Sheep Models of Postinfarction Left Ventricular Remodeling

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Summary. This chapter describes various sheep models that faithfully and consistently reproduce major manifestations of adverse postinfarction left ventricular remodeling following acute myocardial infarctions in patients. The models are produced by simply occluding coronary arteries that supply 21 to 24 percent of the left ventricular mass in different, specific locations. The advantages of these large animal models are illustrated by studies of early and late reperfusion of ischemic myocardium and studies restraining infarct or mitral annular expansion on the remodeling process.

Key words: Acute myocardial infarction, ventricular remodeling, sheep, reperfusion, infarct restraint, collagen, apoptosis.

INTRODUCTION

Nearly 4.8 million Americans live with congestive heart failure (CHF) and each year 550,000 new cases are recognized (1). After diagnosis the five-year mortality is approximately 50% (1); coronary arterial disease causes 68% of all cases (2). In survivors of acute myocardial infarction CHF is caused by postinfarction left ventricular remodeling that fails to produce a compensated left ventricle. The three most common manifestations of adverse postinfarction remodeling are ischemic mitral regurgitation (MR), left ventricular (LV) infarct expansion, and dilated cardiomyopathy (3). Approximately 7% of patients with coronary artery disease undergoing cardiac catheterization have 2+ or greater MR (4,5) and nearly 2 million
Figure 1. Methylene blue injections of the first and third branches of the obtuse marginal branches of the circumflex coronary artery of an excised sheep heart. Note the sharp irregular borders between vascular beds supplied by each coronary artery. APM, anterior papillary muscle; OM1, first obtuse marginal branch (injected); OM2, second marginal branch (not injected); OM3, third marginal branch; PPM, posterior papillary muscle; PDA, posterior descending artery branch of the circumflex coronary artery. Reprinted with permission reference 16.

Americans have some degree of ischemic MR (6). The prevalence of LV infarct expansion and postinfarction dilated cardiomyopathy is not precisely known.

Over the past 14 years we have developed sheep models of the major manifestations of adverse postinfarction LV remodeling. Sheep are ideal models for studying postinfarction LV remodeling for two unique reasons. Sheep have consistent coronary anatomy between animals of the same strain and do not have preformed coronary collaterals (7) nor appear to produce collaterals (Figure 1). All major LV remodeling complications of acute infarction that occur in humans can be modeled in sheep by ligating two or more coronary arteries at strategic locations. These models accurately mimic human disease, but also control for two important confounding variables that have a major impact on postinfarction LV remodeling in patients: differences in coronary anatomy between patients and the effects of varying and unmeasurable collateral coronary blood flow to the infarct.