Value of Gated SPECT in Coronary Artery Disease for Assessment of Myocardial Viability

*MD Thesis Submitted for Partial Fulfillment of M.D Degree in **Cardiology***

By

Yasser George Tadros

MBBch-Msc. Cardiology

Supervisors

Prof. Dr. Osama Mohamed Hassan

Professor of Cardiology - Faculty of Medicine
Ain-Shams University

Prof. Dr. Assem Mohamed Fathi

Professor of Cardiology - Faculty of Medicine
Ain-Shams University

Prof. Dr. Mohsen Mahmoud Mahdi

Assistant Professor of Cardiology - Faculty of Medicine
Ain-Shams University

Prof. Dr. Amr Adel Elsayed

Assistant Professor of Cardiology -Faculty of Medicine
Ain-Shams University

Prof. Dr. Taher Abdel Fatah El Kadi

Consultant of Cardiology -National Heart Institute

Faculty of Medicine- Ain Shams University

2005

INTRODUCTION

Patients with chronic CAD and L.V. dysfunction are at increased risk of cardiac morbidity and mortality during long-term medical therapy. Their risks rise with greater impairment of L.V. function. Identifying the subset of such patients with potentially reversible abnormalities in regional and global L.V. function have been an important goal for the clinician, as both symptoms and, presumably, prognosis are improved with successful revascularization, resulting in improved regional and particularly global function *(Jeroen; 2000 and Garcia, 1990).*

ECG-Gated acquisition of tomographic technetium-99m Sestamibi images offers the ability to obtain both myocardial and ventricular function information simultaneously. Technetium-99m Sestamibi is injected during peak exercise, and imaging can begin as early as 15 minutes later and should begin within 4 hours. Thus these images indicate myocardial perfusion at stress (because technetium-99m Sestamibi undergoes minimal redistribution after injection) and ventricular functions at rest (gating show function during image acquisition-at rest). Functional information obtained includes wall motion, wall thickening, ejection fraction, and ventricular volume *(Chua, 1994 and DePuey, 1993).*

Gated technetium99m Sestamibi studies offer a number of benefits. In patients without known coronary artery disease, gating can help to indicate whether non-reversible defects are artifactual or real, thus reducing the false-positive rate *(DePuey, 1993 and Einser, 1988).*

Fixed defects on myocardial perfusion scans may be the result of soft tissue attenuation, particularly breast attenuation in women. Such artifacts can be a source of false-positive scans and reduced test specificity. Gated technetium99m Sestamibi imaging may help to differentiate attenuation artifacts from areas with truly decreased perfusion (ie, infarcts). Defects resulting from infarction demonstrate decreased wall motion on gated studies, whereas defects resulting from attenuation are associated with normal function *(DePuey, 1993 and Ezekiel, 1992)*. Gated imaging may detect global left ventricular (L.V) dysfunction secondary to non-ischemic cardio-myopathy (primary or cardiomyopathy related to hypertension or substance abuse), or diffuse small vessel disease (such as that found in patients with diabetes).

Functional information provided by the gated study (wall motion) might be useful in the assessment of myocardial viability in patients being considered additional information for risk stratification.

With recent improvements in nuclear medicine computer systems, the added functional information

comes at a minimal additional cost in progressing time. In addition, the ability to obtain perfusion and function information from a single study may obviate the need for additional tests such as radionuclide ventriculography or echocardiography.

AIM OF THE WORK

Aim of this work is to determine the value of gated SPECT "Single Positron Emission Computerized Tomography) as a non-invasive investigation for determination of L.V viability, wall motion, global and segmental function.

CONSEQUENCES OF ISCHEMIA: STUNNING, PRECONDITIONING, HIBERNATION AND THEIR CLINICAL IMPLICATIONS

In experimental studies in the dog, total proximal coronary artery occlusions of up to 15 minutes result in reversible injury, meaning that the myocytes survive this insult. The 15 minutes of ischemia, however, induce numerous changes in the myocardium, including certain monuments to the brief episode of ischemia that may persist for days. One of these monuments is stunned myocardium, which represents "prolonged post-ischemic contractile dysfunction of myocardium salvaged by reperfusion

Episodes of ischemia as short as 5 minutes, followed by reperfusion, protect the heart from a subsequent longer coronary artery occlusion by markedly reducing the amount of necrosis that results from the test episode of ischemia. This phenomenon, called ischemic preconditioning, has been observed in virtually every species in which it has been studied and is a powerful cardioprotective effect.

Ischemic Preconditioning

Definition of ischemic preconditioning:

Although episodes of transient myocardial ischemia can induce the reversible injury of stunned myocardium, they can also protect the heart from extensive necrosis. Murry et al first described the

concept of ischemic preconditioning. In a study reported in 1986, they reported that anesthetized dogs subjected to 40 minutes of circumflex coronary artery occlusion and reperfusion demonstrated a marked reduction of myocardial infarct size when the dogs received 4 brief episodes of 5 minutes of ischemia separated by 5 minutes of reperfusion just before the 40-minute occlusion. It was this reduction in infarct size caused by the previous exposure of the heart to brief episodes of ischemia that was referred to as ischemic preconditioning *(Murry et al., 1986)*

If the duration between the ischemic preconditioning episodes and the long-duration coronary artery occlusion is extended to 24 to 96 hours, however, then the protective effect returns and infarct size is reduced, although not to as great an extent as when the long occlusion occurs shortly after ischemic preconditioning. This later phase of ischemic preconditioning originally was called the second window of protection but now is best called delayed or late preconditioning *(Marber et al.,1993)*

Mechanism(s) of Preconditioning:

The mechanism(s) of ischemic preconditioning appears to be complex and to involve second messenger pathways, as suggested by the pioneering work of Downey's group *(Cohen et al., 2000).* Also, the mechanism of the delayed phase of preconditioning differs in many ways from that of the early phase or

classic preconditioning *(Bolli, 2000).* Myocardium that is fully preconditioned exhibits the striking metabolic changes regarding the metabolic and physiological changes of reversible injury, including a smaller adenine nucleotide pool (ΣAd), ie, Σ(ATP+ADP+AMP), excess intracellular glucose, a creatine phosphate overshoot, and stunning *(Jennings et al., 2001).* In addition, it reacts to a second episode of ischemia much differently than virgin myocardium in that it utilizes ATP and accumulates lactate and H^+ much more slowly. Because low intracellular ATP and high tissue lactate and H^+ are strongly associated with ischemic cell death, it has been postulated that preconditioned tissue dies more slowly because of this reduction in energy demand (*Murry et al., 1990)*

Triggers of Preconditioning With Ischemia:

A trigger is considered to be a substance released during ischemia and possibly during reperfusion that stimulates signaling pathways in the myocytes that cause the changes that allow myocytes to survive a test episode of ischemia longer than virgin myocytes (*Robert et al., 2001).*

Mediators of Preconditioning With Ischemia:

The protective effect caused by ischemia is hypothesized to be caused by a mediator, ie, a change occurring intracellularly as a consequence of the action of a trigger that then somehow protects against ischemia. There are 2 chief candidate mediators: the

K_{ATP} channel (*Downey and Cohen, 2001)* and specific isoforms of protein kinase C (PKC) *(Downey and Yellon, 1997).* The K_{ATP} channel, a channel found in high concentration in the sarcolemma, opens whenever intracellular ATP declines substantially, eg, to the levels found during a 5-minute episode of ischemia in the dog heart. This effect of ischemia can be blocked by pretreatment of the myocardium before the preconditioning episode of ischemia with inhibitors of the K_{ATP} channel, such as glibenclamide and 5-hydroxydecanoate (5HD) (*Yao et al., 1993).* These data support the idea that the K_{ATP} channel is the mediator of the preconditioning effect *(Robert et al., 2001).*

In addition, there is a K_{ATP} channel in the mitochondria. It has been shown that pretreatment with diazoxide pharmacologically preconditions the dog heart and reduces infarct size to much the same extent as preconditioning with ischemia, although this effect is less marked in the in vivo rabbit model *(Pain et al., 2000).*

Adenosine

This nucleoside is released quickly into the extracellular fluid very early in ischemia and is present in concentrations greater than those required to stimulate the receptor. Thus, it is a potential trigger. Also, it has been shown in vivo in both rabbit and dog hearts that adenosine or A_1 agonists of adenosine will pharmacologically precondition the heart against the

effects of a test episode of ischemia (*Liu et al., 1991 and Grover et al., 1992).* Moreover, these effects can be blocked by administration of an inhibitor of the adenosine effect such as 8-(*p*-sulfophenyl)-theophylline or by the K_{ATP} channel inhibitor glibenclamide.

Other Triggers:

Administration of bradykinin (*Wall et al., 1995)* and opioids *(Schultz et al., 1995)* will induce pharmacological preconditioning. Bradykinin and opioids are released during the preconditioning episode of ischemia on a time scale consistent with these agents being involved in the phenomenon.

How Is Myocyte Death Delayed in Preconditioning?

A major mechanism proposed to explain why preconditioned myocytes tolerate ischemia better than virgin myocytes is that the reduced energy demand found in ischemic preconditioned tissue preserves ATP and slows the development of the osmotic load and acidosis (*Murry et al., 1990).* Slowing of the development of these changes, both of which are an invariable accompaniment of ischemic cell death, is consistent with a delay of the transition to irreversibility (*Jennings et al., 1986).* Another unexpected change involves O_2-derived free radicals appearing during reperfusion. Murry et al showed in 1988 that intravenous administration of the free radical scavengers superoxide dismutase and catalase would prevent preconditioning with ischemia in many but not

all dog hearts (*Murry et al., 1988).* These data suggested that free radicals exerted a paradoxical protective rather than deleterious effect in reperfused ischemic myocardium. It was recently suggested that the effect of opening potassium channels in mitochondria with diazoxide and thereby preconditioning the heart is to increase O_2-derived free radical production from the mitochondria. These O_2-derived free radicals could mediate the protective effect through some as yet unknown mechanism that appears to involve mitochondria (*Pain et al., 2000).*

An attempt to show that the mitochondrial ATPase, one of the chief sources of ATP utilization during ischemia, was inhibited more quickly during the prolonged episode of ischemia, a change that would slow ATP depletion, was unsuccessful (*VanderHeide et al., 1996)*

Table (1): Clinical Situations in Which Preconditioning May Occur

Entity	Comment
Repetitive balloon inflations during PTCA	Less chest pain, ST elevation, lactate with sequential inflations. Pharmacological preconditioning may mimic effects of brief ischemia
Preinfarct angina	Associated with smaller infarcts, improved clinical outcomes. Debate in elderly patients
Warm-up phenomenon	Less angina and ECG signs of ischemia when second exercise period occurs after short rest
Studies in human tissue	
Isolated human cardiomyocytes	Exhibit preconditioning-like properties when exposed to simulated ischemia/ reoxygenation. Pharmacological preconditioning has been demonstrated
Isolated human muscle strips	Exhibit preconditioning-like properties and enhanced function with preconditioning ischemia before longer-duration ischemia

(Klonner & Jennings, 2001)

Preconditioning as Therapy

Can ischemic preconditioning be used to treat cardiovascular disorders? Over the past 15 years, a large volume of research has focused on the mechanisms of both early and late ischemic preconditioning *(Bolli, 2000).* Results of these studies have suggested that ischemic preconditioning involves second messenger pathways *(Cohen et al., 2000)*that theoretically could be stimulation and thereby induce the beneficial effects of ischemic preconditioning without ischemia. Conversely, the inhibition of various aspects of these pathways can prevent ischemic preconditioning. Development of preconditioning mimetic agents has shown promise in experimental studies. Examples include adenosine, adenosine agonists, PKC agonists, K_{ATP} channel openers, and NO donors. *(Bolli, 2000).* Translating these beneficial agents to the clinical realm has been tricky, because many of these agents have profound haemodynamic effects. For example, whereas diazoxide, a mitochondrial K_{ATP} channel opener, mimicked preconditioning and reduced cell death in several animal models, it also causes significant hypotension in humans. Nevertheless, some preconditioning mimetic agents already are used clinically, although their use may not be based primarily on the preconditioning concept. Nicorandil is a K_{ATP} channel opener that reduced angina (*Dana et al., 1999).* Adenosine has shown promise when given as an adjunct to cardioplegia; in this setting, it appears to decrease the need for use of

high-dose inotropes after cardiac surgery (*Mentzer et al., 1997).* Adenosine also is being tested as an adjunct to reperfusion in patients with acute myocardial infarction. In the AMISTAD I trial, adenosine reduced infarct size in patients with anterior myocardial infarction. Whether the benefit of adenosine was related to a preconditioning mechanism is not clear, because the drug was given not at pre-occlusion but at reperfusion (*Mahaffey et al., 1999)*

In what clinical scenarios could preconditioning mimetics be useful? Most data in the experimental literature suggest that preconditioning mimetics would need to be given before occlusion to attain a true preconditioning effect with reduction of infarct size at the time of thrombolysis. Unfortunately, this will not be possible in the clinical setting of acute myocardial infarction, unless the patient is taking an oral medicine long-term. And even that might not work, because long-term therapy with a preconditioning mimetic might lead to tachyphylaxis. However, this has never been established experimentally. If tachyphylaxis does not develop, giving preconditioning mimetics to patients at risk of infarction for the purpose of delaying cell death before reperfusion is possible, but only if the agent is relatively nontoxic and has few side effects. Preconditioning mimetic agents clearly can be applied to reduce ischemic damage, when the period of ischemia is controlled and predicted. Two clinical situations that

might benefit from preconditioning mimetics would be before cardiopulmonary bypass or to a heart at the time of removal for transplantation. Providing these agents to patients with unstable angina in which the mimetic might augment the protective effect of angina itself is another area that deserves further study. As mentioned, K_{ATP} channel blockers may show promise in this regard. A preconditioning agent might prevent or reduce the amount of necrosis should the patient develop a myocardial infarction. Such an agent could reduce the amount of ischemia that develops during a high-risk angioplasty procedure in which the occluded vessel supplies a very large risk area. Of course, another approach would be to perform multiple brief balloon inflations that would ischemically precondition the heart. With the advent of stents and perfusion catheters, however, it is unlikely that preconditioning mimetics would have a great practical clinical role in the catheterization laboratory. Finally, preconditioning mimetics might be useful for patients with exercise-induced angina that is not fully controlled by the usual drugs. Taking such agents before an episode of planned exertion might stave off angina. Hence, although preconditioning is one of the most powerful techniques for reducing ischemic necrosis during coronary artery occlusion, its translation into practical use in the clinic will still require significant research and clinical trials before preconditioning mimetics