Introduction

Cardiopulmonary bypass (CPB) remains an essential element of the surgical correction of most congenital and many acquired cardiac lesions. Despite significant advances in the technique, CPB is still complicated by multisystem injury, the mechanisms of which include ischemia–reperfusion (IR) injury and a detrimental systemic inflammatory response ***(Chew et al., 2001).*** Cardiac, pulmonary and neuronal injury and dysfunction remain important clinical problems after CPB ***(Massoudy et al., 2001).***

It is established that exposing the myocardium to brief periods of ischemia and reperfusion induces greater tolerance to a subsequent more prolonged ischemic insult. This endogenous adaptation to ischemia, termed "ischemic preconditioning ***(Eagle et al., 2004).***

Local ischemic preconditioning, induced by short-lived non-fatal ischemia in the target tissue, has been shown to be of benefit in patients undergoing coronary angioplasty and surgical revascularization in some studies ***(Laskey, Beach, 2003).*** The clinical applicability of local preconditioning is limited by the need to induce ischemia in the target organ, a process that itself may induce dysfunction and that is clearly inappropriate for global myocardial protection ***(Lindhardt et al., 2004).***

However, the preconditioning stimulus has systemic effects to protect distant tissues from subsequent ischemia, and this variant is called remote ischemic preconditioning (RIPc). Kharbanda et al. had already reported a protective effect induced by transient limb ischemia in experimental myocardial infarction. Limb ischemia to induce RIPc has potential implications in a variety of clinical IR syndromes and may be easier to induce than local preconditioning ***(Kharbanda et al., 2006).***

Aim of the Work

The aim of the study is to evaluate the efficacy of remote ischemic preconditioning in reducing cardiac and pulmonary injury induced by CPB in adult patients undergoing coronary artery bypass graft surgery.

Anatomy of Coronary Arteries

The heart muscle, like every other organ or tissue in the body, needs oxygen-rich blood to survive. Blood is supplied to the heart by its own vascular system, called coronary circulation; the aorta (the main blood supplier to the body) branches off into two main coronary blood vessels (also called arteries). These coronary arteries branch off into smaller arteries, which supply oxygen-rich blood to the entire heart muscle ***(Moore, 1992)***.

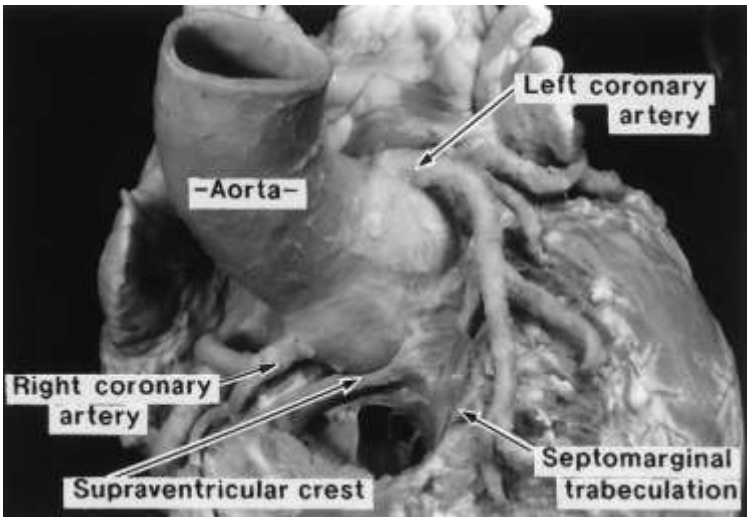

Fig. (1): The aortic origin of the coronary arteries ***(Mill et al., 2008).***

The right and left coronary arteries originate behind their respective aortic valvar leaflets (Fig.1). The orifices usually are located in the upper third of the sinuses of Valsalva, although individual hearts may vary markedly. Because of the oblique plane of the aortic valve, the orifice of the left coronary artery is superior and posterior to that of the right coronary artery. The

coronary arterial tree is divided into three segments; two (the left anterior descending artery and the circumflex artery) arise from a common stem. The third segment is the right coronary artery. The dominance of the coronary circulation (right versus left) usually refers to the artery from which the posterior descending artery originates, not the absolute mass of myocardium perfused by the left or right coronary artery. Right dominance occurs in 85 to 90% of normal individuals. Left dominance occurs slightly more frequently in males than in females ***(Kirklin, Barratt, 1993)***.

From the stand point of surgeon, the coronary artery system is divided into four parts: the left main coronary artery (LMCA), the left anterior descending coronary artery (LAD) and its branches, the left circumflex coronary artery (LCx) and its branches, and the right coronary artery (RCA) and its branches ***(Kouchoukos et al., 2003)***.

Main Stem of the Left Coronary Artery:

The main stem of the left coronary artery courses from the left sinus of Valsalva anteriorly, inferiorly and to the left between the pulmonary trunk and the left atrial appendage (Fig.2). Typically, it is 10 to 20 mm in length but can extend to a length of 40 mm. The left main stem can be absent, with separate orifices in the sinus of Valsalva for its two primary branches (1% of patients). The main stem divides into two major arteries of nearly equal diameter: the left anterior descending artery and the circumflex artery ***(Kirklin, Barratt, 1993)***.

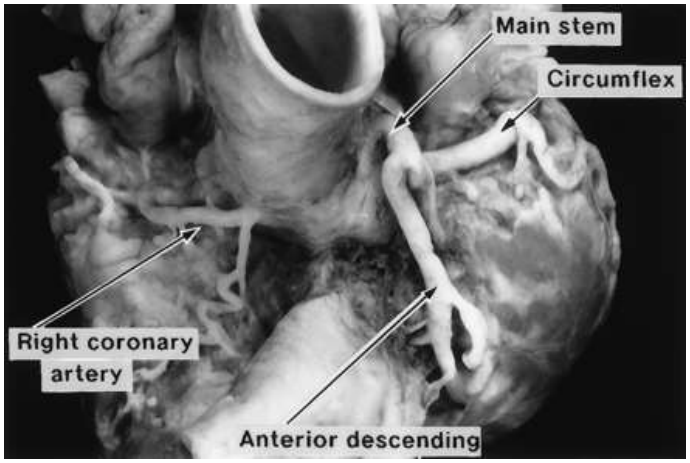

Fig. (2): The main stem of the left coronary artery ***(Mill et al., 2008).***

Left Anterior Descending Artery: (fig. 3)

The "LAD" or left anterior descending artery continues directly from the bifurcation of the left main stem, coursing anteriorly and inferiorly in the anterior interventricular groove, it reaches the apex of the heart in 78% of cases. It passes at first behind the pulmonary artery and then comes forward between that vessel and the left auricula to reach the anterior interventricular sulcus, along which it descends to the incisura apicis cordis. It supplies the anterolateral myocardium, apex, and interventricular septum. The LAD typically supplies 45-55% of the left ventricle (LV) ***(Williams et al., 1995)***.

The LAD gives off three types of branches: diagonals, septal perforators and the right ventricular branches.

- Diagonals: may be 2 to 6 in number, course along the anterolateral wall of the left ventricle and supply this portion of the myocardium. The first diagonal generally

is the largest and may arise from the bifurcation of the left main stem (formerly known as the intermediate artery) ***(Kouchoukos et al., 2003)***.

- The septal perforators branch perpendicularly into the ventricular septum. Typically, there are three to five septal perforators; the initial one is the largest and commonly originates just beyond the takeoff of the first diagonal. This perpendicular origination is a useful marker for identification of the left anterior descending artery on coronary angiograms. The septal perforators supply blood to the anterior two-thirds of the ventricular septum ***(Kirklin, Barratt, 1993)***.

- Right ventricular branches, which may not always be present, supply blood to the anterior surface of the right ventricle. In approximately 4% of hearts, the left anterior descending artery bifurcates proximally and continues as two parallel vessels of approximately equal size down the anterior interventricular groove. Occasionally, the artery wraps around the apex of the left ventricle to feed the distal portion of the posterior interventricular groove. Rarely, it extends along the entire length of the posterior groove to replace the posterior descending artery ***(Schlant, Silverman, 1986).***

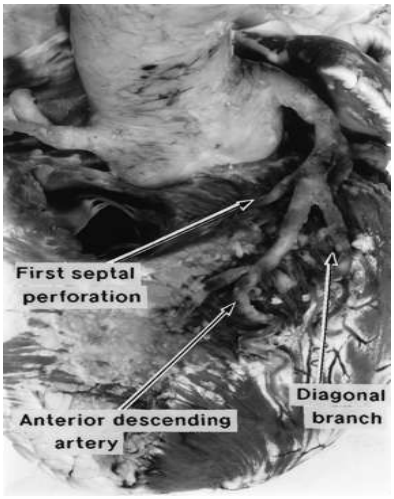

Fig. (3): The important branches of the anterior descending artery are the first septal perforating and diagonal arteries ***(Mill et al., 2008).***

Circumflex Artery: (fig. 4)

The left circumflex coronary artery arises from the left main coronary artery roughly at a right angle to the anterior interventricular branch. It courses along the left atrioventricular groove and in 85 to 95% of patients terminates near the obtuse margin of the left ventricle ***(Schlant, Silverman, 1986)***.

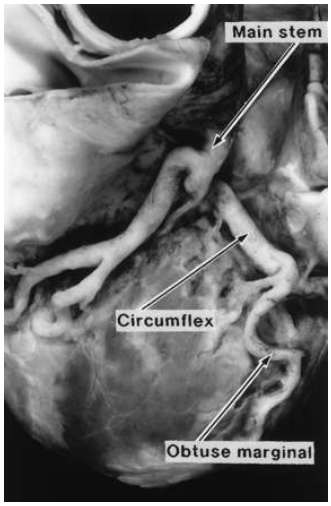

Fig. (4): The important branches of the circumflex artery, seen in anatomic orientation ***(Mill et al., 2008).***

In 10 to 15% of patients, it continues around the atrioventricular groove to the crux of the heart to give rise to the posterior descending artery (left dominance).

The primary branches of the left circumflex coronary artery are the obtuse marginals. They supply blood to the lateral aspect of the left ventricular myocardium, including the posteromedial papillary muscle. Additional branches supply blood to the left atrium and, in 40 to 50% of hearts, the sinus node. When the circumflex coronary artery supplies the posterior descending artery, it also supplies the atrioventricular node ***(Schlant, Silverman, 1986)***.

Right coronary artery (RCA): (fig. 5)

The right coronary artery (RCA) originates above the right cusp of the aortic valve. It travels down the right atrioventricular groove, towards the crux of the heart. The RCA usually is a single large artery; it courses from the aorta anteriorly and laterally before descending in the right atrioventricular groove and curving posteriorly at the acute margin of the right ventricle. In 85-90 % of hearts, the right coronary artery crosses the crux, where it makes a characteristic U-turn before bifurcating into the posterior descending artery and the right posterolateral artery ***(Kirklin, Barratt, 1993)***.

The posterior descending artery runs along the posterior interventricular groove, extending for a variable distance toward the apex of the heart. It gives off perpendicular branches, the posterior septal perforators, that course anteriorly in the

ventricular septum. Typically, these perforators supply the posterior one-third of the ventricular septal myocardium.The right posterolateral artery gives rise to a variable number of branches that supply the posterior surface of the left ventricle ***(Schlant, Silverman, 1986)***.

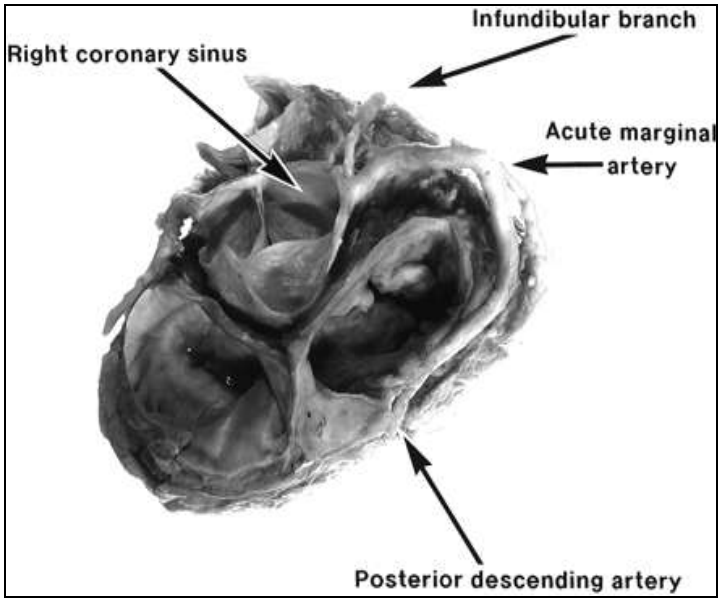

Fig. (5): The relationships and branches of the right coronary artery ***(Mill et al., 2008).***

In 50 to 60% of hearts, the artery to the sinus node arises from the proximal portion of the right coronary artery. The blood supply to the atrioventricular node (in patients with right-dominant circulation) arises from the midportion of the U-shaped segment.

The acute marginal arteries branch from the right coronary artery along the acute margin of the heart, before its bifurcation at the crux. These marginals supply the anterior free

wall of the right ventricle. In 10 to 20% of hearts, one of these acute marginal arteries courses across the diaphragmatic surface of the right ventricle to reach the distal ventricular septum ***(Kirklin, Barratt, 1993)***.

The circulation of the posteroinferior portion of the left ventricular myocardium is quite variable. It may consist of branches of the right coronary artery, the circumflex artery, or both. The right coronary artery supplies important collaterals to the left anterior descending artery through its septal perforators. In addition, its infundibular (or conus) branch, which arises from the proximal portion of the right coronary artery, courses anteriorly over the base of the ventricular infundibulum and may serve as a collateral to the anterior descending artery ***(Kirklin, Barratt, 1993)***.

Kugel's artery is an anastomotic vessel between the proximal right coronary and the circumflex coronary artery that also can provide a branch that runs through the base of the atrial septum to the crux of the heart, where it supplies collateral circulation to the atrioventricular node ***(Kugel, 1927)***.

Physiology of Coronary Arteries

Because the heart is composed primarily of cardiac muscle tissue that continuously contracts and relaxes, it must have a constant supply of oxygen and nutrients. The coronary arteries are the network of blood vessels that carry oxygen- and nutrient - rich blood to the cardiac muscle tissue. The blood leaving the left ventricle exits through the aorta. The coronary arteries are the first vessels to branch off the aorta near the top of the heart and through them; the heart receives (at rest) about 5% of the cardiac output, or 250 ml/min. The coronary arteries are classified as "end circulation", since they represent the only source of blood supply to the myocardium, which is why blockage of these vessels can be so critical ***(Van, Kent, 2002)***.

Normal Coronary Blood Flow:

Resting coronary blood flow is slightly less than 1 ml/g of heart muscle per minute. This blood flow is delivered to the heart through large epicardial conductance vessels and then into the myocardium by penetrating arteries leading to a plexus of capillaries. The bulk of the resistance to coronary flow is in the penetrating arterioles (20 to 120 μm in size). Because the heart is metabolically very active, there is a high density of capillaries such that there is approximately one capillary for every myocyte, with an intercapillary distance at rest of approximately 17 μm. Capillary density is greater in subendocardial myocardium than in subepicardial tissue. When there is an

increased myocardial oxygen demand (e.g., with exercise), myocardial blood flow can increase to three or four times normal (coronary flow reserve). This increased blood flow is accomplished by vasodilation of the resistance vessels and by recruitment of additional capillaries (many of which are closed in the resting state). This capillary recruitment is important in decreasing the intercapillary distance and thereby decreasing the distance that oxygen and nutrients must diffuse through the myocardium. The blood flow pattern from a coronary artery perfusing the left ventricle, measured by flow probe, is phasic in nature, with greater blood flow occurring in diastole than in systole ***(Beyar, 1993).***

The cyclic contraction and relaxation of the left ventricle produce this phasic blood flow pattern by extravascular compression of the arteries and intramyocardial microvessels during systole. There is a gradient in these systolic extravascular compressive forces, being greater or equal to intracavitary pressure in the subendocardial tissue and decreasing toward the subepicardial tissue. Measurement of transmural blood flow distribution during systole shows that subepicardial vessels are perfused preferentially, whereas subendocardial vessels are hypoperfused significantly. Toward the end of systole, blood flow actually reverses in the epicardial surface vessels ***(Yamada et al., 1991)***.

Hence the subendocardial myocardium is perfused primarily during diastole, whereas the subepicardial myocardium

is perfused during both systole and diastole. A greater capillary density per square millimeter in the subendocardium than in the subepicardial tissue facilitates the distribution of blood flow to the inner layer of myocardium, and myocardial blood flow normally is greater in the subendocardial tissue than in the subepicardial tissue ***(Vinten, Weiss, 1981)***.

This places the subendocardium at greater risk of dysfunction, tissue injury, and necrosis during any reduction in perfusion. This is related to (1) the greater systolic compressive forces, (2) the smaller flow reserve owing to a greater degree of vasodilation, and (3) the greater regional oxygen demands owing to wall tension and segmental shortening. If end-diastolic pressure is elevated to 25, 30, or 35 mm Hg, then there is diastolic as well as systolic compression of the subendocardial vasculature. Flow to the subepicardium is effectively autoregulated as long as the pressure in the distal coronary artery is above approximately 40 mm Hg. Flow to the subendocardium, however, is effectively autoregulated only down to a mean distal coronary artery pressure of approximately 60 to 70 mm Hg. Below this level, local coronary flow reserve in the subendocardium is exhausted, and local blood flow decreases linearly with decreases in distal coronary artery pressure. Subendocardial perfusion is further compromised by pathologic processes that increase wall thickness and systolic and diastolic wall tension. Aortic regurgitation in particular threatens the subendocardium because systemic diastolic arterial pressure is reduced and

intraventricular systolic and diastolic pressures are elevated ***(Beyar, 1993)***.

In contrast to the phasic nature of blood flow in the left coronary artery, blood flow in the right coronary artery is relatively constant during the cardiac cycle. The constancy of blood flow is related to the lower intramural pressures and near absence of extravascular compressive forces in the right ventricle compared with the left ventricle ***(Yamada et al., 1991)***.

Control of Coronary Blood Flow:

Coronary blood flow is tightly coupled to the metabolic needs of the heart. Under normal conditions, 70% of the oxygen available in coronary arterial blood is extracted, near the physiologic maximum. Any increase in oxygen delivery comes mostly from an increase in blood flow. To maximize efficiency, local coronary blood flow is precisely controlled by a balance of vasodilator and vasoconstrictor mechanisms, including (1) a *metabolic vasodilator system,* (2) a *neurogenic control system,* and (3) the *vascular endothelium.* Blood flow is controlled by moment-to-moment adjustment of coronary tone of the resistance vessels ***(Bradley, Alpert, 1991)***.

(1) ***The metabolic vasodilator mechanism*** responds rapidly when local blood flow is insufficient to meet metabolic demand. The primary mediator is adenosine generated within the myocyte and released into the interstitial