INTRODUCTION

The importance of detecting viable tissue within dysfunctional myocardium in patients with left ventricular functional impairment due to chronic coronary artery disease has important therapeutic and prognostic implications ***(Rahimtoola 1989; Marwick 1998; Wijns, Vatner et al. 1998).***

Impaired left ventricular function at rest arises in part from regions of ischemic or hibernating myocardium rather than scarred myocardium ***(Braunwald and Rutherford 1986).***

Such asynergic but viable myocardial regions can be identified with radionuclide imaging techniques such as fluorodeoxyglucose metabolic imaging or thallium scintigraphy ***(Dilsizian and Bonow 1993)***. Preserved or enhanced uptake in asynergic myocardial regions identifies viable myocardium ***(Srinivasan, Kitsiou et al. 1998).***

Nitrate Trimetazidine technetium 99-m sestamibi scintigraphy has been proved as a valid sensitive technique in identifying viable myocardium ***(Hafez, 2001)***

Low dose Dobutamine stress echocardiography (DSE) has been demonstrated to be a reliable technique for identification of myocardial viability, but radionuclide myocardial perfusion imaging positron emission tomography remains the reference technique for detection of viable myocardium ***(Pierard, De Landsheere et al. 1990; Bax, Wijns et al. 1997).***

An advantage of positron emission tomography (PET) is the possibility of a quantitative analysis. In contrast, DSE relies on a subjective interpretation of wall motion ***(Hoffmann, Lethen et al. 1996)***. Tissue Doppler imaging (TDI) has been suggested for quantitative analysis of regional myocardial function ***(Katz, Gulati et al. 1997; Hoffmann, Altiok et al. 2002)***. It allows the assessment of local tissue velocities (point velocities). The point velocity of a

specific left ventricular region, however, does not differentiate between active contraction and passive drawing motion related to translation and rotation of the whole heart or contraction of adjacent segments ***(Heimdal, Stoylen et al. 1998)***.

Heimdal, et al. introduced real time strain rate calculation in the longitudinal axis in 1998. Strain rate imaging allows the determination of velocity gradients between two points in space. The resulting contraction variable is independent of passive tethering effects from other regions and therefore appears promising for quantification of regional myocardial function ***(Urheim, Edvardsen et al. 2000)***, ***(Stoylen, Ingul et al. 2003)***. Although the technique has been validated in animal models, there is only little experience in clinical settings ***(Edvardsen, Skulstad et al. 2001; Gotte, van Rossum et al. 2001)***.

AIM OF THE WORK

The aim of this work is to test sensitivity, specificity and quantitative value of strain rate imaging in detection of viable myocardium compared to Nitrate Trimetazidine Technetium 99-m sestamibi scintigraphy.

PATHOLOGICAL AND MOLECULAR BASIS OF MYOCARDIAL ISCHEMIA, STUNNING AND HYBERNATION

With the immense progress in the field of myocardial revascularization over the last two decades, the differentiation of viable from nonviable myocardium has been recognized as an issue of increasing clinical relevance, particularly in patients who are being considered for interventional therapy ***(Dilsizian and Bonow 1993).***

Myocardial viability represents impairment in contractile function that is potentially reversible if blood flow is adequately restored ***(Hoffmann, Lethen et al. 1996)***.

As presumably, improving blood supply to dysfunctional but viable regions results in subsequent improvement in regional and global left ventricular function, heart failure symptoms, functional capacity and long term survival, so an important consideration in re-vascularizing hypokinetic or akinetic myocardial areas is whether they represent viable myocardium with critically endangered local supply - demand balance [ischemia, hibernation or stunning] or whether these areas represent irreversibly damaged, necrotic scar tissue ***(Beller 1996)***. This scenario was supported by the results of several studies in literature where only patients with severe left ventricular dysfunction, that harbored dysfunctional but "viable" myocardium gained most benefit from coronary revascularization ***(Jimenez Borreguero and Ruiz-Salmeron 2003)***.

Myocardial stunning

Post-ischemic dysfunction, or myocardial stunning, is a reversible form of contractile dysfunction that persists after reperfusion despite the absence of irreversible damage and despite restoration of normal or near-normal coronary flow ***(Bolli 1992)***.

It is considered a form of sub-lethal reperfusion injury, whereby reintroduction of oxygen after a period of deprivation as a result of ischemia provokes a transient calcium overload that damages the contractile machinery. The ensuing contractile dysfunction typically lasts for hours or days ***(Kloner 1993)***.The degree of myocardial stunning is determined primarily by coronary stenosis severity, by the degree of attenuation in peak myocardial blood flow as well as by the duration of the antecedent ischemia ***(Barnes and Khan 2003)***.

Molecular basis for myocardial injury

The Sarcolemma, with consequent loss of selective permeability, impairment of calcium- stimulated ATPase activity, calcium transport out of the cell and impairment of Na+, K+-ATPase activity (the net result of these perturbations would be increased trans-sarcolemmal calcium influx and cellular calcium overload). The Sarcoplasmic Reticulum, with consequent impairment of calcium - stimulated ATPase activity and calcium transport. This would result in impaired calcium homeostasis, decreased calcium sequestration, increased free cytosolic calcium, decreased calcium release during systole, and finally excitation - contraction uncoupling.

Other Structures such as the extracellular collagen matrix (with consequent loss of mechanical coupling) or the contractile proteins (with consequent decreased sensitivity to calcium) ***(Bolli 1990).***

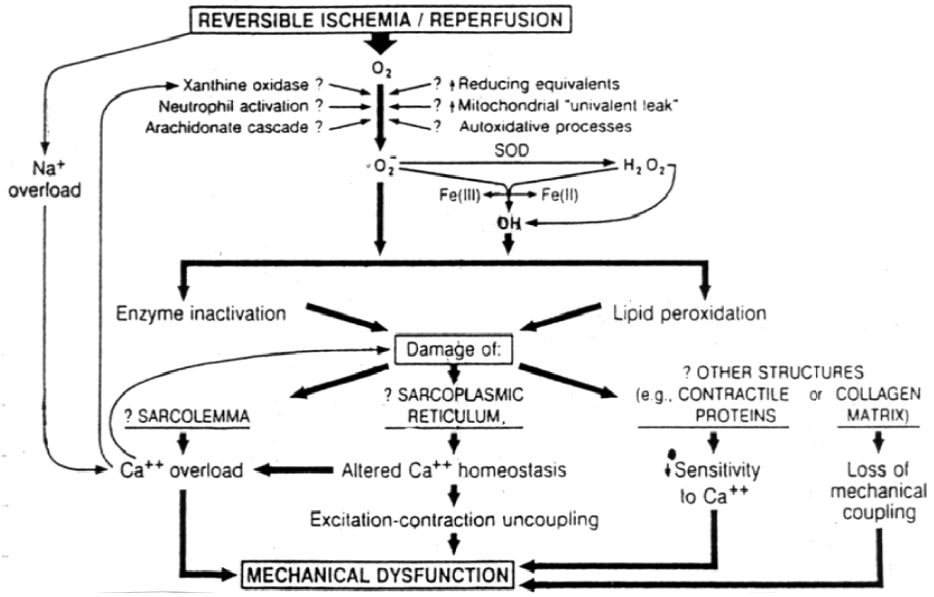

Figure 1: A diagram illustrating a proposal for the pathogenesis of post ischemic myocardial dysfunction that integrates and reconciles different mechanisms into a unifying pathogenetic hypothesis: Transient reversible ischemia followed by reperfusion results in increased production of superoxide radicals (O2-) through several mechanisms, including 1) increased activity of xanthine oxidase, 2) activation of neutrophils, 3) activation of arachidonate cascade, 4) accumulation of reducing equivalents during oxygen deprivation, 5) derangements of intra-mitochondrial electron transport system resulting in increased univalent reduction of oxygen, and 6) auto-oxidation of catecholamines and other substances. Superoxide dismutates (SOD) dismutates O2- to hydrogen peroxide (H2O2) in the presence of catalytic iron, O2- and H2O2 inter-react in a Haber- Weiss reaction to generate the hydroxyl radical (OH). H2O2 can also generate OH in the absence of O2- through a Fenton reaction provided that other substances (such as ascorbate) reduce Fe (III) to Fe (II). O2- and OH attack proteins and polyunsaturated fatty acids, causing enzyme inactivation and lipid peroxidation, respectively. In reversible ischemia, the intensity of this damage is not sufficient to cause cell death but is sufficient to produce dysfunction of key cellular organelles (Quoted from Bolli, 1990).

At the same time, ischemia - reperfusion causes cellular Na+ overload. This could further exaggerate calcium overload by increased Na+ - Ca2+ exchange. An increase in free cytosolic calcium would activate phospholipases and other degenerative enzymes and further exacerbate the injury to the fore-mentioned key sub-cellular structures (sarcolemma, sarcoplasmic reticulum and contractile proteins). In addition, calcium overload could in itself impair contractile performance and contribute to mechanical dysfunction. The ultimate consequence of this complex series of perturbations is a reversible depression of contractility. ***(Bolli 1990).***

Insufficient energy production by mitochondria. Impaired energy use by myofibrils (Arnold, Braunwald et al. 1985; Ambrosio, Jacobus et al. 1987).

Impairment of sympathetic neural responsiveness: this hypothesis has been refused by demonstrating that myocardial stunning can occur in isolated (and thereby denervated) hearts (Heusch, Ferrari et al. 1997)

Damage of extracellular collagen matrix: Collagen damage may contribute to myocardial stunning after multiple ischemic episodes but is unlikely to be a causative factor after a single completely reversible one (Bolli 1990).

Decreased sensitivity of myofilaments to calcium: In vitro studies have postulated two major abnormalities in calcium and myofilament interaction to account for stunning namely (a) reduced maximal calcium activated force development and (b) reduced calcium sensitivity (shortening response per unit change in intracellular calcium). Much of this data is controversial as in vivo studies demonstrated that when the stunned myocardium is challenged with inotropic stimuli (which act by raising intracellular free calcium concentration); it exhibits a normal or near-normal contractile reserve ***(Heusch and Schulz 1997; Chandrashekhar, Prahash et al. 1999).***

In 2000, Korvald, et al. hypothesized that the link between stunning and inefficient contractile work can best be explained by damages to the contractile apparatus and that energetic changes due to alterations in oxidative metabolism or excitation -contraction coupling seem to be of minor importance ***(Korvald, Elvenes et al. 2000).***

The time course of recovery of myocardial contractile function, ATP concentration and ultra-structural changes is still poorly known but has been shown to span between one and two weeks after reflow ***(Gerber, Wijns et al. 1999).***

Myocardial hibernation

Hibernating myocardium is an exquisitely regulated tissue adapting its activity to prevailing circumstances ***(Hearse 1994).***

Proposed theories of myocardial depression in hibernation:

Depression of Contractile Function in hibernation is myocardium cumulative stunning or persistent ischemia or both. Cumulative stunning as a plausible mechanism for chronic myocardial hibernation, Kalra et al., reported that following coronary revascularization, baseline myocardial blood flow remains unchanged, whereas coronary vasodilator reserve is significantly improved. These findings confirm the hypothesis suggesting that continuing and sustained ischemia is unlikely to be the trigger for hibernation ***(Kalra and Zoghbi 2002)***.

More probably, the myocardium is subjected to repetitive, intermittent episodes of reversible ischemia either exercise-induced or related to primary reductions in coronary blood flow such as plaque events, vasoconstriction, and platelet aggregation. In the face of reduced coronary flow reserve, any imposition of stress would result in an imbalance between oxygen demand and supply and consequently precipitate myocardial ischemia. Upon recovery, myocardial stunning is manifested, which, when repeated, culminates in hibernating myocardium and a state of persistent post-ischemic dysfunction ***(Camici and Rimoldi 1999).***

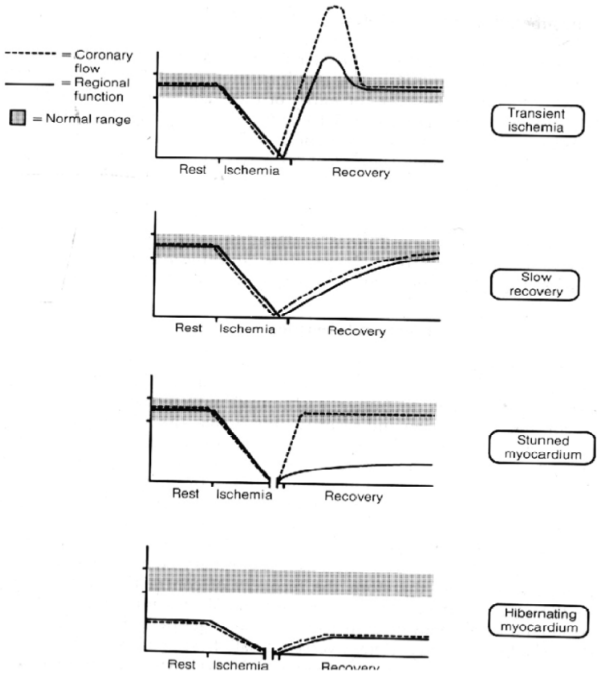

Figure 2: Recovery of regional function after ischemia. The transient ischemic attack is usually followed by complete reactive hyperemia with a post - ischemic contractile rebound (transient ischemia). In the presence of a severe coronary stenosis in the ischemia - producing artery, a slow and partial contractile recovery can be observed (slow recovery). Flow and function remain uncoupled in the stunned myocardium, while they are symmetrically affected in the hibernating myocardium (Quoted From Picano, 1997).

Edwards et al observed that persistent subendocardial hypoperfusion (which may be undetected by the transmural flow measurements with PET) leads to a diminished endocardial perfusion reserve severe enough to cause profound hypokinesis ***(Edwards, Sinusas et al. 1992)***.

Schulz reported that 40 - 50% of patients with coronary artery disease and hibernating myocardium have both reduced baseline flow as well as super-imposed repetitive episodes of stress induced ischemia with subsequent stunning in their daily life ***(Schulz and Heusch 2000).***

Hemodynamic consequences of ischemia and reperfusion

Ischemia is defined as a reduction in rest myocardial blood flow sufficient enough to cause a decrease in myocardial contraction ***(Ross, Gallagher et al. 1986).*** Because of the small extraction reserve of oxygen, decreases in coronary blood flow rapidly translate into decreases in contractile performance. The myocytes are very sensitive and smart cells; as soon as they experience hypoxia or low perfusion, they down-regulate their contractile function to achieve supply- demand balance ***(Al-Khouri and Narula 2000).*** Recovery of regional function after ischemia, (Figure 1), is related to the length of ischemia and, for a given length, to the underlying anatomical conditions of the ischemia - producing artery ***(Picano, Lattanzi et al. 1997)***.

Reperfusion after very short periods of low coronary flow (less than 10 minutes) usually results in rapid and complete restoration of cardiac performance. There is no necrosis and myocardial ultra-structure is normal. On the other hand, when a severe reduction of coronary blood flow persists for more than 20 minutes, myocardial necrosis begins to develop and a "point of no return" is achieved beyond which the restoration of flow is unable to restore regional function due to irreversible myocardial cell damage ***(Vanoverschelde and Melin 1999).***

Between fully reversible ischemia and ischemia lasting more than 20 minutes and invariably associated with necrotic phenomena, there is a blurred transition zone where ischemia is too short to cause myocardial necrosis but long enough to induce a persistent contractile dysfunction - lasting for hours, days and even weeks - after the restoration of flow: the so - called myocardial stunning ***(Picano, Lattanzi et al. 1997).***

With a persistently reduced resting myocardial perfusion due to a critical coronary artery stenosis (for months or years) which is,

however, beyond the critical threshold indispensible to keep the tissue viable, the cardiac myocytes adapt themselves to this chronically reduced energy supply by turning their basal metabolic rate to minimal, which is sufficient for survival but inadequate for meaningful systolic activity. This sustenance state is referred to as hibernating myocardium where hibernating myocytes are viable metabolically active cells but with reduced or abolished contractile function ***(Shivalkar, Flameng et al. 1999; Al-Khouri and Narula 2000).***

Role of Coronary Perfusion Pressure in Hibernation

Alternatively, chronic dysfunction could result from a chronic decrease in coronary perfusion pressure in the post-stenotic bed as coronary pressure has been shown to regulate contractile performance acutely, even in the absence of changes in coronary flow ***(Vanoverschelde, Wijns et al. 1997).***

Ischemic Preconditioning:

Myocardial ischemia plays a central role in the development of myocardial hibernation, so it is possible that one of the mechanisms by which clinically hibernating myocardium survives the disturbance in myocardial blood flow is by being preconditioned ***(Redwood, Ferrari et al. 1998).***

Ischemic preconditioning is a condition by which ischemic myocardium becomes primed or preconditioned by a preceding transient episode of ischemia followed by reperfusion where it downgrades its energy requirements and thus becomes more tolerant at facing a subsequent more prolonged episode of ischemia (i.e. develops less ischemic injury). This phenomenon may also be triggered if the onset of the lethal ischemia is gradual (sub lethal)

rather than sudden, so called intra-ischemic preconditioning ***(Ito 1995).***

Apoptosis in Hibernating Myocardium:

Elsasser, et al. reported that apoptosis, which is the genetically programmed cell death, could be involved in the pathogenesis of chronic myocardial hibernation. ***(Elsasser, Schlepper et al. 1997)***. Although direct histological demonstration of apoptotic cell death in the hibernating myocardium has never been made conclusively, indirect markers of apoptosis, such as DNA fragmentation, have recently been found in some of the more severely affected hibernating cardiac myocytes ***(Valen 2003).***

Continued low grade ischemia, particularly in the subendocardial layers, has been recently proposed as the main trigger for the process of apoptosis through mechanisms that are similar to those in left ventricular remodeling ***(Valen 2003).***

So, reversible ischemia in an area of chronically reduced coronary flow reserve induces regional myocytes loss via an apoptotic mechanism; thus contributing to the progression of chronic coronary disease to heart failure. These observations would probably change the way investigators currently think about myocardial hibernation i.e. as a successful adaptive mechanism by which the myocardium preserves its integrity despite repeated ischemic insults. This would also explain why in some patients with severe structural changes, functional recovery following revascularization remains modest and in the end, largely incomplete ***(Lim, Fallavollita et al. 1999).***

Clinical Importance of Hibernation:

Clinical syndromes consistent with the existence of myocardial hibernation include unstable and stable angina **(Shivalkar, Maes et al. 1996),** acute myocardial infarction **(Adams,**

Norton et al. 1996), left ventricular dysfunction with or without congestive heart failure **(Louie, Laks et al. 1991)** and the ALCAPA syndrome (anomalous left coronary artery from the pulmonary artery) **(Rahimtoola 1997).**

Interrelation between Stunning and Hibernation:

Although their separation is clear-cut from the conceptual and pathophysiological viewpoint, stunning and hibernation are sometimes undistinguishable in the clinical setting. They can coexist in the same patient in space (with islands of hibernated and stunned tissue interspersed with necrotic and / or normal cells) and in time (with early phenomena of acute stunning progressively leading to chronic hibernation, as may occur after an acute myocardial infarction with critical residual stenosis of the infarct related artery). Thus the markedly hypokinetic or akinetic region, which is the target of our diagnostic efforts to recognize myocardial viability, can have a continuous spectrum of damage, from mild to irreversible. So what is clinically important is the distinction between asynergic viable and asynergic but necrotic segments **(Picano, Lattanzi et al. 1997).**

Introduction for imaging for hibernating myocardium

Various approaches have been proposed to predict the reversibility of left ventricular dysfunction after coronary revascularization. These methods rely on assessing basic cellular mechanisms that are known to play a central role in the recovery of systolic function after coronary revascularization. These include sufficient resting myocardial perfusion; maintained cell membrane integrity; preserved metabolic machinery and recruitable inotropic reserve. These phenomena are identified by using either nuclear perfusion imaging modalities [in the form of thallium scintigraphy and positron emission tomography] or by means of pharmacologic

echocardiographic stress testing ***(Vanoverschelde, D'Hondt et al. 1996).***

Pharmacologic stress echocardiography has gained wide acceptance because of its safety, feasibility, diagnostic accuracy and prognostic power as regards the identification of viable myocardium ***(Marwick 2003).***

Low dose dobutamine echocardiography has been an attractive and increasingly used method of identifying viable myocardium through its ability to elicit a β-adrenoreceptor mediated increase in myocardial thickening ***(Grayburn and Hillis 2003).***

DOPPLER AND TISSUE DOPPLER IMAGING

Historical perspective

The Doppler principle was identified, described and analyzed in 1842 in Austria by Christian Doppler, a mathematical professor who was used this method to study these phenomenon on basic science especially physics and astronomy. One century later, ***Setomura*** applied this technique first in the assessment of blood flow velocity in peripheral vessels in 1956 ***(Sutherland, Stewart et al. 1994).***

The story of pulsed wave Doppler tissues imaging (PWDTI) started in Japan in the mid 1980s through the experimental color Doppler visualization of dynamic plaque motion detected by color M-mode and 2D- echocardiography ***(Derumeaux 2000).*** In 1989, ***Karl isaaz*** used a conventional Doppler ultrasound instrument with pulsed Doppler capability and he was able to obtain and describe the normal pulsed Doppler profile of the LV myocardial wall in the parasternal long axis view ***(Sutherland, Stewart et al. 1994).***

The method of strain rate imaging by tissue Doppler was developed at the Norwegian University of Science and Technology in Trondheim, Norway. It was the subject of two doctoral theses, one in technology and one in medicine, and was a result of a successful cooperation between technical research (in strain and velocity gradients) and medical research (in long axis function of the left ventricle ***(Stoylen, Slordahl et al. 2001).*** One of the important points of long axis function had lead to Strain Rate Imaging being applied to longitudinal velocity gradients, thus making the rough method more robust, as well as all segments of the ventricle available for analysis ***(Heimdal, Stoylen et al. 1998).*** The method was originally validated in a mechanical model, in cooperation with the Leuven University, Belgium and described in a method article