Accelerating Reperfusion with Low Frequency Vessel Deformation during Myocardial Infarction

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Abstract

Delay in restoration of vessel patency after coronary infarction is a major factor affecting the survival rate of heart attack patients and the amount of myocardial muscle death. To this end, we propose Arterial Deformation Accelerated Reperfusion (ADAR), a treatment method that can be initiated immediately after the onset of symptoms in the field by a minimally trained individual. It consists in applying mechanical deformation to a major artery to induce pressure waves in the bloodstream at frequencies well above the pulse rate. We discuss the proposed method, introduce an example architecture of a device implementing it and present results from in-vitro studies aiming at validation of the proposed approach.

1. Introduction

Acute myocardial infarction, or heart attack, is a consequence of a complete or prolonged obstruction of a coronary artery. Studies show that myocardial muscle necrosis occurs approximately between 15 to 30 minutes after the onset of symptoms \cite{1}. Therefore, the speed of intervention is the prime factor affecting the amount of myocardial muscle death and thus the patient survival rates. Adjunctive treatment methods that could be initiated prior to patient arrival to cathlab aiming at inducing clot dissolution or even its displacement further down the bloodstream could potentially offer beneficial effects to patients. We propose Arterial Deformation Accelerated Reperfusion (ADAR), an innovative reperfusion acceleration method that can be safely applied by minimally trained personnel in the field as a standalone treatment or in conjunction with injection of thrombolytic drugs. It consists in applying low frequency mechanical actuation (20 Hz to 50 Hz) to induce deformation of a major artery, e.g. the aorta. The vessel deformation creates pressure waves in the bloodstream that reach the coronary arteries and create a non-uniform force distribution on the clot surface inducing shear stresses and deforming it axially. Furthermore, a high degree of turbulence is initiated in the blood helping in drug delivery to the clot even in absence of flow. The external actuation can be applied using a simple mechanical massager device placed over a major artery.

Application of low frequency mechanical vibrations has been proposed as a safe and effective substitute to ultrasound that can be adjunctly used with fibrinolytic medications to accelerate reperfusion \cite{2, 3}. Diastolic Timed Vibrator, a device applying mechanical vibrations in synchronism with the heart cycle of the patient has been introduced and analyzed \cite{4, 5}. Although potentially offering beneficial effects, its mechanism is based on vibrating the heart, which in turn induces vibration of the coronary arteries. Such application requires synchronization with the heart cycle and invokes concerns about the impact of this technique on the contractile action of the weakened heart. In this work, instead of vibrating the entire heart, we propose to deliver the mechanical stimulus to the occlusion through pressure waves in the bloodstream. There are several known cases where external actuation is employed to improve heart function \cite{6, 7}. Nevertheless, to our knowledge, applying mechanical deformation to vessels at frequencies significantly higher than the pulse rate have not been investigated yet in view of accelerating reperfusion. Such method would be safer than vibrating the entire heart or applying high power ultrasound to the occlusion and would not require complicated equipment and thus could be suitable for application by a minimally trained individual in the field.

2. ADAR system architecture

Architecture of a device that could be used to apply the proposed ADAR method is presented in Fig. 1. It is composed of an application device, a control unit, a feedback system and a user interface. The application device can be either a therapeutic massager with adjustable displacement amplitude and frequency or even a compression cuff capable of high frequency deformations. A force sensor...
and an accelerometer are added to the application device to provide feedback measurement allowing adjustment of operational parameters. The control system interprets the signals acquired from the sensors installed on the application device, but more importantly uses a high frequency blood pressure monitor to provide positioning feedback. Finally, ECG signal is used for assessing the method efficiency based on the level of ST segment elevation.

Figure 1. System architecture used to perform Arterial Deformation Assisted Reperfusion (ADAR).

A feedback system is necessary to confirm that the deformation induced by the device creates sufficient pressure variations in the bloodstream. We propose to use a high frequency flow sensor, either ultrasound Doppler probe or a very sensitive force sensor placed over the carotid artery. Since the distance from the aortic arch to the carotid artery is approximately equal to the distance from the aortic arch to the coronary arteries, we hypothesize that the pressure variations detected at the carotid should closely correspond to the pressure variations at the occlusion site in the coronary arteries. This feedback system would not be used to perform measurements of the pressure wave amplitude, but rather to choose an optimal placement of the device to maximize the pressure variation amplitude. Therefore, it would be subject independent and no calibration would be necessary.

3. Materials and methods

The experiments described in this paper were performed at the University of British Columbia Farm, 6182 South Campus Road, Vancouver, BC, Canada, in accordance with ethics approval 2009s0630 and protocol 1028E-11.

3.1. In-vitro setup

The in-vitro tests were performed using a stenosed, heparinized flow system with aortic-like pressure variations subject to direct deformation of a large fluid carrying vessel. Schematic of the flow system used is presented in Fig. 2.

A rolling peristaltic pump (Manostat 72-300-000) induced flow of a buffer fluid in the system through a set of eight stenosis sites, a larger diameter tube section subject to deformation, a bypass with adjustable lumen and a constant temperature beaker (Vanlab, VWR Scientific Inc.). The diameters and materials of the tubing were chosen to resemble the dimensions and the mechanical properties of human arteries:

- the abdominal section of the aorta [8] for the actuated part made of a 120 mm long section of PVC tube with ID of 9.5 mm (8000-0120, Thermo Scientific).
- human coronary arteries [9] for the stenosed sections made of a 120 mm long elements of PVC tube with ID of 4.76 mm (TMT-187A-50, Tygon).

The buffer fluid was a solution of 2000 Units of heparin (H3393, Sigma-Aldrich, Saint Louis, MI) in 1000 ml of 0.9% Sodium Chloride IV injection USP solution (Baxter International, Deerfield, IL). The fluid was brought to 37°C prior to the experiment and kept at a constant temperature. The stenosis sites were constructed through insertion of a 15 mm piece of tubing with ID of 1.59 mm (TMT-062B-10) into the 4.76 mm diameter, 120 mm long tube section. The resulting structure presented a 90% luminal stenosis. Installation of particular stenosed elements was randomized between the actuated and the reference setups. A bypass was installed providing a path around the stenosis sites to resemble vessel obstruction in an actual organism where not all arteries are blocked at the same time and to enable regulation of pressure in the system. The total capacity of the system, excluding the fluid in the beaker was around 210 ml. The fluid pressure was measured on the upstream edge of the stenosis sites using an integrated pressure sensor (MPXM2053GS, Freescale Semiconductor, Austin, TX).

A reference system, identical to the actuated system except for the actuation mechanism and sharing the same fluid in the beaker was used in every experiment to provide a baseline result.

3.2. Clot preparation

Clots were created from fresh blood collected from the left jugular vein of a sheep (female, Ovis aries, Suffolk breed) elevated in a controlled environment at the UBC
Figure 2. The in-vitro setup used to validate the principle of operation of ADAR.

Farm. For each experiment, a 60 ml syringe was filled with blood and immediately distributed into sterile silicon tubing with internal diameter identical to the larger diameter of the stenosed vessel (4.76 mm). Blood samples were held at 37°C for 90 minutes and then inspected visually for retraction. The retracted clot was then cut into 15 mm pieces, weighted, and then the pieces were inserted into the 16 stenosed tube sections. Average mass of clots was 196 mg, \( \sigma = 51 \) mg. After insertion of clots into the system, the peristaltic pump was activated for 120 seconds to pressurize the system and verify occlusion stability. Occlusions that perfused within this time were clamped and labeled as immediate perfusions and disregarded.

3.3. Actuation

After the initial 120 seconds, the larger section of the actuated setup, located approximately 60 cm from the occlusion, was subject to deformation applied using a lever system connected to a DC motor rotating at 24 Hz and imposing a vertical movement of an aluminum beam deforming the larger diameter tube by up to 3 mm (10% luminal stenosis). A bi-axial MEMS accelerometer (AD22286, Analog Devices, Cambridge, MA) was used to measure the motion at the actuation site. Figure 3 presents the acceleration recorded at the actuation site and the pressure recorded at the occlusion site. During the experiment, each narrowing was immediately clamped after perfusion to maintain pressure in the system. The pump was stopped after 20 minutes of actuation and all the non-perfused clots were removed.

4. Experimental results

Throughout the experiments, 37 clots were actuated and 18 were used as reference. On top of that, 2 clots in the reference system and 2 clots in the actuated system perfused immediately.

Figure 3. Acceleration patterns recorded at the actuation site and the pressure variation recorded at the occlusion site.

Figure 4 presents the cumulative percentage of perfusion times during the in-vitro experiment. While there was no perfusions in the reference system after 20 minutes, over 95% of occluded narrowings perfused within 16 minutes of actuation resulting in TIMI 3 flow in the actuated system. Only one occlusion did not perfuse within 20 minutes in the actuated system.

5. Discussion

The in-vitro experiments demonstrated a potential for accelerating reperfusion of occluded vessels by remote vessel deformation. Not only the proposed method could improve the treatment efficacy, but also removes the need for the complicated synchronization of vibrations with the heart cycle as required in the previous heart vibration methods. Furthermore, the mechanical stimulus can be applied on any major vessel as opposed to the necessity of application directly in the delicate chest area.

As can be seen in Fig. 3, deformation of the fluid car-

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Figure 4. Distribution of reperfusion times during the in-vitro testing of ADAR.

rizing vessel induces significant pressure variations at the occlusion site. The pressure variations impose shear stress on the clot wall and thus induce mechanical deformation leading to its faster disintegration. In presence of thrombolytic drugs, the pressure variations would improve mixing of drugs in the bloodstream and facilitate drug delivery to the occlusion sites.

The concept of the device assumes that deformation of a large blood carrying vessel, e.g. the abdominal section of the aorta, would induce pressure waves that would travel through the bloodstream, reach the heart and thus the coronary arteries. If pressure variations used in this study can be induced at the occlusion site, our experiments indicate that it could lead to faster reperfusion.

The presented study uses a simplified in-vitro setup to model human circulatory system. This setup has obvious drawbacks, the principal one being different mechanical properties of the vessels and thus different pressure wave propagation characteristics. Furthermore, we have used a saline solution as the carrier fluid, whereas blood has a much higher viscosity, which can further dampen the pressure waves and limit its impact on the occlusion. We plan to address these issues in future experiments.

6. Conclusion

The presented results confirm our hypothesis that low frequency mechanical deformation drastically accelerates reperfusion of arteries blocked by blood clots, even if applied at a significant distance from the occlusion site. Thus, externally induced aorta deformation is a potential adjunct method during the pre-hospitalization phase of heart attack treatment.

In the future, we will investigate the mechanism of vessel deformation induced by transcutaneous application of stimulus and the effect of device location on the amplitude of the induced pressure waves. We will also continue development the proposed ADAR device.

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References


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