Assessment of Myocardial Viability by Pharmacological Stress Echocardiography

Summary of PhD thesis

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INTRODUCTION

When facing dangerous environmental situations, most animal species react with a sympathoadrenergic "fight or flight" activation; others - like the opossum - react with a vagal sympathoinhibitory discharge, or "playing dead" reaction, which in this way discourages possible predators. The myocardium reacts to dangerous situations with an opossum-like behavior. In several "altered myocardial states" (ischemia, hibernation, stunning), when the local supply-demand balance of the cell is critically endangered, the cell minimizes energy expenditure used for development of contractile force (accounting at rest for about 60% of the high energy phosphates produced by cell metabolism) and utilizes whatever is left for the maintenance of cellular integrity. The echocardiographic counterpart of this cellular strategic choice is the regional asynergy of viable segments. The depressed function is undistinguishable from infarction state: but, differently from necrosis, the segmental dysfunction can be transiently normalized by the proper inotropic stimulus.

A blurred transition zone exists between the fully reversible ischemia and the ischemia lasting more than 15-20 minutes invariably associated with necrotic phenomena. Within this gray zone, 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. The stunned myocardium is different from "hibernated" myocardium, in which myocardial perfusion is chronically reduced (for months or years), but remains beyond the critical threshold indispensable to keep the tissue viable - although with depressed performance. While in the stunned myocardium a metabolic alteration causes an unbalance between energy supply and produced work, the hibernating myocardial cell adapts itself to a chronically reduced energy supply, and its survival is guaranteed by a reduced or abolished contractile function. Rahimtoola referred to the hibernating heart as a "smart heart", appropriately down-regulating its biochemical and physiological activity as an act of self preservation aimed at ensuring the long-term survival of the anatomical and physiological integrity of its constituent cardiac cells.

The persistent but reversible post-ischemic dysfunction was initially an experimental observation - described by Heyndrix and later popularized with the successful term of myocardial stunning by Braunwald in 1982. Conversely, myocardial hibernation was a clinical impression - copyrighted by a cardiac surgeon, Rahimtoola, to describe hearts with severely depressed resting preoperative function spectacularly recovering following revascularization.

Although their separation is clear-cut from the conceptual and pathophysiologic 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 it may occur after an acute myocardial infarction with critical residual stenosis of the infarct related artery). What is clinically important is the separation between asynergic viable and asynergic but necrotic segments.

The clinical cardiologist can address this issue with a variety of imaging techniques, including nuclear and echocardiographic methods. The markedly hypokinetic or akinetic region, which is the target of our diagnostic efforts of recognition of myocardial viability can have a continuous spectrum of damage, from mild to irreversible. The different diagnostic probes sample different markers of viability cascade. If a function is strictly essential to cell survival - for instance, cell membrane integrity - it will be lost only for advanced, close to irreversible, degrees of damage. Conversely, other functions, such as functional response to low level inotropic stimulation, indicate that the damage is limited, and the segment is highly likely to recover. The hibernation has different depth, like sleep stages, which correspond to different progressive levels of myocardial damage and decreasing chances of detecting a prompt functional recovery upon revascularization.

segments. Accordingly, the principal aim of our work was to develop alternative pharmacological stress echocardiography methods for viability detection:

1. To assess the potential of an "infra-low' dose of dipyridamole to selectively identify myocardial viability, independently evaluated by low dose dobutamine.
2. To determine the flow-function relationship during coronary vasodilatory stress in patients with coronary artery disease and baseline dysfunction.
3. To evaluate the effects of combined administration of infra-low dose dipyridamole and low dose dobutamine on assessment of myocardial viability.
4. To investigate the relation between radioisotopic and echocardiographic markers of myocardial viability and their correlation with functional recovery after coronary revascularization.
5. To assess the prognostic value of myocardial viability recognized as a contractile response to vasodilator stimulation in patients with left ventricular dysfunction in a large scale, prospective, multicentre, observational study.

RESULTS

1. Forty patients with history of myocardial infarction, angiographically proven coronary artery disease, and resting wall motion dyssynergy on the left ventricle were studied with low dose dobutamine echo (5μ/kg/min followed by 10 μg/Kg/min, each step lasting 3 min) and with an infra-low dose dipyridamole (0.28 mg/Kg over 4 min) echocardiography. Coronary revascularization was performed in 22 patients. Of the 243 segments with baseline dyssynergy, 70 were responders (improved wall motion) with both dipyridamole and dobutamine, 157 were non responders with both dipyridamole and dobutamine; and 16 showed discordant results. The overall concordance of dipyridamole and dobutamine was 93%. Using funcional recovery after revascularization as a gold standard, The sensitivity of dipyridamole and dobutamine was 76% and 78%, respectively (p=ns). The specificity of both tests was 94%.

2. Thirty-four patients with rest wall motion dyssynergy by two-dimensional echocardiography and with angiographically proved coronary artery disease underwent in combination with two-dimensional echocardiographic monitoring: 1) low dose (5 to 10 μg/Kg per min over 3 min) dobutamine infusion; 2) infra-low dose (0.28 mg/Kg over 4 min) dipyridamole infusion; 3) combination of infra-low dose dipyridamole infusion immediately followed by low

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