Progression of AF is associated with physical and electrical remodeling of the heart, and currently available animal models of AF are dominated by large animals such as dogs, goats, sheep, and pigs. In fact, historically, arrhythmias were studied in larger mammals, as it was believed that arrhythmia did not occur in mice due to their lack of critical cardiac mass[34] (Janse and Rosen, 2006). Additionally, the hearts of larger animals (e.g., non-human primates, dogs, etc.) are more similar to human hearts than those of mice and rats. In 1999, however, the theory of critical cardiac mass was disproven,[35] and since that time, a number of transgenic mouse models of AF have been reported in the literature. These models have been useful in studying the underlying mechanism of AF, but their utility in the identification of compounds capable of treating AF has as yet to be validated.[36]

The majority of AF drug discovery research employs large animal models such as the sterile pericarditis dog model (Figure 7.13). This dog model

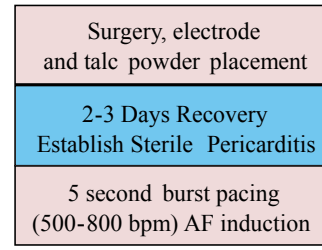

FIGURE 7.13 In the sterile pericarditis dog model, the presence of talc powder in the pericardium causes inflammation. Atrial fibrillation (AF) can be induced with a burst pacing protocol 2–3 days after surgery.

of AF exhibits a high incidence of sustained AF with strong similarity to clinically observed AF after an open-heart surgery. In this model, surgical ablation of the pacemaker tissue in the heart, implantation of a pacemaker, and insertion of talc powder into the pericardium is followed by a 2- to 3-day recovery period. The presence of talc causes pericarditis, an inflammation of the pericardium, and this, in turn, renders the dog susceptible to induction of AF via burst pacing (5–10 s of 500–800 beats per minutes via implanted pacemaker). Severity of AF can be measured in terms of the average duration of AF induced via burst pacing and the overall AF inducibility (the number of AF episodes lasting longer than 60 s after a set number of attempts). In the presence of compounds with antiarrhythmic properties, the average duration of AF and the AF inducibility will decrease when compared with vehicle treatment.

An alternative model that is particularly useful for evaluating drugs that may prevent electrical remodeling can be created by subjecting an animal, usually a dog, to extended periods of high heart rates (Figure 7.14). In this pacing model, surgical implantation of monitoring electrodes and a pacemaker is followed by a 2-week recovery period. Once the animal is