The Dog Model of Left Ventricular Remodeling After Myocardial Infarction

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ABSTRACT

Background: For over a century, the dog model has been used widely in research studying cardiovascular physiology pertinent to humans. It has been specially applied, over the past 2 decades, in research on the pathophysiology and treatment of left ventricular (LV) remodeling and heart failure.

Methods and Results: Because progressive LV remodeling and the march to heart failure are major problems facing myocardial infarction (MI) survivors, the dog model of acute MI was modified for the study of LV structural remodeling and dysfunction during post-MI healing (especially anterior MI). The dog model of post-MI LV remodeling, as the other models, has contributed to our understanding of the pathophysiology of LV remodeling and underlying mechanisms, and to the development of improved therapeutic strategies. Recent increase in costs and public concern over their use in research should be considered when using this model.

Conclusions: This is an important model for studying strategies to prevent severe LV remodeling in humans.

Key Words: Healing, reperfusion, echocardiography, collagen.

Introduction

Models for studying left ventricular (LV) remodeling after myocardial infarction (MI) and heart failure range from those involving large animals (eg, the dog, pig, sheep) to those involving small animals (eg, the rabbit, rat, mouse). The models can be classified into those in which the initial insult is regional (eg, MI, reperfused infarction, direct current (DC) shock injury), global (eg, pressure overload, volume overload, tachycardia/ventricular pacing, microembolization), or genetic. The processes of LV remodeling and healing after MI are dynamic and time-dependent, and progress in parallel. Thus, remodeling spans the phases of infarction, healing before and after collagen deposition, and subsequent scar formation. Several points need to be considered when deciding which model to use. Caution should clearly be exercised in extrapolating results from animals, even large animals, to humans. No ideal large animal model exists for studying cardiac remodeling in humans. Major differences among large animal models should be recognized, such as differences in coronary circulation, infarct location, healing, neurohumoral pathways, and receptor populations. The importance of the extracellular matrix and the potential differences in its contribution to the remodeling process in various models should also be considered. Finally, whether we can prevent, reverse, or correct cardiac remodeling more easily in one model versus another should be considered. This review focuses on the canine post-MI model of LV remodeling.
Post-infarct Remodeling in the Dog

Both anesthetized and conscious dog models of MI after coronary artery ligation have been adapted for studies of chronic LV remodeling during post-MI healing. The chronically instrumented dog model has been validated for postmortem quantitation of infarct scar size relative to the risk region and for the mapping of regional myocardial blood flow, regional function by two-dimensional echocardiography (2D echo), regional collagen content, and topography and regional bulging in transverse and long-axis planes. In the dog model healing is completed over a period of about 6 weeks. The exact duration of healing is dependent on infarct size and transmurality. Serial noninvasive imaging with 2D echo permits in vivo quantitation of changes in regional and global shape, structure, and function with relative ease. It is therefore especially suitable for studies of post-MI remodeling. Serial hemodynamic parameters (eg, atrial and arterial pressures) are recorded via indwelling catheters. Sonomicrometer implants allow continuous serial measurements of regional wall thickness and cavity dimensions. Serial electrocardiograms can also be monitored continuously.

The collateral-rich dog model of predominantly subendocardial infarction can be modified to consistently produce transmural anteropapical infarcts and aneurysms by separately ligating visible collateral feeders below the coronary ligation. Ligation of the mid-left anterior descending coronary artery, together with ligation of the collateral inflow, results in transmural infarcts that are still small (≤20% LV), therefore long-term mortality is fairly low (10%-15%). In addition, because the infarcts are transmural, significant remodeling with aneurysmal bulging occurs. Higher coronary occlusions result in large infarcts and lower survival rates beyond one week (mortality >15%). Thus, the modified dog model is useful for chronic studies of changes in structure, geometry, and function during healing in survivors of acute MI.

Methodological and Other Practical Details

We prefer 18- to 21-kg mongrel dogs for chronic studies. Instrumentation is done under general anesthesia (barbiturate or isoflurane), using a limited left lateral thoracotomy and room air ventilation in a sterile surgical suite. Indwelling catheters (jugular vein, carotid artery, and left atrium) are inserted and exteriorized behind the neck. We use mid-left anterior descending coronary artery ligation because anterior MI results in more LV remodeling and dysfunction. For some studies of inferior MI, we use mid-left circumflex coronary artery ligation. The 48-hour mortality with both types of occlusion is ≤15%. In the last 100 animals with MI studied in our laboratory, the mortality was actually <10% and morbidity <10%. Reperfusion after 2 to 3 hours causes higher 48-hour mortality (≤25%) related to arrhythmias. We use collateral obliteration with ligation of visible epicardial vessels feeding the risk zone to increase transmurality. This carries a higher 48-hour mortality (≤35%), but the degree of anteropapical remodeling is dramatic, resembling the sheep model. We also implant sonomicrometer or sonometric crystals to study thickening and shape. In some animals, we implant a snare device or balloon occluder for late occlusion in the conscious state. We have begun monitoring our animals postoperatively over the first 24 to 48 hours and administering analgesics for pain control. Animals usually recover from surgery within 48 hours. Subsequently, regular catheter care is carried out to ensure catheter patency. We use telemetry implants in some animals, thus avoiding the need for catheter care.

We usually record serial hemodynamics (aortic and left atrial pressures, EKG) and 2D echo at baseline before occlusion and serially postocclusion at 4 hours, 3 days, and weekly over 6 weeks or more. Serial functional and topographical parameters on 2D echo include LV volumes (Simpson’s Rule) and LV mass (myocardial volume x 1.05), LV function (LV asynergy, ejection fraction, shape index, and globularity index), and LV regional topography (expansion index, thinning ratio, apical bulge, and aneurysm). We use radioactive microspheres to measure regional myocardial flow. Animals are usually euthanized at 6 weeks, and hearts are used for topographic and other studies. Hearts are arrested in diastole with intravenous potassium chloride (KCl) and formalin-fixed in distension to preserve diastolic proportions. The risk region is determined using postmortem coronary arteriograms and radiographs of the whole heart and transverse sections. Infarct or scar size is measured by computerized planimetry. Long-axis LV topographic parameters from whole heart radiographs include shape index and extent of apical bulge. We perform histopathology and measure regional hydroxyproline (mg/g dry tissue). Analyses are done in a blinded fashion on coded data. Pertinent special procedures include scanning microscopy on fresh samples for assessment of matrix integrity and measurement of the LV rupture threshold. Because dogs, like humans, derive a substantial amount of angiotensin II from chymase, this model is useful for translational research and evaluation of effects of therapies such as angiotensin II receptor antagonists (ARBs).
Discussion

The canine model of post-MI LV remodeling has contributed to knowledge of the progressive pathophysiologic changes associated with the MI healing process.2 The ease with which 2D echo can be performed on awake dogs has provided insights into the in vivo shape, structural, and functional changes after MI. However, the post-MI dog model has not been as effective for studying remodeling during moderate-to-severe heart failure as the tachycardia-induced heart failure model,3 the microembolization heart failure model,29,30 or after a large MI as in the rat.25 This is because post-MI canine survivors tend to have infarcts averaging 20% LV at 2 days and 10% at 6 weeks. Moreover, even animals with the relatively small infarcts in this model31 or the discrete DC-shock necrosis model32 show evidence of significant neurohumoral activation. The recent escalation in the cost of dogs for research has become a major concern. As the dog is considered “man’s best friend,” attention to the humane care of the animals is an important aspect of their use in research on prevention of cardiac remodeling.

References

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