a level of 3 (except with the wedged catheter), how this correlate to CPP and APV is impossible to judge since the APV is affected by the injection and the CPP is post study calculated. By itself, APV is correlated to CPP as shown in figure 4.

6) Results, table 1.
The unit for APV has changed from cm/s to ml/min, please explain this. Have you measured the diameter of the LAD for this calculation and how.

Answer: No, this is a mistake. Has been revised. We thank the reviewer for pointing this out.

7) Results, second paragraph.
Doppler flow curves in the coronary artery (LAD) at baseline and during mechanical chest compressions were obtained with some technical challenges. Doppler coronary flow could not be obtained during sinus rhythm after restoring circulation. This must be mentioned in the discussion. It appears to be contradictory to what would be expected that measurements were possible during mechanical compression and at baseline, but not at all during the 15 minutes of post-ROSC observation. This should be commented in detail.
The impact of hyperaemia in the ROSC phase did interfere with the Doppler curves, but hyperaemia in the fase with mechanical chest compressions did only have little influence. This discrepancy should be commented in the discussion and the impact of boluses of epinephrine during defibrillation should be discussed.

**Answer:** The recording of Doppler curves in the ROSC phase was not possible on the Doppler machine due to aliasing and tracking problems (of APV) with the machine during the very large reactive hyperemia seen. Continual manual adjustments had to be made because this doppler machine had difficulties to adjust to this large flow increase. Because measurements were so frequently out of range for the machine to measure we could not present the data but can say with certainty that there is a large amount of hyperemia, but we could not quantify it in measurements. Samples can be seen in Figure 1.

8) Results, Figure 2.
Information regarding the amount of data must be added in the figure legend. Is the data from one pig or a mean of all sampled data from 10 pigs. The figure seems quite “smooth”. It looks like all the 8 pigs had ROSC within the same minute after defibrillation, which I imagine would not be the case.

**Answer:** Figure 2 shows the mean of all sampled data from 10 pigs that has been time adjusted to the same time line, this has been added to the figure text.

9) Results.
Information about number of defibrillations is missing. Please mention how many times defibrillation was performed, dose of adrenaline administered during resuscitation. Mean time for restoring circulation would also be important.

**Answer:** Seven animals Regained ROSC following the first defibrillation, two pigs required 3 defibrillation attempts to regain ROSC, two animals never regained ROSC of which one was excluded due to misplacement of the device before start of chest compressions. This has been added to the result section.

10) Results, second last paragraph.
The correlation between CPP and APV during chest compressions is clear, but the authors should comment on the differences in the measurements at baseline, why are there no agreement between the two methods. As data after restoring circulation is missing too, it is hard to be convinced that the Doppler method is capable of measuring real coronary blood flow.
Answer: This is a very good point by the reviewer. Calculation of CPP during normal circulation is done by the difference between the right atrial diastolic pressure and the diastolic arterial pressure. The Doppler method has been verified in several models of which only a few are referenced in the background. We strongly believe that measurements of APV is a validated method for measuring real coronary blood flow, thus not a novel method. The initial measurements of APV and CPP at baseline are within the normal range for pigs. During VF without compressions both CPP and APV severely decrease. Then almost immediately following initiation of chest compressions both CPP and APV increase. APV increases to above baseline while CPP only increases to above 20 mmHg. Interestingly, APV and CPP correlate quite well during the VF phase although CPP is much lower than at baseline. Following successful ROSC, CPP once again approaches baseline values while APV, after an initial increase, gradually decreases to return to the baseline values. This is a finding we felt should be published. The APV value is primarily driven by hyperemia caused by a post ischemic state and probably a release of a number of endogenous substances such as ATP and catecholamine’s. CPP however only correlates with a theoretical calculation of the coronary perfusion pressure which does not take into account a dilatation or constriction of the capillary bed of the myocardium which is of course of great importance for the actual coronary flow when measuring APV. Measurements of the proximal diameter of coronary arteries during angiograms indicate that there is very little difference in diameter of the coronary vessels during the baseline, VF and ROSC phases. We could introduce a section on this if the reviewer would like us to but feel that this would significantly extend the size of the manuscript and probably need an additional figure. Therefore we have not gone into detail of this in the manuscript.

11) Conclusion.
Your conclusion “that mechanical chest compressions can, at minimum, reestablish coronary blood flow in non-diseased coronary arteries during cardiac arrest” could be modified. Only if the flow wire is indeed able to show flow during mechanical compression this would be case, but other than the CPP there is no evidence presented to support this.

Answer: Please see answer to question 8 above.

- Minor Essential Revisions
1) The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

Answer: Have been corrected.

- Discretionary Revisions
These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.

1) Results, table 2.
Does not add further information, can be omitted.
Answer: It has been omitted.
2) Results, last paragraph.
Could you revise this paragraph to clarify whenever the differences mentioned are between the two time periods or differences from normal values.

Answer: What have been compared has been clarified

3) Results, Table 3.
Please comment on the lactate level after 10 min, why is the mean lactate level lower in the venous sample? You may choose to omit the venous blood gases and instead present arterial gases after achieving ROSC if these data are available.

Answer: Venous blood gases have been omitted and the ROSC period has been added.

4) Discussion, third paragraph.
The following sentence needs to be clarified in regard of the relation between CPP and TIMI flow, which has not been documented in the data presented. "During ongoing mechanical chest compressions, coronary blood flow was actually equal or greater than baseline levels despite cardiac arrest, indicating that a mean CPP was well above 20 mmHg can result in TIMI III flow and that TIMI-flow judgment can be used when assessing the blood flow effects on mechanical chest compressions in the cath-lab."

Answer: Has been clarified