Mechanisms of collateral development and hemodynamics of gradual coronary occlusion 1)

Mechanismen der kollateralen Entwicklung und die Hämodynamik langsam fortschreitender Koronarokklusion

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With 13 figures and 2 tables

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Summary

The mechanisms for development of collaterals following a gradual occlusion (Ameroid technique) of one the coronary arteries in the dog were investigated. A control systems approach, based on quantitative experimental data, was utilized. The peripheral coronary pressure, peripheral coronary flow, coronary reserve flow, collateral resistance, peripheral coronary resistance, oxygen availability and demand were among the parameters studied. These variables were followed through the preocclusion phase, occlusion phase, ischemic phase, and post-ischemic phase of a gradual coronary constriction. The simulation studies were examined for the following basic assumptions: 1) ischemia is the sole stimulus for collateral development, 2) the peripheral coronary vasculature exhibits autoregulation and the peripheral coronary resistance increases during ischemia, 3) autoregulation occurs but during ischemia the peripheral vasculature remains maximally dilated without increase in resistance, and 4) the peripheral coronary vasculature is non-autoregulatory. It was concluded that neither ischemia nor a pressure differential can solely account for collateral development. It is believed that ischemia begins the collateral growth process and it is sustained by the pressure differential (or some manifestation thereof) during the post-ischemic phase. Assumption 2 is most consistent with both physiological and clinical data. The autoregulatory capacity of the peripheral coronary bed allows a constriction of 76% before the resting coronary flow is impaired.

Introduction

The development of coronary collaterals following an acute or gradual occlusion of one of the major coronary arteries has been investigated by a number of workers in the field. For many years it has been thought that collaterals were anatomically present but physiologically dormant until a pressure difference across these vessels, due to a coronary occlusion, caused

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them to passively dilate and supply blood to the affected coronary bed. This may very well be the case in a femoral artery occlusion as shown by Windblad (41), Rosenthal (32), and Conrad (8), but probably only applies to a limited extent in the coronary circulation. Recent work by Schaper has shown that collateral development in the heart is an active process in which vascular growth occurs to resupply the myocardium (33). Schaper has been able to demonstrate that the mitotic index is highest at 3 weeks following a gradual occlusion and persists for at least 8 weeks but that radioactive DNA is not found after 12 months.

One of the most intriguing questions arising from this research has centered about the mechanism(s) by which collaterals are stimulated to grow. Liebow (27) has suggested that the factors believed to influence or stimulate vascular growth fall into three categories: 1) forces of a mechanical nature, 2) forces of a chemical nature, and 3) hereditary factors.

**Mechanical forces**

In 1924 Spalteholz suggested that the pressure within the collaterals induces the transformation of collaterals. Gregg (16) proposed that the pressure gradient over the collaterals is the stimulus for collateral growth. One of the oldest theories attributes the collateral expansion to blood flow velocity within the collaterals (40, 38). Recently, it has been suggested by Schaper (35) that the tangential sheer forces acting upon the collateral wall are responsible for vascular growth.

**Chemical forces**

There has been general agreement that tissue hypoxia is an obvious causative factor for collateral growth. Tissue hypoxia leads to vasodilation. As to the precise mechanism(s) coupling hypoxia with cellular proliferation and formation of new collateral vessels, little is known (33). The only certain knowledge we have at this time is that the difference between oxygen demand and availability to the myocardium causes dilation of coronary resistance vessels. When this oxygen deficit persists for some time, these vessels may transform into a collateral artery.

Guyton and Carrier (18) have shown that oxygen per se can affect vasodilation in skeletal muscles. Haddy (19), on the other hand, believes that the role of oxygen in the coronary circulation is questionable. Berne (4) has proposed adenosine as the mediator governing the changes in the coronary resistance vessels. In chronic hypoxia many vasoactive substances are released from the myocardial cells; lactic acid, potassium, magnesium, adenosine, intermediate metabolites of the Krebs cycle, and hyperosmolality, all of which cause vasodilation (30). Certainly it is difficult to say whether the mechanism(s) responsible for acute vasodilation are the same that operate to cause vascular growth during chronic hypoxia.

**Hereditary factors**

Hereditary factors can play several roles in the process of collateral development. The existence as well as distribution of collaterals is species determinant. Thus, the dog exhibits a preponderance of epicardial collaterals, the pig a preponderance of endocardial collaterals, the human a