INTRODUCTION

Brain natriuretic peptide (BMP) and N-terminal pre-natriuretic BNP has gain a great deal of attention in recent years and became an area of intense research as available biomarker in evaluating heart disease, since its physiological release has been related to conditions that inflict a stressful load on the heart, using BNP as biomarker is a routine practice in many centers around the world.

Higher levels of brain natriuretic peptide (BNP) and N-terminal pro-natriuretic peptide (NT-proBNP) in the first few days after AMI is a powerful predictor of LV dysfunction, prognosis in heart failure and death ***(Omland et al., 1996)***.

The benefit of prompt, expertly performed primary percutaneous coronary intervention (PPCI) for acute ST elevation myocardial infarction (STEMI) is now well established. When performed rapidly by an experienced team ***(Keeley et al., 2003).***

Primary percutaneous coronary intervention improves survival rates in patients with acute myocardial infarction (AMI) as compared with thrombolytic therapy, in large part due to better and sustained antegrade epicardial perfusion (thrombolysis in myocardial infarction [TIMI] grade 3 flow) ***(Weaver et al., 1997).***

Nevertheless, failure of achieve TIMI 3 flow (i.e., suboptimal TIMI flow) after PPCI still occurs in the first

few days after AMI is a powerful predictor of LV dysfunction, prognosis in heart failure and death ***(Omland et al., 1996).***

Aim of the Work

The aim of the work is to identify the impact of final suboptimal TIMI flow (TIMI 0-2 vs. TIMI 3) on brain natriuretic peptide.

CHAPTER (1): SUBOPTIMAL FINAL TIMI FLOW

Overview

The TIMI flow grading system is a widely used method of grading coronary flow ***(TIMI, 1985).*** While the TMPG Assesses perfusion in the capillary bed at the tissue level ***(Cannon et al., 2000),*** the TIMI flow grade is used to assess epicardial coronary blood flow.

Clinical Importance and Evaluation

The Thrombolysis in Myocardial Infarction (TIMI) flow grade classification scheme has been widely used to assess coronary blood flow in acute coronary syndromes ***(The TIIMI Study Group, 1985)***. The association of the TIMI Flow Grades (TFG)s with clinical outcomes including mortality has been well documented ***(Simes et al., 1995; The GUSTO Angiographic Investigators, 1993; Vogt et al., 1993; Karagounis et al., 1992; Anderson et al., 1993; Gibson et al., 1996)***, although the association of the TFGs with mortality must be interpreted with caution as there are several confounders:

- The majority of TIMI grade 2 flow is observed in the left anterior descending artery (LAD) territory, whereas the majority of TIMI grade 3 flow is observed

in the right coronary artery (RCA) ***(Gibson et al., 1996)***. Thus, the improved mortality observed among patients with TIMI grade 3 flow may be explained at least in part by the fact that inferior myocardial infarction (MI) location is associated with a lower mortality rate ***(Gibson et al., 1996)***.

- The clinical improvement associated with TIMI grade 3 flow may be nonlinear. For example, greater clinical benefits may be observed if a closed artery (TFG 0/1) is opened with even slow flow (TIMI grade 2 flow) compared with the improvement that might occur if an artery with TIMI grade 2 flow is converted to TIMI grade 3 flow.

- As more arteries with TIMI grade 2 flow are treated with adjunctive percutaneous coronary intervention (PCI), the prognosis associated with this flow grade may improve. The fact that patients who were treated with an inferior fibrinolytic monotherapy strategy faired so well in GUSTO V may be explained in part by the fact that these patients underwent PCI more often ***(The GUSTO Investigators, 2001; Hudson et al., 2001).*** Two-year follow-up in more recent studies indicates that the survival advantage of TIMI grade 3 flow over TIMI grade 2 flow at 2 years may not be as great as it once was in the era before aggressive utilization of rescue and adjunctive (PCI) ***(Gibson et al., 2002)***.

TIMI Flow Grade (TFG)

TIMI Flow Grade 0

No perfusion. No antegrade flow beyond the point of occlusion ***(Gibson et al., 1999; Gibson et al., 1999; Gibson et al., 2002).***

TIMI Flow Grade 1

Penetration without perfusion. Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence ***(Gibson et al., 1999; Gibson et al., 1999; Gibson et al., 2002)***.

This category is subdivided into:

- 1.0: dye minimally leaks past the area of obstruction.
- 1.5: dye leaks well past the area of obstruction but fails to opacify the entire coronary bed.

TIMI Flow Grade 2

Partial perfusion. Contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly

slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel (i.e. opposite coronary artery or the coronary bed proximal to the obstruction) ***(Gibson et al., 1999; Gibson et al., 1999; Gibson et al., 2002)***.

This category is subdivided into:

- 2.0: TIMI 2 slow flow, dye markedly delayed in opacifying distal vasculature.
- 2.5: TIMI 2 fast flow, dye minimally delayed in opacifying distal vasculature.

TIMI Flow Grade 3

Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery ***(Gibson et al., 1999; Gibson et al., 1999; Gibson et al., 2002)***.

TIMI Flow Grade 4

TIMI grade 4 flow is a term developed by Dr. Michael Gibson, M.S., M.D. to describe hyperemic flow on a coronary arteriogram ***(Gibson et al., 2008)***.

Hyperemic flow on a coronary arteriogram is defined qualitatively as near instantaneous filling of the coronary artery with dye, and quantitatively as a corrected TIMI frame count < 14 frames. Hyperemic flow in a coronary artery may be due to either repayment of oxygen debt following ischemia due to a balloon inflation for instance, or distal embolization. If it is due to distal embolization, and if impaired myocardial perfusion is present (TIMI myocardial perfusion grade 0 or TIMI myocardial perfusion grade 1), then the mortality associated with TIMI grade 4 flow is actually **higher** than that of TIMI grade 3 flow ***(Gibson et al., 2008)***. In this scenario, the hyperemic flow is a surrogate or marker of endogenous adenosine release due to distal embolization, rather than being causally related to adverse outcomes.

Historical Perspective

The no-reflow concept was first suggested in brain ischemia ***(Majno et al., 1967)***.

Brains of rabbits that suffered a brief 2 1/2 minutes of ischemia had normal blood flow when the ischemia was relieved. When the rabbits were exposed to longer ischemic periods, normal flow to brain tissues was not restored, even after relief of the vessel obstruction. Prolonged ischemia resulted in significant changes in the microvasculature that

interfered with normal flow to the brain cells. The existence of this phenomenon was confirmed in a variety of animal models of brain ischemia ***(Ames et al., 1968; Asno et al., 1977)***. It was also shown in a variety of other organs, including skin ***(Chait et al., 1978; May et al., 1995)***, skeletal muscle ***(Allen et al., 1995)***, and the kidney ***(Summers and Jamison, 1971; Johnston and Latta, 1977).*** Kloner et al, ***(Kloner et al., 1975)*** sought to find out whether the no-reflow phenomenon would be observed in ischemic canine hearts and whether it was related to microvascular damage. Dogs were subjected to 40 or 90 minutes of proximal coronary artery occlusion. When the coronary occlusion was relieved after 40 minutes of occlusion, the blood flow was restored to the damaged myocardium as assessed by markers of perfusion such as thioflavin S and carbon black. However, after 90 minutes of coronary occlusion, there was only partial restoration of blood flow to the myocardial tissue, despite virtual elimination of the coronary occlusion. Anatomic perfusion defects were prominent in the subendocardial myocardium when thioflavin S or carbon black was injected into the vasculature after restoration of epicardial coronary flow. Electron microscopic examination of the cardiac microvasculature within the anatomic no-reflow zones revealed significant capillary damage in the form of swollen endothelium and intraluminal endothelial

protrusions and, less commonly, intraluminal platelets and fibrin thrombi. These changes, coupled with interstitial and myocardial cellular edema, could compress the capillaries and be responsible for the no-reflow phenomenon. The longer ischemia lasts, the more likely the no-reflow phenomenon is to occur. Microvascular damage did not appear to be the primary cause of myocardial cell damage because the no-reflow area appeared to be confined to areas of tissue that were already necrotic ***(Kloner et al., 1975; Kloner, 1980).*** In a similar model, Willerson et al, ***(Willerson et al., 1975)*** documented reduced myocardial blood flow in no-reflow zones and an increase in the coronary vascular resistance, specifically in the subendocardium. As suggested in 1974, "recent advances, such as coronary bypass surgery and the development of fibrinolytic agents, eventually may make it possible to release coronary occlusions." Twenty-six years later, these techniques and transluminal coronary interventions became the standard therapy of acute myocardial infarction. It was percutaneous coronary interventions in particular that brought the no-reflow phenomenon to light because it could be seen with the naked eye in human hearts in the setting of acute myocardial infarction.

Pathophysiology

Understanding the pathophysiology of the no-reflow phenomenon is the key for managing this condition. After prolonged cessation of coronary occlusion and restoration of blood flow to the epicardial coronary arteries, there is sufficient structural damage to the microvasculature to prevent restoration of normal blood flow to the cardiac myocytes.

This may lead to inadequate healing of the cardiac scar. In addition, it may prevent the development of future collateral flow. This phenomenon appears to be more pronounced in the subendocardium in a manner similar to the wavefront phenomenon of the ischemic cardiac death ***(Summers and Jamison, 1971).*** It is more pronounced with longer periods of coronary occlusions.2 No reflow appears to be a process rather than an immediate event that occurs at the moment of reperfusion. Experimental studies showed that the no-reflow area increases with time after reperfusion ***(Willerson et al., 1975; Reimer et al., 1977)***. Although it is clear that abnormalities at the level of the microvasculature caused the no-reflow phenomenon, the exact mechanism is uncertain; a variety of factors probably contribute to it.

Microscopic examination showed that the cardiac cells within the no-reflow area were swollen. The capillary

endothelium was damaged and exhibited areas of regional swelling with large intraluminal protrusions that in some cases appeared to plug the capillary lumen. Cellular edema compressing the capillaries was confirmed in more than one experiment ***(Ambrosio et al., 1989; Kloner, 1993; Manciet et al., 1994).*** This may explain the occasional benefit noted with dexamethasone10 or mannitol ***(Gavin et al., 1983; Nellis et al., 1980).*** Cell contracture in the ischemic zone also may contribute to the microvascular compression ***(Lee et al., 1980; Humphry and Gavin, 1985).***

Intravascular plugging by fibrin or platelets may also contribute to the no-reflow phenomenon ***(Topol and Yadav, 2000; Cuypers and Matakas, 1974).*** Beneficial effects of ibuprofen ***(Hataya et al., 1999)***, prostaglandin E1, and vascular washout with heparinized saline ***(Calhoun et al., 1999)*** support the concept that these blood elements may be important. In a no-reflow model of a New Zealand white rabbit study by Golino et al, ***(Golino et al., 1987),*** platelet depletion markedly reduced the extent of no-reflow zones.

Leukocyte intravascular plugging appears to play an important role in the pathophysiology of no reflow. Engler et al, ***(Engler et al., 1983)*** showed that the no-reflow areas had evidence of capillary leukocyte plugging. Although there was no difference in no-reflow zones between the

neutropenic animals and the control group in a gerbil cerebral ischemia model ***(Aspey et al., 1989; Mercuri et al., 1990),*** other studies showed that reperfusion leads to rapid accumulation of leukocytes in the microvasculature of the dog heart ***(Sheridan et al., 1996).*** This may be mediated by CD18-dependent leukocyte adhesion ***(Jerome et al., 1993)*** and may play some role in the genesis of the no-reflow phenomenon. Byrne et al ***(Byrne et al., 1992)*** found that reperfusion with leukocyte-depleted blood may reduce cardiac no reflow.

Furthermore, in a rat model of irreversible hemorrhagic shock, the no-reflow phenomenon was prevented by rendering the animals neutropenic ***(Barroso et al., 1988).*** Leukocytes may interfere with blood flow by mechanical plugging and perhaps by their release of oxygen free radicals that will add further injury to the capillary endothelium ***(Kloner, 1989; Engler et al., 1986).*** Thus, the no-reflow phenomenon is likely multifactorial. During the ischemic phase, endothelial damage, including endothelial swelling and myocyte edema, led to initial no-reflow zones. With reperfusion, additional edema, myocyte contraction, platelets, fibrin, and leukocyte plugging resulted in expansion of the no-reflow zones over the early hours of reperfusion. Platelet and leukocyte depletion and vasodilators appeared to lessen no reflow ***(Humphrey et al., 1982; Westin and Hedén, 1988).***

Diminished flow through the microvasculature compared with normal zones is usually referred to as "low reflow ***(Arteaga et al., 1999).***" An additional mechanism plays a very important role during short-term intervention in acute myocardial infarction. Microemboli of atherosclerotic debris, blood clots, and platelet plugs are released into the microcirculation, particularly with restoration of normal blood flow by thrombolysis, angioplasty, stenting, or other percutaneous intervention. Although this is more common in vein graft intervention, it is to be expected in native coronary arteries. A variety of new, innovative devices are now in clinical practice and in the research phase to filter these microemboli during the interventional procedure.

Predictors of No-Reflow

Since the above mentioned theories were proposed, multiple possible predictors of no-reflow have been studied. Age, smoking, time-to-treatment interval, left ventricular ejection fraction (LVEF), previous myocardial infarction, Killip class, serum creatinine, CRP, B-type natriuretic peptide (BNP), baseline TIMI flow grade, and initial perfusion defect may all predict the development of no-reflow ***(Gjin et al., 2010).***

Because of the potential role of platelets in induction and perpetuation of no-reflow, mediators affecting platelet

activation, such as thromboxane A2 (TXA2), might be involved in no-reflow. TXA2 is a key mediator of platelet activation and aggregation, and an important mediator of platelet-induced coronary artery constriction ***(Patrono et al., 2005; Fitzgeral, 1991).*** Endothelin-1 (ET-1), a potent endothelium-derived vasoconstrictor peptide, might aggravate no-reflow by promoting reperfusion injury, triggering inflammatory response, and attenuating antioxidant defense ***(Niccoli et al., 2006).*** In one study ***(Niccoli et al., 2008),*** TXA2 plasma levels, ET-1 plasma levels and left anterior descending coronary artery (LAD) as the culprit vessel were significant predictors of angiographic no-reflow, whereas TXA2 and ET-1 plasma levels were the only independent predictors of lack of ST-segment resolution.

In another study ***(Ingo et al., 2010),*** patients with angiographically (TIMI flow equal to or less than 2), electrocardiographically (ST-resolution of less than 30 percent) and magnetic resonance imaging (MRI)-detected (presence of micro-vascular obstruction) no-reflow had significantly higher ET-1 level on admission. This was the only significant predictor of MRI-detected no-reflow together with left ventricular ejection fraction. An elevated ET-1 level was also a significant predictor of long-term mortality.