Angiogenesis: a Future Treatment Approach for Coronary Heart Disease
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Coronary artery disease is a leading cause of morbidity and mortality in Canada and the western world. Despite increased awareness, better management of risk factors, and improved non-surgical and surgical treatment modalities, coronary artery disease can sometimes involve the vessels of some patients so severely that medications, angioplasty and coronary artery bypass grafting may be unsuccessful at alleviating heart symptoms and preventing complications. However, patients may in the future benefit from a biologically-based therapy called therapeutic angiogenesis, which recreates the highly potent physiologic processes that occur during growth and development in every animal and human being, with the goal of forming new blood vessels in the adult heart.

What is angiogenesis?
Angiogenesis is the formation of new blood vessels from preexisting ones. This process occurs somewhat naturally in the heart of patients who progressively develop coronary disease over a number of months to years, yet to a degree that is usually insufficient to completely alleviate cardiac symptoms and prevent subsequent complications. The sequence of events leading to angiogenesis is depicted in Figure 1. Angiogenesis is a very complex process, and it is believed that the actions of growth factors and of a locally produced gas called nitric oxide interplay to detach, multiply, rearrange, and recruit cells in order to create new blood vessels. It is possible to stimulate this process by administering growth factors directly into the heart muscle, therefore resulting in the heart getting new blood and oxygen, and potentially cure angina.

How is angiogenesis done?
There are several ways to perform therapeutic angiogenesis; however, although many approaches have worked well in animals, most are still of unproven efficacy in humans. There is nevertheless little doubt that angiogenesis will eventually work, since it recreates the very potent processes that lead to new blood vessels during growth of every human being. We recently reported the results of a clinical research study in which a surgical method of administering growth factors in combination with coronary artery bypass grafting was evaluated (1). Patients with a severely diseased coronary artery that was not bypassable at the time of surgery were randomly allocated to receive either a growth factor or a sterile, inactive salt solution in the heart muscle supplied by this diseased artery, while the other coronary arteries were bypassed in a routine fashion (Figure 2). Three years after the surgery, patients who received the growth factor along the diseased coronary artery still had less angina than those who received the inactive salt solution.

When will angiogenesis be available for heart patients?
Much research remains to be done in the complex field of angiogenesis, and consequently the modality is still at the experimental stage. Our laboratory at the University of Ottawa Heart Institute is actively involved in angiogenesis research, and some patients for whom conventional methods of coronary disease treatment have failed or are very likely to fail will be offered to participate in a carefully regulated research protocol later this year. This research will examine the role of the nitric oxide gas on clinical angiogenesis. Patients with coronary artery blockages almost always have an additional problem called “coronary endothelial dysfunction”. This means that the existing blood vessels in the heart muscle of these patients produce too little nitric oxide gas, which acts as an essential co-factor for the angiogenesis process (Figure 1). There are
however potential ways for patients with coronary disease to increase the amount of nitric oxide gas produced in their heart muscle, such as diet supplementation with L-arginine, moderate vitamin C intake, lowering of blood cholesterol and homocysteine levels, or moderate exercise. In this regard, our research will combine dietary L-arginine supplementation with the administration of growth factors in order to make angiogenesis clinically more effective.

In summary, angiogenesis is a promising modality for the treatment of coronary heart disease. It is at present still experimental, reserved for selected patients with very severe disease, but with ongoing research efforts it is likely that angiogenesis will one day become a first-line modality that will benefit many patients with coronary heart disease.

References
Figure 1. Angiogenesis is the creation of new blood vessels from pre-existing ones. Substances called growth factors (GF) stimulate this process and can be administered non-surgically or surgically. A gas called nitric oxide (NO) that is locally produced in the heart is believed to be essential to allow the growth factors to work.
Figure 2. Growth factors can be implanted at the time of coronary artery bypass grafting around an artery that is not graftable, while graftable arteries are bypassed in a routine fashion. This approach, which currently remains experimental, has previously been shown to be clinically effective in alleviating angina.