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Role of Myocardial Contractions on Coronary Vasoactivity

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Background: Heart failure (HF) is accompanied by alteration of hemodynamic conditions, which is due to the triggers of complex reflex changes in the sympathetic, endocrine, and rennin systems [1–2]. A critical effect of HF is reduced blood flow (ischemia) in the cardiovascular system resulting from mild to severe reduction in cardiac output (CO) due to dysfunction of myocardial contractility. It is known that coronary flow is regulated by many factors, including metabolic demand, perfusion pressure, oxidative stress, etc. Vascular vasodilation and vasoconstriction change microcirculation resistance and therefore regulate coronary circulation. However, it is not clear whether myocardial contractility may affect coronary tone to regulate coronary circulation in HF, i.e., the role the extrinsic mechanics in coronary arteriole tone. It is recognized that the extrinsic compression on blood vessel wall during skeletal muscle contraction is an independent regulator of vascular tone (3-4). Myocardial contraction also leads to such compression on intra-myocardial arterioles. Therefore, we hypothesize that myocardial contractility will change the arteriole tone to regulate coronary circulation. The myocardial contractility under physiological conditions stimulates an arteriolar vasodilation. The reduced myocardial contractility compromised in HF may weaken the vascular vasodilation and reduce blood flow in coronary microcirculation.

Materials and Methods: The animal experiments were performed in accordance with national and local ethical guidelines, including the Principles of Laboratory Animal Care, the Guide for the Care and Use of Laboratory Animals and the National Society for Medical Research, and an approved IACUC protocol regarding the use of animals in research. Pigs weighing 52 ± 14 kg (33–69 kg) were used in this study. The pigs were fasted overnight and surgical anesthesia was induced with TKX (Telazol 10 mg/kg, Ketamine 5 mg/kg, Xylazine 5 mg/kg) and maintained with isoflurane 1-2%.

In ex-vivo experiments, we isolated healthy swine myocardial arteriole segments (n=69). To provide external pressure, the experimental setup was assembled to create an isovolumic system within a sealable transparent box [5]. The isovolumic system consisted of a chamber with two connectors which bridge the blood vessel and rigid tubes. One tube connected to a 50 ml flask with PSS and the flask was pressurized with a pressure regulator to inflate the vessel at the desired intraluminal pressure. Another tube connected with a tuohy-borst adapter mounted with a solid state pressure transducer to monitor the intraluminal pressure. The PSS contained 1% dialyzed albumin aerated with mixed gas (22% O_2, 5% CO_2, balanced with 73% N_2) filled the chamber and tubes before vessel cannulation. A CCD camera on a microscope transfered the image of vessel to computer that digitized the external diameter of the vessel. The arteriole segments were cannulated on the tubing, inflated to physiological pressure, and exposed to cyclic transmural pressure generated by either intraluminal or extraluminal pressure pulses to simulate compression in contracting myocardium. The segments were pre-contracted to an approximate 60% diameter with Endothelin-1 at concentration of 10^{-8} to 10^{-7} mol/L. The vessel segments were then exposed to cyclic transmural pressure from 100 to 0 mmHg which was generated either by pulse extra-luminal pressure from 0 to 100 mmHg at 1 Hz while the intraluminal pressure was maintained at 100 mmHg. The endothelium-independent vasodilation was induced with sodium nitroprusside (SNP, 10^{-10} to 10^{-5} mol/L) to verify the sensitivity of vascular smooth muscle (VSM) to nitric oxide (NO).

We previously used swine tachycardia HF model to alter myocardial contractility [6]. Myocardium cannot efficiently contract when heart rate is higher than 160 bpm in tachycardia model, i.e., myocardial contractility was weakened. The coronary flow was monitored to observe the change of coronary perfusion. The procedure to implant pacemaker was as follows: A thoracotomy was performed along the fourth intercostal space and the chest cavity was opened to fully expose the heart. Two platinum pacemaker electrodes were placed on the surface in the lateral LV free wall at 0.5cm apart and secured by suture. The pacemaker was placed in a percutaneous pocket near the neck for easy access. The function of the pace maker was tested and the pacing threshold was determined. Pacing was started one or two weeks after the animals were completely recovered from surgery. The initial pacing rate was set at 170, 190, and 210 beats/min. A transonic flow probe was implanted on left anterior descending (LAD) artery.

Results: *In ex vivo* experiment, we found that the external pressure pulses elicited vasodilation of coronary arterioles. The vasodilation in response to pressure was dependent to changes in arteriole diameter. Agonist-induced endothelium-dependent and -independent vasodilation was used to verify endothelial and vascular smooth muscle cell viability. Vasodilation in response to cyclic changes in transmural pressure was smaller than that elicited by pharmacological activation of the NO signaling pathway. The vasodilation was attenuated by inhibition of NO synthase and by mechanical removal of the endothelium. We determined that integrin played a role in cyclic compression-induced endothelial NO production and thereby in the vasodilation of small arteries during cyclic transmural pressure loading.

The hemodynamic parameters were analyzed in tachycardia HF swine model. When heart rate increased over 160 bpm, the left ventricular end diastolic volume was slightly increased from 65 ± 22 to 67 ± 18 ml in tachycardia, which indicates little change during myocardial relaxation. The artery pressure was not changed significantly. The ejection fraction was drastically reduced by approximately 40% in tachycardia HF model. The left ventricular systolic factor was drastically decreased by approximately 50%. The ejection fraction and left ventricular systolic factor are indices of myocardial contraction. The decrease in these parameters suggests attenuation of myocardial contraction. We observed an instantaneous decrease in coronary flow of approximately 15%. The observations implicate that normal myocardial contraction is one of the stimulators of coronary arterioles vasodilation. When myocardial contraction is attenuated, the vasodilation elicited by the contraction is weakened, which increases vascular tone and decreases perfusion flow.
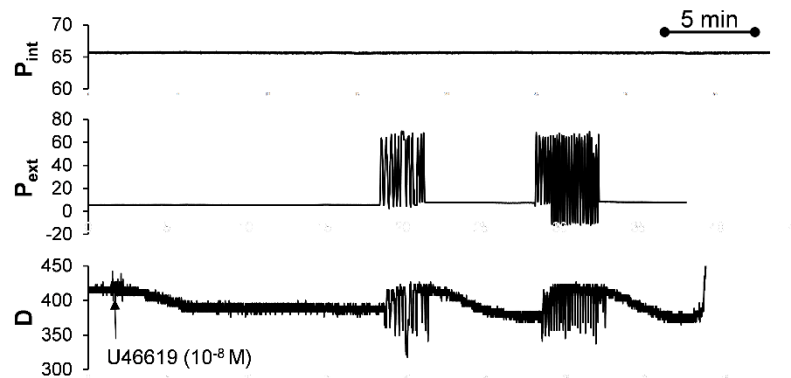

Figure 1. Typical diameter variation of coronary arterial segment with pre-constriction was caused by cyclic extrinsic pressures that were generated by extra-luminal pressure variation. P_{int} was the intra-luminal pressure constant at 66 mmHg. P_{ext}, extra-luminal pressure cyclically varied from 0 to 66 mmHg.

Conclusions: The *ex vivo* experiments and *in vivo* validation suggest that the myocardial contractility is one of the stimulators of coronary arterioles and therefore plays a role in coronary arterial circulation.

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