POST OPERATIVE MORBIDITY AND 3 YEARS SURVIVAL RATE IN DIABETIC AND NON DIABETIC PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Latar Belakang

Penyakit kencing manis adalah salah satu daripada risiko kepada penyakit jantung and juga dikaitkan dengan komplikasi selepas pembedahan pintasan jantung. Tujuan kajian ini dijalankan adalah untuk mengenalpasti sama ada penyakit ini memberi kesan langsung terhadap komplikasi selepas pembedahan pintasan jantung and kadar kematian sehingga 3 tahun selepas pembedahan dijalankan.

Kaedah kajian

Kajian ini melibatkan seramai 205 pesakit yang menjalani pembedahan pintasan jantung secara elektif di Unit Kardiotorasik Hospital Universiti Sains Malaysia, Kubang Kerian bermula dari Januari 2002 hingga Disember 2005. Kumpulan kajian dibahagikan kepada 2 iaitu pesakit jantung yang menghidap kencing manis dan pesakit yang tidak menghidap kencing manis. Seramai 90 pesakit (43.9%) menghidap kencing manis dan 115 pesakit (56.1%) tidak menghidap penyakit tersebut. Terdapat seramai 169 (82.4%) pesakit lelaki dan 36 (17.6%) pesakit wanita. Pesakit berumur dalam lingkungan 39 ke 77 tahun.

Keputusan kajian

Data yang diperoleh menunjukkan bahawa pesakit kencing manis mempunyai kadar "ejection fraction" jantung yang lebih lemah (59% vs 62%, p= 0.03) dan latarbelakang penyakit buah pinggang (25.6% vs 16.6%, p=0.02). Tiada perbezaan ketara diantara kedua-dua kumpulan dikenalpasti dari segi latarbelakang penyakit-penyakit lain seperti tekanan darah tinggi, tahap kolesterol tinggi, penyakit lelah atau asma, sejarah merokok dan penyakit angina ahmar atau strok.

Tiada perbezaan juga dikenalpasti dari segi jangkamasa penggunaan mesin pintasan jantung dan paru-paru, isipadu cecair "cardioplegia" yang digunakan, jangkamasa "aortic cross clamped" dan bilangan pintasan jantung yang dijalankan.

Analisa selepas pembedahan menunjukkan pesakit kencing manis mempunyai risiko yang lebih tinggi untuk mendapat jangkitan kuman pada bahagian saluran darah diambil, biasanya di bahagian kaki atau paha (61.1% vs 23.5%, $p<0.001$) serta kegagalan buah pinggang selepas pembedahan (27.7% vs 7.8%, $p<0.001$). Walaubagaimanapun, tiada perbezaan dikenalpasti di antara kedua-dua kumpulan dari segi komplikasi lain iaitu jangkitan kuman pada luka dada, jangkitan kuman paru-paru, pendarahan teruk, gangguan ritma jantung dan angina ahmar. Kajian susulan sehingga 3 tahun menunjukkan lebih ramai pesakit kencing manis dimasukkan ke wad atas alasan berkaitan jantung selepas pembedahan (42.2% vs 27.8%, $p=0.03$). Tiada perbezaan dari segi kadar pembedahan semula atau serangan jantung selepas pembedahan. Kadar kematian keseluruhannya adalah seramai 15 orang dalam tempoh 3 tahun di mana 10 orang meninggal dunia dalam tempoh 30 hari pertama. Data kajian ini menunjukkan tiada perbezaan kadar kematian dikenalpasti antara kedua-dua kumpulan pada 30 hari pertama atau sehingga 3 tahun.

Kesimpulan

Kajian ini menyokong kajian sebelumnya bahawa penyakit kencing manis memberi kesan terhadap komplikasi pembedahan pintasan jantung terutamanya jangkitan kuman pada luka pembedahan dan kegagalan buah pinggang. Walaubagaimanapun, adalah sukar untuk mengatakan bahawa kadar kematian adalah berkaitan dengan penyakit ini kerana jumlah kematian keseluruhan yang kecil.

VII ABSTRACT

Background

Diabetes mellitus is a risk factor for development of coronary artery disease and also being linked to worse outcomes after coronary artery bypass grafting (CABG). The purpose of the study is to evaluate the post operative morbidity and survival rate at 3 years following CABG in patients with diabetes mellitus compared to non diabetics.

Methodology

This study was done on 205 patients who underwent elective isolated CABG in Cardiothoracic Unit, Hospital Universiti Sains Malaysia, Kubang Kerian from January 2002 to December 2005. Our study group were divided into diabetes and non diabetes. 90 patients (43.9%) were diabetics and 115 (56.1%) were non diabetics. There were 169 (82.4%) male patients and 36 (17.6%) female patients. Patients' age ranged from 39 to 77 years old.

Results

The data showed that diabetic patients had poorer ejection fraction (59% vs 62%, p= 0.03) and preoperative renal failure (25.6% vs 16.6%, p=0.02). There were no significant difference in term of other comorbidities between diabetes and non diabetes group , which were hypertension, chronic obstructive airway disease (COAD), smoking status, cerebrovascular accident (CVA), and hyperlipidaemia (HPL).

Intraoperative findings showed no significant findings between both groups which include cardiopulmonary bypass (CPB) time, amount of cardioplegia, aortic cross clamped time and number of bypass performed.

Post operative outcome revealed that diabetic patients had higher risk of developing harvested site infection (61.1% vs 23.5%, $p<0.001$) and post operative renal failure (27.7% vs 7.8%, $p<0.001$). However, no significant differences were noted in other post operative complications, which were sternal wound infection, pneumonia, post operative bleeding, arrythmias and CVA. During follow up until 3 years post operatively, we found that diabetic patients were more frequently being readmitted due to cardiac causes (42.2% vs 27.8%, $p=0.03$). No differences in term of reoperation rate and recurrent angina post CABG. Overall mortality until 3 years post CABG was 15 patients where 10 patients died within 30 days. We reported that no significant outcome between both groups in term of 30 days mortality and 3 years survival rate.

Conclusion

As conclusion, this study supported the evidence that diabetes mellitus were the significant prognostic factors for some post CABG complications especially harvested site infection and post operative renal failure. However, it is difficult to really determine either the disease contribute to post operative death or not in view of small overall number of mortality .

1.0 INTRODUCTION

Diabetes Mellitus is one of the common diseases encountered in Kelantanese population and considered as a risk factor for development of coronary artery disease. In comparison with western population which recorded prevalence of 20% to 30% of Diabetes Mellitus among patients with coronary artery disease , the prevalence in our population is much more higher, which is 30% to 45% (Barsness *et al*, 1997,Szabo *et al*, 2002). The management strategies for coronary artery disease in diabetic patients are similar compared to non diabetics, namely by medical therapy, percutaneous angioplasty (PTCA) or coronary artery bypass graft surgery (CABG). However this metabolic disease is usually being linked to less favorable outcomes after the above interventions. The nature of coronary artery disease in diabetics, quality of harvested graft and post operative management of glucose monitoring were mentioned to be the reasons. Despite of the above findings, some studies still conclude non significant differences in term of post operative outcomes between both groups (Mehran *et al*, 2004, Szabo *et al*, 2002). The purpose of the study is to evaluate the post operative morbidity and survival rate at 3 years following CABG in patients with diabetes mellitus compared to non diabetics.

2.0 LITERATURE REVIEW

2.1 ANATOMY : ARTERIAL SUPPLY OF THE HEART

The arterial supply of the heart is provided by right and left coronary arteries, which arise from ascending aorta just above the aortic valve.

The right coronary artery arises from anterior aortic sinus of the ascending aorta and run forward between the pulmonary trunk and the right auricle. It descends in the atrioventricular groove, giving branches to the right atrium and right ventricle. At the inferior border of the heart, it continues posteriorly along the atrioventricular groove to anastomose with the left coronary artery. It gives off a marginal branch, which supplies the right ventricle, and posterior interventricular branch which supplies both ventricles. The posterior interventricular branch anastomoses with the anterior interventricular branch of the left coronary artery in the posterior interventricular groove.

The left coronary artery, which is larger than the right, arises from the left posterior aortic sinus of the ascending aorta and passes forward between pulmonary trunk and the left auricle. It then enters the atrioventricular groove (also known as left main stem artery) and divides into anterior interventricular branch (or anterior descending branch), and circumflex branch. The anterior interventricular branch runs down to the apex of the heart in the anterior interventricular groove. It then passes around the apex to anastomose with the posterior interventricular branch of the right coronary artery. The anterior interventricular branch supplies the right and left ventricles as well as the ventricular septum. The circumflex branch follows the atrioventricular groove, winds around the left

margin of the heart, and ends by anastomosing with the right coronary artery. The circumflex branch supplies the left atrium and the left ventricle.

The commonest variations affect the blood supply to the diaphragmatic surface of both ventricles. Here the origin, size and distribution of the posterior interventricular artery are variable. In the case of "right dominance" the posterior interventricular artery is a large branch of the right coronary artery, whereas in the case of "left dominance" the posterior interventricular artery is a branch of left coronary artery.

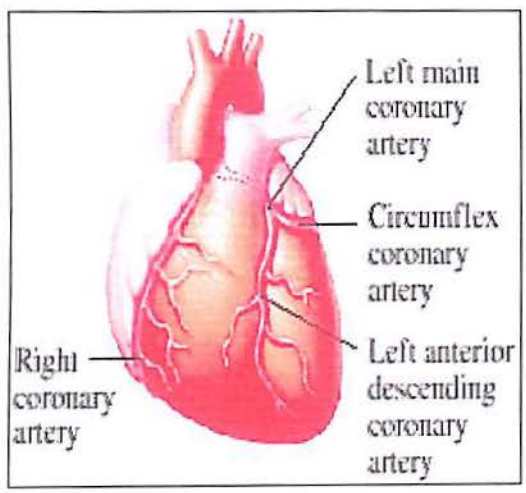

Figure 1 : Arterial Supply of the Heart
(permission from www.forbesheartcenter.com)

2.2 PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE

Atherogenesis is a complex interaction of risk factors including cells of the arterial wall and the blood as well as molecular messages that they exchange. When the arterial endothelium encounters certain bacterial products, or risk factors (hyperlipidemia, vasoconstrictor hormones in hypertension, products of glycoxidation associated with hyperglycemia, or proinflammatory cytokines derived from excess adipose tissue), these cells augment the expression of adhesion molecules that promote sticking of blood leukocytes to the inner surface of the arterial wall (called formation of fatty streaks) (Chilton, 2004). Once adhered to arterial intima, the blood leukocytes (mainly macrophages and T cell lymphocytes) communicate with endothelial and smooth muscle cells, the endogenous cells of arterial wall. Once this communication occurs, the smooth muscle cells will migrate from tunica media to the intima. These cells proliferate and elaborate a rich and complex extracellular matrix. In concert with endothelial cells and monocytes, they secrete matrix metalloproteinases (MMPs) in response to various oxidative, hemodynamic, inflammatory and autoimmune signals. MMPs, in balance with their endogenous tissue inhibitors, modulate numerous function of vascular cells, including activation, proliferation, migration, and cell death, as well as new vessels formation, geometric remodeling, healing, or destruction of extracellular matrix of arteries and the myocardium. Certain constituents of the extracellular matrix binds lipoproteins, prolongs their residence in the intima, and render them more susceptible to oxidative modification and glycation (nonenzymatic conjugation with sugar). These

products of lipoprotein modification, including oxidized phospholipids and advanced glycation end products, sustain and propogate the inflammatory response. As the lesion progresses, calcification may then occur through mechanism similar to those in bone formation. In addition to proliferation, cell death commonly occurs in the established atherosclerotic lesion. The death of lipid laden macrophages can lead to extracellular deposition of tissue factors. The extracellular lipid that accumulates in the intima can coalesce and form the classic, lipid rich necrotic core of the atherosclerotic plaque (Chilton, 2004).

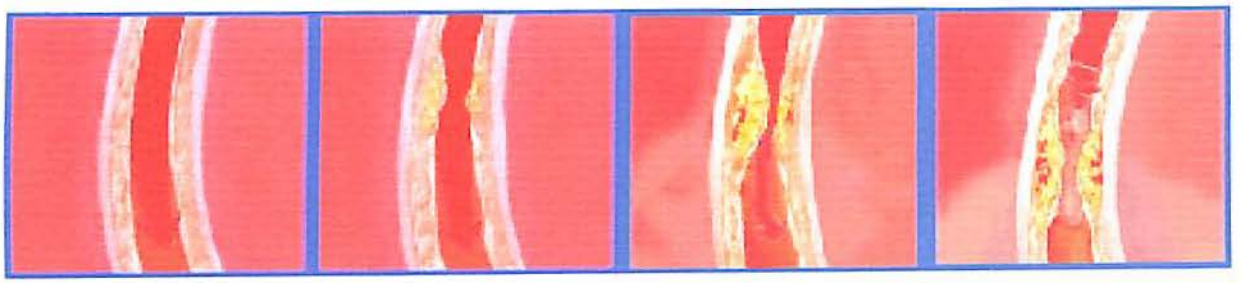

Figure 2 : Chronological sequence of coronary artery disease (pictures from left to right) from healthy artery, then damaged artery followed by narrowed artery and finally blocked. (permission from www.forbesheartcenter.com)

2.3 PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROME

As recently as the 1980's, some uncertainty of prevailed with regard to the causative role of thrombosis in acute coronary syndrome (ACS). A number of microanatomic mechanism underlie ACS thrombosis. According to autopsy studies, a through and through rupture of the plaque's protective fibrous cap most commonly cause lethal coronary thrombosis. Other mechanisms include superficial erosion, interplaque haemorrhage, and the erosion of calcified nodule (Chilton, 2004).

Disrupted coronary plaques provoke thrombosis in several ways. First, contact with collagen in the plaques' extracellular matrix can trigger platelet aggregation. Second, tissue factor produced by macrophages and smooth muscle cells activates the coagulation cascade. The disrupted plaque thereby represents as a "solid state" stimulus to both thrombosis and coagulation, and these pathways reinforce each other, as thrombin generation amplifies the activation of platelets and other cells in the lesion. Conversion of fibrinogen to fibrin and release of von Willebrand factor (VWF) from activated platelets can provide the cross linking molecular bridges between platelets that yield the dense network of platelets entrapped in fibrin (white arterial thrombus) (Chilton, 2004).

Besides the "solid state" of the disrupted plaque, the "fluid phase" of blood can predispose toward coronary thrombosis. Plasminogen activator inhibitor 1 (PAI-1) extinguishes the body's natural fibrinolytic mechanism that combats the persistence and accumulation of thrombi by inhibiting urokinase-like and tissue type plasminogen activity. Circulating PAI-1 increase in diabetes and obesity, and mediators of

hypertension such as angiotensin II can augment PAI-1 expression. These fluid phase changes lead to the concept of "vulnerable plaques".

"Vulnerable plaques" are defined as thrombosis prone or at risk of rapid progression and exhibit some combination of active inflammation, thinning cap with large lipid core, endothelial denudation with superficial platelet aggregation, fissures or greater than 90% stenosis (Chilton, 2004). Vulnerable patient is a term to identify subjects with high likelihood of having cardiac events in the near future.

2.4 MANAGEMENT STRATEGIES OF CORONARY ARTERY DISEASE

2.4.1 TREATMENT OPTIONS FOR CORONARY ARTERY DISEASE

Several alternative treatments for coronary artery disease (CAD) exist. Medical management; for example lipid lowering drugs, antihypertensives, sublingual nitrates, avoidance of risk factors such as cessation of smoking and tight blood sugar control in diabetics are important to prevent further deterioration of the disease. Percutaneous coronary angioplasty (PTCA) is more effective than medical management in relieving symptoms but repeat procedures are required post PTCA. Coronary artery bypass graft surgery (CABG) is the preferred treatment for patients with diffuse coronary disease which are not amendable to treatment with PTCA, disease of three coronary vessels, and disease of the left main coronary artery (left main coronary artery disease is associated with sudden death). CABG also is the treatment option for patient with concurrent valvular heart disease that also requires operation.

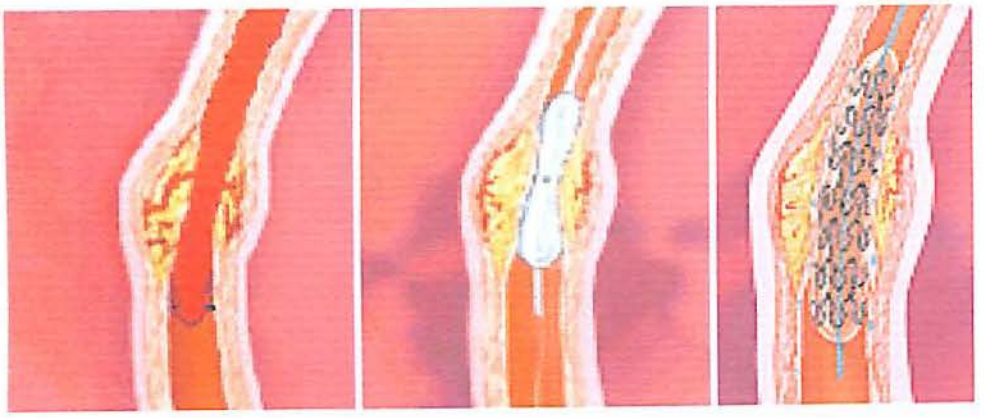

Figure 3: Coronary angioplasty. The blood flow to the heart muscle decreases due to build up of plaque. The balloon compresses the plaque against the artery wall. The stent is expanded in the artery. (permission from www.forbesheartcenter.com)

2.4.2 CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)

CABG is the surgical procedure performed to relieve angina and reduce risk of death from coronary artery disease (CAD). Arteries or veins from elsewhere in the patient's body are grafted from the aorta to the coronary arteries to bypass the atherosclerotic narrowing and improve the blood supplying the myocardium. This surgery is performed on beating heart or non beating heart using the cardiopulmonary bypass machine.

The surgeon will review the coronary angiogram prior to the surgery and identify the lesions (blockage) in the coronary arteries. The surgeon then can estimate the number of bypass grafts which will be anastomosed, but the final decision is made in the operating room upon examination of the heart.

The term single bypass, double bypass, triple bypass and quadruple bypass refer to the number of coronary arteries bypassed in the procedure. However, a greater number of bypasses does not imply a person is "sicker", nor does a lesser number imply a person is "healthier". A person with large amount of coronary artery disease may receive fewer bypass grafts due to lack of suitable "target vessels". A coronary artery may be unsuitable for bypass grafting if it is small (<1mm or < 1.5 mm depending on surgeon preference), heavily calcified (meaning the artery does not have a section free of CAD), or intramyocardial (meaning the artery is located within the heart muscles rather than on the surface of the heart).

The choice of grafts or conduits is highly surgeon and institution dependent. Typically, the left internal mammary artery (LIMA) is grafted to the left anterior descending artery.

The right internal mammary artery, the great saphenous vein from the leg and the radial artery are frequently used. The left gastroepiploic artery from the stomach is infrequently used due to difficult mobilization from the abdomen.

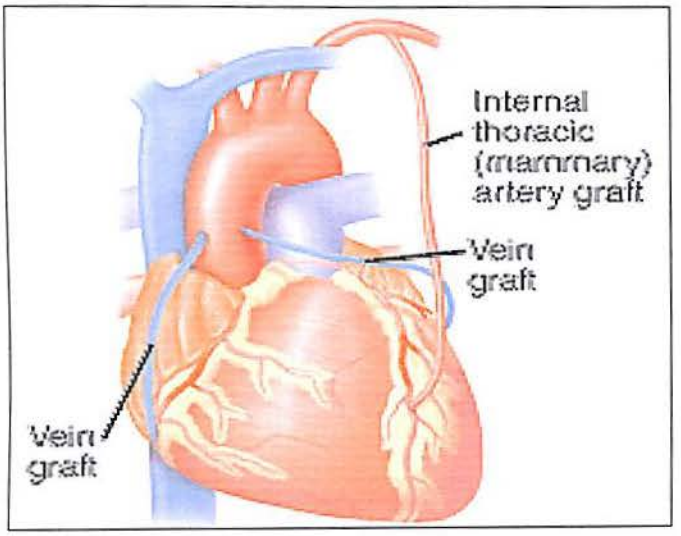

Figure 4 : Coronary artery bypass grafting with venous graft and arterial (LIMA) graft. (permission from www.forbesheartcenter.com)

2.4.3 HISTORY OF CORONARY ARTERY BYPASS GRAFTING (CABG)

The history of advances in CABG started in late 19th century. In 1876, Adam Hammer established that angina pain could be attributed to blockage of at least one coronary artery. Since then, people started to think regarding methods of myocardial revascularization. Arthur Vineberg in 1950 accomplished myocardial revascularization by rerouting internal mammary artery into heart muscles, allowing side branch to bleed into heart muscle. The first successful open heart surgery was performed by Dr John Gibbon in 1953 using cardiopulmonary bypass machine. 2 years later, Sidney Smith harvested the saphenous vein from the leg and used it as the first venous graft for revascularization. In 1968, Rene G Favolaro achieved restoration of coronary blood flow in 171 patients with multiple saphenous vein grafts in several different anatomical positions. First off pump CABG (beating heart) was established by Benetti, Calafiore and Subramiam in 1973. They made direct anastomosis between left internal mammary artery and left anterior descending artery through 10 cm incisions between ribs. Tissue stabilizers was first introduced by Professor Cornelius Borst in 1997. The stabilizer utilized suction technology to stabilize the coronary target for off pump revascularization.

2.4.4 GRAFT PATENCY

Graft patency is a term used to describe the chance that a graft remain open. A graft considered patent if there is flow through the graft without significant stenosis (>70% diameter) in the graft. It is important because graft can become diseased or occluded after bypass surgery is performed.

Graft patency depends on several factors. Type of graft used, the size of coronary artery that the graft is anastomosed with and skill of the surgeon are the important factors. Arterial grafts (especially left internal mammary grafts) are longer lasting than vein grafts because the artery is more robust than the vein and being already connected to the arterial tree. However, arterial grafts (internal mammary or radial artery) are more sensitive to rough handling than saphenous veins and may go into spasm if not handled properly.

Graft patency rates are best achieved with in situ left internal mammary artery (the proximal end is left connected to the subclavian artery) with the distal end being anastomosed with the coronary artery. Compared to arterial grafts, saphenous vein grafts have the worst patency rates, however they are more available as the patients can have multiple segments of the saphenous vein used to bypass different arteries. If the vein grafts are used, the valves of the veins have to be removed or the veins are turned around so that the valves do not occlude blood flow in the graft.

2.5 CARDIOPULMONARY BYPASS (CPB)

2.5.1 COMPONENT AND MECHANISM OF FUNCTION OF CPB

Cardiopulmonary bypass (CPB) is a technique that temporarily takes over the function of the heart and lungs during surgery to maintain the circulation of the blood and the oxygen content of the body. CPB machines are operated by allied health professional known as perfusionists in association with the surgeon who connect the pump to the patient's body. Besides CABG, other procedures that require CPB are cardiac valve replacement, repair of congenital heart defects, transplantations (heart and lung) and repair of large aneurysms (aortic and cerebral aneurysms).The first successful open heart surgery using CPB machine was performed by Dr John Gibbon on 6th May 1953 in Philadelphia.

CPB consists of connective tubing, a blood reservoir, heat exchanger and filter. Prior to initiation of CPB, the extracorporeal pump circuit is primed with crystalloid solution or blood. This is important to dilute the cooled blood which has high viscosity. Multiple cannulae are sewn to establish CPB circuit, namely venous cannulae (placed in the vena cavae or right atrium), arterial cannula (placed at distal ascending aorta) and cardioplegia cannula. Venous cannulae drain deoxygenated blood by gravity through connective tubing into the reservoir. The blood is then pumped to an oxygenator where carbon dioxide is removed and oxygen is transferred to the blood. Blood temperature may be adjusted by the use of heat exchanger. Whole body hypothermia is usually induced while patient is on CPB. The body temperature is usually kept at 28°C to 32°C. The patient is administered heparin to prevent clotting. The blood is then filtered to reduce the potential for embolism and is pumped back to the body through an arterial cannula.

Once CPB has been initiated, the heart is allowed to beat or it may be temporarily arrested by administration of cardioplegia solution. Cardioplegia is a cold crystalloid or blood solution that contains a high concentration of potassium. The solution may be administered to the coronary vasculature in a normograde fashion through a cannula (proximal aorta) or retrograde through a canulla in the coronary sinus. The potassium is used to induce cardiac arrest. The cold temperature of the cardioplegia solution reduces the oxygen requirements of the myocardium and helps to preserve the heart during the ischemic period.

2.5.2 COMPLICATION OF CARDIOPULMONARY BYPASS (CPB)

CPB is a safe procedure and the mortality directly attributable to its effect is less than 1%. CPB does however result in whole body inflammatory response due to systemic activation of inflammatory mediators including complement and white blood cells in the extracorporeal circuit. The syndrome is characterized by temporary and usually reversible deficiencies in coagulation as well as cardiac, cerebral and respiratory and renal function. The most severe complication of CPB is severe cerebral damage in 1-2% of patients. This is more common in elderly patients, in those with proven cerebrovascular disease and in patients undergoing valve replacement due to embolization of air and calcified debris from the valve. One third of them suffers subtle neurophysiological impairment which recovers in the majority within 3 to 6 months.

2.6 DIABETES MELLITUS : ASSOCIATION WITH CORONARY ARTERY DISEASE AND BYPASS SURGERY.

In general ,approximately 20% to 30% of patients who have undergone coronary artery bypass grafting (CABG) have Diabetes Mellitus (DM) (Barsness *et al*, 1997, Szabo *et al*, 2002). However the prevelance is higher among Kelantanese population which is around 36%. As mentioned before, possible mechanisms for the association between diabetes and coronary artery disease include abnormalities in lipid metabolism, nitric oxide activity, platelet function, coagulation and autonomic function.

Diabetes is not only a risk factor for coronary artery disease (CAD), but it is also determine the outcome after coronary artery bypass grafting (CABG). Diffuse coronary artery disease, a greater number of involved coronary vessels, more rapid progression of the atherosclerotic disease and more compromised left ventricular function in diabetic patients are the factors that contribute to less favorable post operative morbidity and mortality (Lorusso *et al*, 2003). The previous studies showed different results relating DM to complications following CABG especially on short term mortality and morbidity (Szabo *et al*, 2002). Post operative survival rates are only studied after 5 years which still give contradicting results.

In the perspective of Malaysian population, no local evidence so far comparing the outcome between diabetics and non diabetics after CABG, even though the population affected is much higher compared to general population.