Objective: The functionality of tissue-engineered heart valves (TEHVs) often decreases over time due to leaflet retraction. Since mechanical factors play an important role in the remodeling process of cardiovascular tissues, understanding the interplay between mechanics and remodeling is crucial for developing TEHVs with long-term functionality. Previously, we suggested a valve design that could prevent or minimize leaflet shortening after implantation. The goal of the present study was to investigate the in vivo remodeling process with this new design and understand and predict the (robustness of the) remodeling process using computational models. Methods: TEHVs with the new design were implanted in the pulmonary position of sheep (n = 3) for a period of a full year. Valve functionality was monitored every four weeks via cMRI, and tissue composition and organization after remodeling were investigated in the explants. Based on the initial geometry and material properties of the valves before implantation, a computational model was used to predict and understand (the robustness of) the in vivo remodeling process. This model included cell contractility, cell-mediated collagen contraction, and strain-dependent collagen remodeling. Results: For the first time, all TEHVs preserved their functionality throughout the complete implantation period. The collagen fibers appeared to remodel from an initial random distribution towards a circumferentially oriented collagen network. Furthermore, the contractility of the cells in the valve appeared to be low. Our computational model was able to quantitatively predict the remodeling response of the valves when cell contractility was assumed to be low. Variations in cell contractility and initial leaflet thickness in the model demonstrated that valve functionality after remodeling is most sensitive to cell contractility, whereas the collagen architecture appeared to be quite insensitive to changes in cell contractility or leaflet thickness. Conclusions: Our combined computational-experimental efforts confirmed that TEHVs can maintain their functionality during a one-year follow-up period when the initial valve design is chosen carefully. Computational models were essential in defining a rational design, and predicting the most important determinants in the remodeling process. We gratefully acknowledge the support of the EU ([FP7/2007–2013], grant agreement no. 242008), and the Netherlands CardioVascular Research Initiative (CVON2012-01).