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Improvement of ischaemic left ventricular dysfunction in a clinical setting

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Aim of this study was to investigate the effects of nisoldipine on regional myocardial bloodflow (MBF) in dyssynergic but viable myocardium after myocardial infarction (MI). 15 patients with isolated left anterior descending coronary (LAD) stenosis were studied 1 month after first MI. Patients underwent F18-deoxyglucose imaging, while MBF was measured using positron emission tomography and ¹³N-ammonia, at baseline and following dobutamine infusion (10 mcg/Kg/min over 5 min, DOB). MBF measurements were repeated 24 hours later after nisoldipine (10 mg bid). Among a total of 132 LAD related regions, 30 showed normal wall motion at 2D-echo and normal metabolic activity, 68 showed wall motion abnormality and preserved deoxyglucose uptake, while 32 dyssynergic regions were necrotic.

Reduced baseline MBF values were found in necrotic and dyssynergic viable regions but only viable regions maintained residual perfusion reserve. After nisoldipine treatment a significant improvement in baseline MBF occurred only in viable segments. Thus, in dyssynergic viable myocardium, nisoldipine selectively improved basal perfusion. *J Clin Basic Cardiol 1999; 2: 61-3.*

Key words: hibernation, nisoldipine, heart, ischaemia

The pathogenetic mechanism of myocardial hibernation has not been fully established. Wall motion abnormalities, occurring early after an acute myocardial infarction, may be reversible or permanent [1]. Thrombolytic therapy increases the probability of early reperfusion and may increase the probability of reversible dysfunction [2]. The infarcted segments may show resting hypoperfusion, despite a preserved viability, and functional recovery once perfusion is restored by coronary angioplasty or grafting [3]. Because enhanced left ventricular function after revascularization is associated with improved survival [4], diagnostic procedures that identify reversible dyssynergy may provide significant prognostic information [5]. Recent studies have shown that the presence of both viable and ischaemic myocardium detected by positron emission tomography is associated with increased incidence of cardiac events at follow-up.

Stress echocardiography has recently gained widespread use for the detection of viability and ischaemia. Low dose dobutamine has been shown to improve wall thickening suggesting myocardial viability in dyssynergic segments after myocardial infarction.

The deterioration of contractility in these segments at high doses of dobutamine is a sign of myocardial ischaemia, and this finding correlates with significant residual stenosis in the infarct-related artery.

Positron emission tomography (PET) provides improved imaging capabilities compared with single photon emission computed tomography (SPECT) by correcting for photon attenuation and permitting the noninvasive measurement of regional myocardial blood flow (in absolute terms and myocardial substrate utilisation). Viable myocardium is identified on the basis of enhanced or preserved metabolic activity in underperfused and dysfunctional myocardial regions [6]. In animal models β -adrenergic stimulation improves contraction in areas of reversible postischemic dysfunction [7, 8]. In patients with critically stenosed coronary arteries the administration of a positive inotropic agent may merely increase myocardial demand in the setting of reduced coronary flow reserve, thereby producing myocardial ischaemia and persistent

regional dysfunction. Despite this conceptual limitation, recent studies have demonstrated that echocardiography and dobutamine at a low dose could be used to identify dyssynergic but viable myocardial segments [9] and to predict accurately the extent of recovery in revascularized patients [10]. In the absence of new myocardial infarction, progressing ventricular remodeling and/or myocardial ischaemia in areas adjacent to the myocardial necrosis or in other areas in patients with multivessel disease are likely to play an important role in progressive deterioration of left ventricular function [11]. Even in the absence of clinical signs of active ischaemia, the presence of dysfunctional viable chronically underperfused myocardium (hibernating myocardium) may create a vicious circle inducing calcium overload and diastolic dysfunction [12].

Nisoldipine, a second-generation calcium antagonist, can dilate the coronary arteries and improve both systolic and diastolic function in hypokinetic areas, and therefore represents a potentially effective drug in the management of postischaemic viable myocardium [13].

The present study was undertaken to assess the effects of oral nisoldipine on myocardial blood flow in basal conditions and after dobutamine in dyssynergic but viable segments.

Methods

Between January 1993 and June 1994 15 patients were selected from those admitted to the Department of Cardiology of the University of Genova with a diagnosis of acute myocardial infarction. After about 1 month, the same patients were readmitted to the CNR Institute of Clinical Physiology in Pisa to perform the PET study.

Inclusion criteria were informed consent, ≤ 75 years of age, diagnosis of acute anterior myocardial infarction defined on the basis of typical prolonged chest pain, peak creatinine kinase > 2 SD above normal, ≥ 1.0 -mm ST segment elevation in ≥ 2 precordial leads on the initial electrocardiogram (ECG), first infarction with dyssynergy in the territory of left anterior descending coronary artery, and presence of coronary artery disease confirmed by angiographic evidence of single vessel

narrowing ($\geq 70\%$) of the infarct related artery with no occlusion.

Exclusion criteria were technically difficult echocardiogram, significant valvular disease, postinfarction angina or infarction complicated by severe haemodynamic instability, uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and diastolic blood pressure > 110 mmHg), sustained ventricular tachycardia or ventricular fibrillation, and history of adverse reaction to dobutamine or calcium antagonists. Diabetic patients and patients who requested concomitant therapy with inotropic drugs were also excluded.

None of the 15 patients received beta-adrenergic blocking drugs or inotropic agents before the study.

Diagnostic procedures

Coronary angiography and ventriculography

Coronary cineangiograms were performed using Judkin's technique. All coronary stenoses were evaluated by 2 blinded investigators.

Selective injection of left and right coronary arteries was performed in multiple orthogonal views. The culprit lesion was identified by angiographic criteria for thrombus or severity of stenosis.

The percent luminal diameter stenosis was derived using the caliper technique, by comparing the diameter of the stenosis with that of the most normal-appearing region proximal to the stenosis.

Significant lesions were defined as $\geq 70\%$ diameter on an epicardial coronary artery or a major branch vessel.

Dobutamine echocardiography

Dobutamine echocardiography was performed between 7 and 10 days after the infarction and repeated 1 month later just before PET. Patients were placed in the left lateral decubitus position and dobutamine echocardiography images were obtained using commercially available equipment. Dobutamine was infused intravenously at 5 and 10 $\mu\text{g/kg/min}$ over 5 minutes.

Echocardiography was recorded at baseline and 2 minutes after each dose of dobutamine.

Arterial blood pressure (cuff manometer) and 12-lead ECG were recorded at baseline and every 5 minutes. The regional wall motion was assessed according to the American Society of Echocardiography recommendations.

Positron emission tomography

The PET study included both metabolic imaging using [^{18}F] fluorodeoxyglucose (FDG) and quantitation of myocardial blood flow by [^{13}N] ammonia. FDG was injected after a glucose load to assess FDG utilization in viable tissue. Viable segments were compared with those assessed by dobutamine echocardiography, which showed improvement of previously abnormal wall motion.

ECG was monitored throughout the procedure, blood pressure, heart rate, and blood samples for assay of substrate availability (free fatty acids, glucose, ketone bodies, lactate) and insulin levels were taken at the time of FDG administration. Myocardial metabolic rate (glucose utilization) was measured from the FDG images by Patlak graphical analysis of the image data. [^{13}N] ammonia was injected at baseline (15 mCi) and 50 minutes later, during dobutamine infusion. Then the effects of oral nisoldipine 10 mg twice daily on myocardial blood flow at rest and during dobutamine were studied. The following parameters were examined after PET: areas with abnormal substrate utilization; regional myocardial metabolic rate of

glucose utilization in these areas; absolute myocardial blood flow (specific flow) in mL/min/g of the septal, anterior, and posterolateral walls of the left ventricle; the effects of dobutamine on myocardial blood flow; the effect of nisoldipine on both resting and dobutamine myocardial blood flow; correlations between the metabolic pattern and myocardial blood flow.

Results

Clinical and haemodynamic findings

No patient had important side effects as a result of the study. Baseline and dobutamine rate pressure products were quite similar during echo and during tomographic acquisitions; dobutamine administration increased rate pressure product modestly but significantly. No patient showed diagnostic ST-T segment changes nor complained of chest pain during both dobutamine echocardiography and positron emission tomographic study. Nisoldipine administration did not induce significant changes in rate pressure product both at baseline and following dobutamine.

Wall motion data

Among the total of 180 segments analysed in the 15 patients, 48 regions were remote to infarction and showed normal wall motion in all cases. Among the 132 regions supplied by the left anterior descending coronary artery, 31 showed normal regional function, while 101 showed baseline wall motion abnormalities scored as hypokinesis or akinesis in 45 and 56 segments respectively.

On the basis of FDG uptake, 99/132 (75%) of segments supplied by the left anterior descending coronary artery were scored as viable. The prevalence of necrotic segments increased together with the severity of dysfunction: in fact, a reduced deoxyglucose uptake was observed in 1/31 (3%), 8/45 (18%) and 24/56 (43%) of regions with normal wall motion, hypokinesis and akinesis, respectively.

Blood flow was higher in these 99 viable segments than in the 33 necrotic regions (0.72 ± 0.28 vs 0.46 ± 0.18 mL.min $^{-1}$.g $^{-1}$, respectively, $p < 0.01$). Dobutamine regional myocardial blood flow values showed an even larger difference (0.98 ± 0.39 vs 0.58 ± 0.27 mL.min $^{-1}$.g $^{-1}$, respectively, $p < 0.01$).

Effect of nisoldipine on resting perfusion

Nisoldipine administration was well tolerated in all patients. Resting myocardial blood flow showed a significant increase in viable dyssynergic territories (from 0.65 ± 0.27 to 0.77 ± 0.26 mL.min $^{-1}$.g $^{-1}$, $p < 0.01$). By contrast, resting perfusion did not show any change both in dyssynergic necrotic segments (from 0.47 ± 0.20 to 0.48 ± 0.22 mL.min $^{-1}$.g $^{-1}$, ns) and in viable regions with normal wall motion (from 0.76 ± 0.27 to 0.79 ± 0.24 mL.min $^{-1}$.g $^{-1}$, ns).

Interestingly, when all viable segments supplied by the left anterior descending coronary artery were considered, a significant inverse relationship was observed between resting perfusion and percent flow increase induced by nisoldipine ($r = -0.62$, $p < 0.01$). By contrast this relationship was not observed when necrotic regions were analysed ($r = -0.32$, ns).

Relationship between wall motion and blood flow in viable myocardium

When all segments with preserved deoxyglucose uptake were considered, regions with wall motion abnormalities showed a lower resting blood flow than regions with normal contractile function (0.65 ± 0.27 vs 0.83 ± 0.26 mL.min $^{-1}$.g $^{-1}$, respectively, $p < 0.01$). The degree of dysfunction was correlated with the degree of hypoperfusion; in fact, akinetic segments

showed lower baseline flow values than areas with either hypokinesis or normal wall motion at rest.

Both groups of segments showed a significant vasodilation in response to inotropic stimulation ($154 \pm 55\%$ vs $150 \pm 51\%$, respectively, ns), however dyssynergic regions still showed lower dobutamine flow values than segments with normal wall motion.

Interestingly, these two groups of regions showed a different response to nisoldipine. In fact, dyssynergic segments showed a higher vasodilation in response to this calcium-channel blocker than segments with normal wall motion ($126 \pm 37\%$ vs $104 \pm 34\%$, respectively, $p < 0.01$). As a consequence, the reduction in baseline flow observed in dyssynergic segments was no longer observed following nisoldipine (0.77 ± 0.26 vs $0.82 \pm 0.25 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$, respectively, $p < 0.01$).

Discussion

These data suggest that nisoldipine selectively enhances blood flow in myocardial regions with resting hypoperfusion and dysfunction, whereas no significant flow change can be detected in regions supplied by angiographically normal coronary arteries, in infarction-related regions with preserved blood flow and function, or in necrotic regions. In necrotic regions, no changes in resting or dobutamine blood flow were observed after nisoldipine, which suggests that when measured by a method such as PET, the selective action of vasoactive drugs can be identified. Interestingly, a large overlap was observed in the degree of resting hypoperfusion between necrotic and viable regions; however, regional dyssynergy was also observed in segments with relatively preserved baseline blood flow, which suggests the persistence of myocardial stunning at the time of the study (1 month after acute infarction).

These findings strengthen the relevance of metabolic imaging with PET in the detection of myocardial viability. Moreover, the possibility of obtaining absolute measurements of regional myocardial blood flow renders this methodology a powerful tool to evaluate accurately the effects of drugs used in coronary artery disease. In fact, using PET, we observed that nisoldipine selectively ameliorates perfusion in hibernating myocardium without affecting the microvascular reactivity of myocardial regions not characterized by resting hypoperfusion. Several studies reported the relevance of chronic flow reduction in the pathogenesis of contractile dysfunction in hibernating myocardium. It is now well recognized that hypo-

perfused myocardium can down-regulate its own contractile performance to meet reduced blood flow supply [14]. Although this mechanism can probably prevent the occurrence of necrosis, the reduction in overall cardiac function can induce further pathophysiological changes leading to an increased risk of cardiac death.

References

1. Wilson JL, Ramathan KB, Ingram LA, Mirvis DM. Effects of residual stenosis on infarct size and regional transmural myocardial blood flow after reperfusion. *Am Heart J* 1988; 116: 1523-9.
2. Ress JCJ, Simoons ML, Van der Wall EE, Van Eeinge MJ, Vermeer F. Long term improvement in global left ventricular function after early thrombolytic treatment in acute myocardial infarction: report of a randomized multicenter trial of intracoronary streptokinase in acute myocardial infarction. *Br Heart J* 1986; 56: 414-21.
3. Chatterjee K, Swan HJC, Parmely WW, Sustaita H, Marcus HS. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. *Circulation* 1973; 47: 276-86.
4. Alderman EL, Fisher LD, Litwin P, Kaiser GC, Myers WO. Result of coronary artery surgery in patients with poor left ventricular function (CASS). *Circulation* 1983; 68: 785-95.
5. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation* 1993; 87: 1-20.
6. Tillish JH, Brunken R, Marshall R, Schwaiger M, Mandelkorn M. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986; 314: 884-8.
7. Ellis SG, Wynne J, Braunwald E, Henschke CI, Sandor T. Response of reperfusion-salvaged, stunned myocardium to inotropic stimulation. *Am Heart J* 1984; 107: 13-9.
8. Mercier JC, Lando U, Kanmatsuse K, Ninomiya K, Meerbaum S. Divergent effects of inotropic stimulation on the ischemic and severely depressed reperfusion myocardium. *Circulation* 1982; 66: 397-400.
9. Smart SC, Sawada S, Ryan T, Segar D, Atheron L, Berkovitz K, Bourdillon PDV, Feigenbaum H. Low dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction. *Circulation* 1993; 88: 405-15.
10. Barilla F, Gheorghide M, Alam M, Khaja F, Goldstein S. Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization. *Am Heart J* 1991; 12: 1522-31.
11. McKay RG, Pfeffer MA, Pasternak RC. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. *Circulation* 1986; 74: 693-702.
12. Sharpe N, Smith H, Murphy J, Hannan S. Treatment of patients with symptomless ventricular dysfunction after myocardial infarction. *Lancet* 1988; i: 256-9.
13. Pouler H, Van Eyll C, Gume O, Rousseau F. Analysis of the mechanism underlying the changes in left ventricular filling dynamics during oral nisoldipine therapy in patients with anterior myocardial infarction. *Eur Heart J* 1992; 13: 952-9.
14. Bristow JD, Arai AE, Anselone Panteley GA. Response to myocardial ischemia as a regulated process. *Circulation* 1991; 84: 2580-7.

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