Alleviation of Myocardial Ischemia by the Development of Coronary Collateral Circulation

MASATOSHI FUJITA, M.D. AND SHIGETAKE SASAYAMA, M.D.

Coronary collateral vessels provide alternate routes for delivery of blood to myocardium distal to obstructed major coronary arteries. For many years, clinicians have considered the collateral pathways to be a great source of compensation for coronary artery obstructions. The purpose of this article will be to describe the physiological characteristics of the development of coronary collateral circulation in conscious dogs, and to consider whether heparin treatment augments the collateral development in both the experimental and clinical settings.

Repeated brief coronary occlusions in conscious dogs.

In 1981, Franklin and co-workers developed for the first time, a dog experimental model, where the coronary collateral circulation adequate for resting metabolic requirement of the myocardium to be rendered ischemic could be successfully induced by repeated 2-min left circumflex coronary artery (LCCA) occlusions. This elegant model has provided a variety of information on the development of coronary collateral circulation alterations in coronary perfusion territory and regional myocardial hypertrophy as a result of repetitive ischemic episodes. Briefly stated, the procedure involves 2-min total occlusion of the LCCA repeated hourly 7 to 8 times daily in the conscious dog instrumented for measurement of the LCCA flow and regional myocardial function. After approximately 150 2-min LCCA occlusions, there was no sustained reduction in myocardial function in the region perfused by the LCCA and there was negligible reactive hyperemia following release of the occlusion (Fig. 1). These indirect indices of regional myocardial perfusion indicate that repeated brief LCCA occlusions develop the coronary collateral circulation sufficient for the myocardial metabolic activity at rest. Further, we directly observed that the collateral blood flow from the LCCA to the area supplied by the occluded left anterior descendent artery (LAD) is augmented gradually as a result of the development of collateral circulation to the LCCA area.

An advantage of this animal model over previous models for study of coronary collateral circulation is that the stimulus for the development of collateral perfusion can be assessed quantitatively as a number of 2-min coronary occlusions. With the use of this model, it became possible to evaluate the effects of drugs on the rate of the development of collateral circulation.

Heparin augments angiogenesis in vitro.

In the 1960s, although it had already been recognized that mast cells accumulate in the vicinity of new blood vessels accompanying conditions such as chronic inflammation and neoplasia, the role of mast cells was unclear. In 1976, Kessler et al. observed that there was a 40-fold increase in the density of mast cells around the pellet of tumor extracts implanted on the chorioallantoic membrane of the chick embryo. However, mast cells alone did not induce angiogenesis. Based upon this evidence, it was speculated that mast cells potentiate capillary growth, but can't initiate it. Mast cell products include heparin, histamine, chondroitin

KEYWORDS:
Angiogenesis
Heparin exercise treatment
Repeated coronary occlusion
Treadmill exercise

The Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan
Mailing address: Masatoshi Fujita, M.D., The Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan

Fig. 1. Original tracings of left ventricular pressure (LVP), its first derivative (DP/Dt), segment length in the subendocardium perfused by the left circumflex coronary artery (LCCA), phasic and averaged LCCA flow velocity, and heart rate before, during, and after a 2-min LCCA occlusion prior to (left panel) and following (right panel) collateral development. (Reproduced from Heart Vessels by permission).

Fig. 2. Number of 2-min left circumflex coronary artery occlusions needed for the collateral development in dogs with and without heparin.

Sulfates etc. Among these compounds, it has been shown that only heparin can stimulate endothelial migration. Further, Taylor and Folkman demonstrated that heparin could facilitate angiogenesis induced by human hepatoma extracts implanted on the chick embryo. Thus, although it has been documented that heparin can enhance angiogenesis, the precise mechanism for this action of heparin has not yet been clarified. From that point of view, we evaluated, using the aforementioned animal model, whether heparin facilitates the
necessary for the collateral development. Indeed, some dogs had well-developed pre-existent collateral vessels (Fig. 3). These dogs were excluded from analysis. Secondly, it is well appreciated that a fixed coronary constriction promotes the growth of collateral channels. Therefore, the patency of the LCCA was evaluated with great caution throughout the experiment. It is reported that in the absence of coronary stenosis, the peak reactive hyperemic flow after release of a brief occlusion is 4–6 times of the resting coronary flow in conscious dogs. In our study, if the maximal reactive hyperemic flow was reduced below 3-fold of the preocclusion resting flow in a given dog, it was discarded from the data (Fig. 4). The patency of the LCCA was checked during the first occlusion of each day, because there was a remarkable functional regression in the collateral circulation following 16 hours interruption of repeated occlusions, and the coronary occlusion after such a long interval produced almost the same reactive hyperemic response as the first coronary occlusion! Thus, it was documented that the subcutaneously administered heparin accelerates the collateral development in conscious dogs.

Heparin is also effective for the collateral development in humans.

Here again, it should be emphasized that a single use of heparin cannot enhance the development of a collateral circulation, and the existence of angiogenic factors probably related to myocardial ischemia is prerequisite for angio genesis. Accordingly, the symptom limited treadmill exercise was utilized to produce severe myocardial ischemia in patients with chronic stable effort angina. All the variables of treadmill capacity were increased significantly in patients who had 20 exercise periods with heparin pretreatment, whereas these indices in those without heparin remained unchanged, despite 20 exercise periods (Fig. 5 and 6). Repeat coronary cineangiography revealed a significant increase in the extent of visualization of collateral channels to the myocardium at jeopardy (Fig. 7). Further, to clarify the actual increase in the collateral perfusion reserve with heparin exercise treatment, postspacing left ventriculography was performed in some patients (Fig. 8). Thus, heparin enhances exercise-induced coronary collateral development with a resultant attenuation of myocardial ischemia under conditions of augmented myocardial oxygen requirement.
**Fig. 4.** Two-min left circumflex coronary artery (LCCA) occlusion with (lower panel) and without (upper panel) LCCA stenosis. The peak reactive hyperemic flow is decreased by the LCCA stenosis.

**Fig. 5.** Changes in exercise time (left panel) and maximal double product (right panel) before and after 20 treadmill exercise periods with (closed circle, solid line) and without (open circle, broken line) heparin pretreatment. ***p < 0.001 compared with values before exercise with heparin pretreatment. (Reproduced from Circulation by permission).
Fig. 6. Changes in double product at the onset of angina (left panel) and double product at 0.1 mV ST segment depression (right panel) before and after 20 exercise periods with (closed circle, solid line) and without (open circle, broken line) heparin pretreatment. *p < 0.05, **p < 0.01 compared with values before exercise with heparin pretreatment. (Reproduced from Circulation\textsuperscript{17} by permission).

Heparin exercise treatment is a new therapeutic modality in combination with conventional medical therapy, such as β-blockers, nitrates and calcium-channel blockers in patients with coronary artery disease.

Acknowledgment

We thank Masami Kosugi for preparation of the manuscript.

REFERENCES


BEFORE TREATMENT

CONTROL

AFTER TREATMENT

CONTROL

POST-PACING

Fig.8. Left ventriculograms from a patient with a total occlusion of the right coronary artery were analyzed with a previously reported method. Before heparin exercise treatment, a rapid cardiac pacing induced severe hypokinesis in the inferior wall (upper panel). After treatment, the left ventricular wall motion was well preserved against the same rate of pacing stress.

MCKOWN MD, FRANKLIN D: Regional myocardial volume alterations induced by brief repeated coronary occlusion in conscious dogs. J Am Coll Cardiol 12: 1048, 1988