Current Review

Endothelial Function Related to Vascular Tone in Cardiac Surgery

Guo-Wei He, MD, PhD, DSc (Professor)[a,b,*]

[a] *Department of Surgery, The Chinese University of Hong Kong & Wuhan Heart Institute, The Central Hospital, Wuhan, China*
[b] *Starr Academic Center, Providence Heart Institute, Department of Surgery, Oregon Health and Science University, Portland, OR, USA*

Vascular endothelium has multiple functions including regulating of vascular tone, preventing platelet aggregation, anti-proliferation, etc. An intact endothelial function is essential to the maintenance of an adequate vascular tone, to prevent platelet aggregation in the intimal surface of blood vessels, to prevent smooth muscle proliferation, and to prevent atherosclerosis.

This review focuses on endothelial function related to the vascular tone in cardiac surgery. The review is composed by three sections. In the first section, normal endothelial function related to vascular tone is described. In the second section, coronary endothelial function related to cardiac arrest and cardioplegic exposure is reviewed. In the third section, the endothelial function in the coronary bypass grafts is summarised. It is particularly important to understand that coronary endothelial dysfunction may be one of the major causes of low perfusion of the myocardium after cardiac arrest or donor heart preservation. Further, endothelium plays a major role in the maintenance of vascular tone and in the long-term patency of CABG grafts. The characteristics of endothelium in arterial and venous grafts and the correlation to the long-term patency are now more understood. A number of methods have been suggested to protect endothelial function in either coronary circulation or in coronary artery bypass grafts during cardiac surgery but further investigations in this field are warranted.

(Heart Lung and Circulation 2005;14:13–18)

Keywords. Cardiac surgery; Endothelium-derived relaxing factor; Nitric oxide; Endothelium-derived hyperpolarizing factor; EDHF; Potassium channels; Coronary artery; Cardioplegia

Vascular endothelium has multiple functions including regulating vascular tone, preventing platelet aggregation, anti-proliferation, etc.[1] All these functions are important in physiological and pathophysiological status. Intact endothelial function is essential to the maintain an adequate vascular tone, to prevent platelet aggregation in the intimal surface of blood vessels, to prevent smooth muscle proliferation, and to prevent atherosclerosis.

These functions are all related to cardiac surgery. For example, the function of preventing platelet aggregation is directly related to the inflammatory process during and after cardiopulmonary bypass. Again, the antri-proliferation effect of the endothelium determines the long-term patency of coronary artery bypass grafts and the occurrence of atherosclerotic disease after heart transplantation. Among those functions, the regulation of vascular tone –endothelium-dependent relaxation is particularly important in cardiac surgery. This is due to the fact that coronary perfusion is the vital factor for myocardial function and therefore is one of the key points for the success of all kinds of cardiac operations. Further, adequate vascular tone determines blood flow in the coronary bypass grafts in coronary artery surgery. The endothelium-dependent relaxation is mediated by three endothelium-derived relaxing factors (EDRFs)—nitric oxide (NO), prostacyclin (PGI_2), and an unidentified endothelium-derived hyperpolarizing factor (EDHF). Therefore, we will review vascular endothelial function related to vascular tone in the following three sections: (1) normal endothelial function; (2) coronary endothelial function in cardiac surgery; and (3) endothelial function in coronary artery bypass grafts.

Nitric Oxide and Other Endothelium-Derived Relaxing Factors ($EDRF_s$)

Prostaglandin I_2 (PGI_2)

PGI_2 is the first defined relaxing factor derived from endothelium.[2] When activated by stimuli, the enzyme phospholipase A_2 in endothelial cells converts membrane phospholipids to arachidonic acid (AA) that is subsequently metabolized to PGI_2, thromboxane A_2, and several

* Present address: Department of Surgery, The Chinese University of Hong Kong, Block B, 5A, Prince of Wales Hospital, Shatin, N.T., Hong Kong. Tel.: +852 2645 0519; fax: +852 2645 1762.
E-mail address: gwhe@surgery.cuhk.edu.hk.

1443-9506/04/$30.00
doi:10.1016/j.hlc.2004.11.003

other prostaglandins (PGE_2, $PGF_{2\alpha}$, PGD_2) by cyclooxygenase (COX). PGI_2 causes vasorelaxation in most arteries, including the coronary bed. The vascular relaxation induced by PGI_2 is mediated by the rise of cyclic 3′, 5′-adenosine monophosphate (cAMP) that leads to the extrusion of Ca^{2+} from the cytosol and decreased sensitivity of the contractile apparatus to Ca^{2+}. Different types of potassium (K^+) channels are involved in the PGI_2-mediated hyperpolarization in various vasculatures.

Nitric Oxide

Furchgott and Zawadzki (1980) postulated that upon stimulation of acetylcholine, endothelial cells release another vasodilator substance distinguished from PGI_2.[3] Ignarro and co-workers (1987) clarified the chemical identity of EDRF as nitric oxide (NO).[4] NO is synthesized from the amino acid L-arginine by NO synthase (NOS). There are at least two major NOS isoforms. One is expressed constitutively in neurons and vasculature that is involved in cell communication and is activated by an increase in intracellular calcium. The other isoenzyme exists in macrophages to participate in host defense and is not normally found in endothelial cells or vascular smooth muscle unless induced by cytokines.[5] In the vascular system, the endothelium-derived NO diffuses out of endothelial cell and a portion of it arrives at the underlying smooth muscle cell layer. The subsequent up-regulation of cyclic 3′, 5′-guanosine monophosphate (cGMP) in the smooth muscle results in the activation of cGMP-dependent protein kinase that leads to vasorelaxation.[6] It has been demonstrated that several types of K^+ channels are also involved in NO-mediated hyperpolarization.

Endothelial-Derived Hyperpolarising Factor

The endothelium-dependent hyperpolarisation and relaxation are only partially inhibited or not changed with the presence of COX and NOS inhibitors,[7,8] indicating the existence of a novel vasorelaxant agent named endothelial-derived hyperpolarising factor (EDHF), which is distinct from PGI_2 and NO. The introduction of the non-NO and non-PGI_2 pathway in the vascular system arouses fierce debate regarding the nature of EDHF. Several substances have been suggested to be EDHF, such as epoxyeicosatrienoic acid (EETs), anadamide, K^+, H_2O_2, citrulline, NH_3 and ATP.[9] It has also been suggested that the so-called EDHF is merely an electrical signal conducted from the endothelial cell to the underlying smooth muscle cell through myoendothelial gap junctions, the intercellular connections between the layer of endothelium and smooth muscle.[10,11] EDHF hyperpolarizes and relaxes blood vessels through opening of certain K^+ channels, particularly KCa channels on the smooth muscle cell.[7,8,11]

Endothelial Function Related to Vascular Tone in Cardiac Surgery

Endothelium has multiple functions that play a key role in maintaining vascular tone and in preventing platelet aggregation and atherosclerosis, as mentioned above. Probably the most immediate effect of endothelial dysfunction is seen in coronary endothelium after cardiac arrest for open heart surgery (or donor heart preserved with organ preservation solutions) and in the endothelium of the coronary artery bypass grafts.

Coronary Endothelial Function Related to Ischemia/Reperfusion in Cardiac Surgery

During cardiac surgery, the heart is arrested and subjected to ischemia-reperfusion injury. To protect the heart, cardioplegia is usually used to initially stop and then to maintain the still condition of the heart that not only facilitates the precise operation but more importantly minimizes the energy consumption of the heart during this period.

In case of heart transplantation, cardioplegia or organ preservation solutions are used to preserve the donor heart or other organs. During the preservation and the transplantation, the donor heart is subjected to ischemia injury. When the heart starts to beat, it is subjected to reperfusion injury and therefore the ischemia/reperfusion injury is a key point in heart transplantation.

During these procedures, damage (or protection) to the endothelium may result from a number of factors such as (1) direct action of the solutions due to their intrinsic characteristics (the components of the solution); (2) adjuncts to the cardioplegic procedure such as hypothermia or the infusion pressure acting both as independent factors and through their interaction with cardioplegic solutions; (3) the effect of ischemia-reperfusion injury; and (4) other factors involved in isolated working heart models or in vivo models when these models are used to study endothelial function.

The ischemia-reperfusion injury may involve both myocytes and coronary endothelium-smooth muscle. Therefore, the protection of the heart should also involve these two aspects. The injury to the heart involves (1) the ischemia-reperfusion injury to the myocytes and coronary circulation and (2) possible injury to the coronary circulation by the cardioplegia due to its hyperkalemic components. The injury to the coronary circulation may involve both NO and EDHF mechanisms. The NO mechanism is susceptible to ischemia-reperfusion whereas the EDHF mechanism may be altered by hyperkalemic cardioplegia. To further protect the heart, supplemental therapy for NO and optimizing the components of cardioplegia to restore the EDHF-mechanism may be important.

NO and EDHF are thought to be the two major mechanisms in the endothelium-smooth muscle interaction that is particularly important in maintaining adequate vascular tone.[12] It is generally recognized that the NO and EDHF mechanisms are the two major pathways in the coronary circulation related to cardiac surgery.

Therefore, protection of the endothelium-smooth muscle interaction should include these two important functions.

Dysfunction of NO and Protection of NO-Related Function in Coronary Circulation

DYSFUNCTION OF NO. Dysfunction of the NO mechanism is mainly due to ischemia-reperfusion injury but not due