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Intrapericardial Delivery of Amiodarone Rapidly Achieves Therapeutic Levels in the Atrium

Juan Marcano, MD, Karla Campos, MD, Victor Rodriguez, MD, Kelly Handy, BS, M. Alan Brewer, MBA, William E. Cohn, MD

Department of Cardiovascular Surgery, Texas Heart Institute, Houston, Texas, USA

ABSTRACT

Background: Amiodarone is widely used worldwide as an important drug for managing supraventricular arrhythmias, regardless of its association with potentially severe side effects due to systemic toxicity. Amiodarone reduces the incidence of atrial fibrillation after cardiac surgery, but oral therapy requires a presurgery loading period, lasting from 1 to 4 weeks. In this study, we showed that it is possible to rapidly obtain therapeutic cardiac tissue levels of the drug by infusing aqueous amiodarone intrapericardially, without appreciable systemic exposure. We also examined the long-term histologic safety of intrapericardial infusion.

Methods: In this observational study, 9 adult sheep, randomized into 3 groups of 3 animals each, were given low (2.5 -mg/h), medium (10-mg/h), or high (50-mg/h) dosages of amiodarone by continuous infusion intrapericardially for 72 hours. An intrapericardial drain prevented tamponade from fluid build-up. Levels of amiodarone and its active metabolite, desethylamiodarone (DEA), were assessed both in plasma and in transmural biopsy specimens taken from the left atrial appendage and left and right ventricular myocardium. Cardiac, hepatic, and renal functions were also assessed. Humane euthanization was performed after 3 months, and cardiac and thoracic tissues were assessed for evidence of epicarditis, severe fibrotic changes, or other adverse effects potentially caused by the local amiodarone administration.

Results: Pericardial infusion resulted in rapid uptake and high concentrations of amiodarone and DEA in the myocardial tissues, without an appreciable systemic presence of either drug. The highest and lowest levels of these agents were observed in the left atrium and left ventricle, respectively. Drug concentrations in all cardiac biopsy specimens were similar to, or higher than, those reportedly observed in patients taking long-term oral amiodarone. At 90 days, postmortem microscopic, biochemical, and hematologic evaluation of end-organ tissues from the 8 surviving sheep showed no adverse effects. Excessive inflammation or fibrotic changes were not observed in these 8 sheep. The ninth sheep died prematurely, and its death was deemed not to be related to this study.

Conclusions: Short-term intrapericardial delivery of amiodarone is a safe method for rapidly obtaining therapeutic atrial-tissue drug levels. When begun perioperatively, this method may prevent postoperative atrial fibrillation similarly to oral or intravenous amiodarone therapy. However, we have shown that pericardial administration avoids systemic drug distribution and thus may greatly decrease the systemic complications resulting from this drug.

INTRODUCTION

After open heart surgery, the incidence of supraventricular arrhythmias ranges from 5% to 40%, atrial fibrillation (AF) being the most common type [Frost 1992; Aranki 1996; Mathew 1996]. Elderly patients, particularly those undergoing valve procedures, are at increased risk for AF. In patients older than 75 years, the incidence of AF is 48% to 64% after aortic valve and mitral valve operations, respectively. Postoperative AF is an independent predictor of stroke and congestive heart failure, which contribute to morbidity, hospital length of stay, and healthcare costs. Indeed, AF is associated with a 2-fold increase in both postoperative stroke and ventricular fibrillation [Wolf 1991; Prystowsky 1996].

Amiodarone is a class III antiarrhythmic agent that is widely used worldwide for managing AF and life-threatening ventricular arrhythmias. Although there is a general consensus that amiodarone is effective in preventing and treating postoperative AF, oral administration requires a lengthy loading period (up to 4 weeks) [Marcus 1981] and sometimes results in suboptimal efficacy. In addition, although intravenous amiodarone administration provides exceptional efficacy, it is also associated with greater systemic toxicity and still requires more than 24 hours for tissue uptake and full clinical effectiveness. Amiodarone's long half-life and high lipid solubility are key contributors to its major adverse effects, which include pulmonary toxicity, hepatic toxicity, thyroid dysfunction, neurologic dysfunction, and skin discoloration. In AF patients who receive amiodarone at doses ≥200 mg/day, the

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Correspondence: William E. Cohn, MD, MC 2-114A, PO Box 20345, Houston, Texas 77225-0345, USA; 832-355-3000; fax: 832-355-9004 (email: wcohn@texasheart.org).

risk of pulmonary fibrosis is increased by as much as 50% [Jackevicius 2011].

Previous animal studies have shown that various antiarrhythmic drugs are able to be absorbed from the epicardial surface of the heart. Amiodarone, a highly lipid-soluble substance, is no exception, being widely distributed after administration. Ayers and colleagues [Ayers 1996] demonstrated that direct infusion of amiodarone into the pericardial space results in rapid accumulation of therapeutic tissue levels and is efficacious for prolongation of action potentials and suppression of atrial arrhythmias (despite an absence of significant systemic levels of the drug). After short-term intrapericardial delivery of amiodarone, Bolderman and colleagues [Bolderman 2009] demonstrated a steep transmural drug-concentration gradient, with a similar distribution across both atrial walls, increased atrial and ventricular effective refractory periods, and decreased serum concentrations. It is unknown, however, whether more prolonged cardiac exposure to topical intrapericardial amiodarone may result in excessive accumulation of this agent in the myocardial tissue and/or local inflammation that leads to scarring, fibrosis, or other adverse effects.

In this study, we investigated cardiac tissue and plasma drug levels resulting from a 3-day course of amiodarone delivered intrapericardially in an ovine model. Three dosages of the drug were tested, and the resulting atrial tissue, ventricular tissue, and systemic levels (in plasma) were assessed for each dosage. We allowed the animals to survive for 3 months after drug delivery and then assessed the longer-term histologic effects of these intrapericardial treatments on the epicardium, myocardium, and pericardium.

MATERIALS AND METHODS

Animal Model

The experiments were conducted on 9 adult Hampshire/Suffolk crossbred sheep weighing 54 to 71 kg each. All animals received humane care in compliance with the Principles of Laboratory Animal Care (National Society of Medical Research) and the Guide for the Care and Use of Laboratory Animals (National Institute of Health Publication No. 85-23, revised 1996). Our Institutional Animal Care and Use Committee approved the protocol used for this study. Before surgery, each animal underwent baseline hematology and biochemistry tests (Table 1).

Amiodarone Dosages

The sheep were randomized into 3 experimental groups of 3 animals each, with each group receiving a different amiodarone concentration. We did not include a control group in the study's design because (1) the design objective was to examine the long-term safety profile for the overall method, (2) we wished to minimize the total number of sheep to be killed, and (3) the study team has extensive experience with epicardial and myocardial pathology resulting from open heart surgical procedures in chronic sheep studies. Each sheep underwent a continuous intrapericardial infusion of amiodarone for 72 hours; the low-dosage group received 2.5 mg/h, the medium-dosage group 10 mg/h, and the high-dosage group 50 mg/h. To keep the infusion rate at 5 mL/h in all groups, we diluted 125 mg, 500 mg, or 2500 mg of amiodarone in 250 mL of 5% dextrose in water, thereby obtaining 0.5-mg/mL, 2-mg/mL, and 10-mg/mL concentrations, respectively.

Anesthesia, Surgical Technique, and Postoperative Care

First Operation. Diazepam (0.2-0.5 mg/kg, intravenously [IV]) and ketamine (5-20 mg/kg, IV) were administered to induce anesthesia. After intubation was achieved, isoflurane (0.5%-3.0%) in oxygen (40%-100%) was given to maintain general anesthesia. The left carotid artery was exposed, and a polyethylene catheter was inserted for arterial pressure monitoring. A central venous catheter was placed through the left external jugular vein to measure the right atrial pressure. The pleural space was entered through a left minithoracotomy (3-4 cm) in the fifth intercostal space. A 3-mm opening was created at the base of the pericardium. Two 10-cm, 17-gauge multifenestrated catheters were inserted in the pericardial space: 1 anterior and 1 posterior to the atrioventricular groove. The 2 catheters were tunneled through the chest wall to exit near the animal's spine, where they were connected to a single, self-contained elastomeric autonomous infusion pump (On-Q PainBuster Catheter System; I-Flow Corporation, Lake Forest, CA, USA). This catheter and self-contained pump system is intended for the continuous infusion of a local anesthetic directly into the surgical site for postoperative pain relief. In this study, we modified the pump and catheters so that they continuously delivered amiodarone at a predetermined infusion rate of 5 mL/h for 72 hours. A Jackson-Pratt fenestrated suction drain was also placed in the pericardial space to prevent tamponade if excess infusion fluids accumulated. The chest was then closed, and the sheep was transferred to the intensive care unit for monitoring. All the animals were continuously monitored for arterial pressure, right atrial pressure, and urinary output. They also were examined daily with regard to appetite, infection, and neurologic status. Suction was applied to the Jackson-Pratt drain for 10 minutes every 10 hours until termination of the amiodarone infusion.

Second Operation. After 72 hours of amiodarone infusion, each sheep was prepared for surgery in the same manner as for the first operation. The amiodarone infusion was stopped when the animal entered the operating room. Each sheep underwent a left thoracotomy, which was extended through the anterior axillary line from the previous incision for appropriate pericardial exposure. After the pericardium was incised, the infusion and suction catheters were withdrawn, and the entire chest cavity was irrigated with 5 L of warm saline and suctioned multiple times to prevent drug contamination of tissues obtained for biopsy. Specimens were taken from the left atrial appendage, left ventricular (LV) myocardium, and right ventricular (RV) myocardium for evaluation of amiodarone and desethylamiodarone (DEA) levels in these tissues. In addition, blood samples were obtained for evaluation of amiodarone and DEA levels, hematologic results, and biochemistry values. After hemostasis was achieved, the chest was closed in standard fashion.

Table 1. Hematologic and Biochemical Values.*

	Low-Dosage Group		Medium-Dosage Group		High-Dosage Group		All Groups	
Variable	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint	Baseline	Endpoint
WBCs, 10^3/μL	5.8±0.6	7.3±2.2	6.1±5.5	10.2±2.4	11.2±9.8	4.4±1.8	7.9±6.3	6.9±3.0
RBCs, 10^6/μL	11.60±0.79	9.51±0.26	11.80±0.92	10.96±0.36	10.72±0.87	10.04±0.84	11.32±0.88	10.07±0.77
Hgb, g/dL	12.2±1.3	10.3±0.1	13.6±0.6	12.9±1.2	11.7±0.7	10.4±0.8	12.4±1.1	11.0±1.3
Hct, %	34.3±4.0	30.6±0.9	39.9±0.8	39.5±3.3	32.5±3.6	29.8±3.1	35.0±4.3	32.5±4.8
PLTs, 10^3/μL	359.0±90.2	300.7±129.0	274.5±68.6	233.5±166.2	377.7±85.2	248.3±101.1	344.9±83.9	264.3±112.1
PT, seconds	13.3±0.1	13.3±0.5	14.6±1.0	13.6±0.4	14.6±1.2	13.8±1.1	14.1±1.0	13.6±0.7
INR	1.34±0.01	1.35±0.10	1.66±0.25	1.41±0.10	1.66±0.29	1.47±0.24	1.54±0.24	1.41±0.16
PTT, seconds	26.8±10.2	30.8±15.7	24.8±3.0	28.9±6.6	39.1±5.0	40.2±16.7	30.9±9.2	33.8±13.6
Fibrinogen, mg/dL	292.7±25.9	292.0±53.4	270.0±141.4	190.0±48.1	260.3±19.0	232.3±180.9	274.9±58.2	244.1±111.2
Reticulocytes, %	<0.1±0.0	<0.1±0.0	<0.1±0.0	<0.1±0.0	<0.1±0.0	<0.1±0.0	<0.1±0.0	<0.1±0.0
PF Hgb, mg/dL	5.19±0.73	3.19±0.49	6.81±0.16	6.05±2.16	8.58±6.96	3.42±2.51	6.87±4.06	3.99±2.04
BUN, mg/dL	18.7±3.5	19.3±6.1	19.0±2.8	20.0±2.8	20.0±4.0	18.3±4.5	19.3±3.1	19.1±4.3
Creatinine, mg/dL	0.9±0.1	1.0±0.1	1.1±0.1	1.0±0.1	1.1±0.1	1.0±0.1	1.0±0.1	1.0±0.1
SGPT, IU/L	17.7±9.7	27.7±25.4	11.0±7.1	8.0±2.8	15.3±4.0	13.0±0.0	15.1±6.8	17.3±16.3
SGOT, IU/L	209.0±182.0	198.0±190.1	159.0±131.5	85.5±41.7	81.0±11.8	254.3±255.4	148.5±124.6	191.0±184.7
D bilirubin, mg/dL	0.1±0.1	0.1±0.1	0.1±0.0	0.1±0.0	0.1±0.1	0.1±0.0	0.1±0.1	0.1±0.0
T bilirubin, mg/dL	0.1±0.1	0.2±0.1	0.2±0.1	0.2±0.1	0.1±0.1	0.2±0.1	0.1±0.1	0.2±0.1
GGT, U/L	130.0±104.5	69.3±28.2	79.5±3.5	55.0±1.4	46.7±5.5	88.7±63.8	86.1±68.1	73.0±39.9
LDH, IU/L	509.0±275.4	602.7±533.9	389.5±77.1	298.0±36.8	326.7±72.2	641.7±469.3	410.8±176.9	541.1±409.2
ALK, IU/L	276.3±103.2	215.0±42.2	351.0±94.8	157.5±58.7	202.7±82.4	244.7±151.6	267.4±100.5	211.8±94.2
CK, IU/L	169.0±98.7	594.3±923.8	121.5±38.9	83.5±31.8	102.7±31.8	65.7±42.9	132.3±65.4	268.4±563.4
T protein, g/dL	6.4±0.6	7.2±0.8	7.1±1.1	6.4±0.6	6.6±0.4	7.1±0.6	6.7±0.6	7.0±0.7
Glucose, mg/dL	71.0±1.7	74.0±5.6	70.5±6.4	69.0±2.8	69.7±8.5	69.7±3.8	70.4±5.3	71.1±4.5

*All parameters are expressed as mean ± standard deviation. WBCs indicate white blood cells; RBCs, red blood cells; Hgb, hemoglobin; Hct, hematocrit; PLTs, platelets; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; PF, plasma free; BUN, blood urea nitrogen; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase; D, direct; T, total; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; ALK, alkaline phosphatase; CK, creatine kinase.

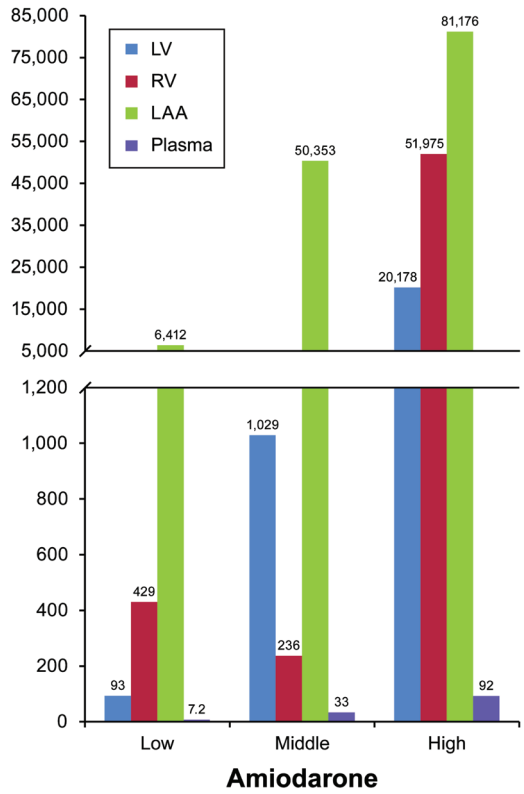

Figure 1. Tissue and plasma concentrations of amiodarone in sheep at preoperative baseline and after 72 hours of intrapericardial amiodarone infusion. Three dosages were tested: low (2.5 mg/h), medium (10 mg/h), and high (50 mg/h). The data are expressed as ng/mL. LV indicates left ventricular biopsy; RV, right ventricular biopsy; LAA, left atrial appendage biopsy.

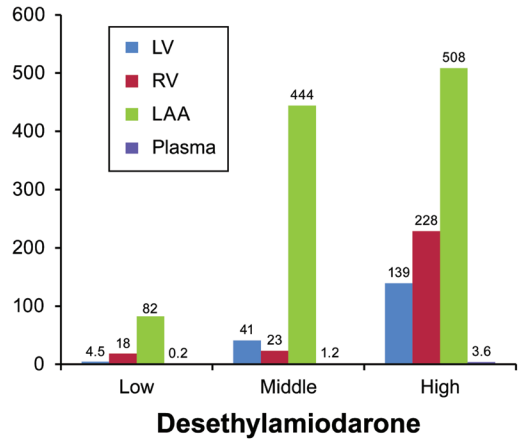

Figure 2. Tissue and plasma concentrations of desethylamiodarone (DEA), the active metabolite of amiodarone, in sheep after 72 hours of intrapericardial amiodarone infusion. Three dosages were tested: low (2.5 mg/h), medium (10 mg/h), and high (50 mg/h). The data are expressed as ng/mL. LV indicates left ventricular biopsy; RV, right ventricular biopsy; LAA, left atrial appendage biopsy.

The sheep were allowed to recover and to survive until the end of the 90-day study. They continued to be examined daily with regard to appetite, infection, and neurologic status. At the end of the study, blood samples were obtained for complete hematologic and biochemistry profiles. Heparin (3 mg/kg, IV) was then administered, and the animals were given a commercially available euthanasia solution (0.22 mL/kg, IV).

Postmortem Histopathologic Examination

Gross and microscopic qualitative evaluation of tissue samples from the 9 sheep was performed in our Department of Cardiovascular Pathology by a veterinary pathologist who was independent of the research team. The pathologist and technicians involved in the histologic assessments were blinded in regard to drug concentration.

Postmortem evaluation included a thorough examination of the heart and of the thoracic and abdominal viscera, including analysis of the pericardium and epicardium for fibrosis and/or constrictive pericarditis. The heart, lungs, kidneys, and liver were then placed in either 10% buffered formalin or Karnovsky's solution (10:1 fixative-to-tissue volume) and processed for paraffin sectioning. Slides were then stained with hematoxylin & eosin (H&E). Each slide underwent qualitative assessment. Tissue drug levels were analyzed for amiodarone and DEA by means of a qualified liquid chromatography–tandem mass spectrometry method. Samples were prepared by using a protein precipitation technique for plasma and a solid-phase extraction technique for tissue samples.

RESULTS

Overall Results

All 9 sheep recovered from surgery without complications. Eight of them reached the scheduled study endpoint (90 days). The 1 premature death occurred on the third day after the second operation; this sheep was electively euthanized at the discretion of the veterinarian because of acute ruminal stasis, a complication deemed not to be related to this study. None of the surviving animals experienced anorexia, infection, or neurologic disorders.

Tissue and Plasma Amiodarone and DEA Levels at 72 Hours

Figures 1 and 2 show the amiodarone (Figure 1) and DEA (Figure 2) concentrations in the left atrial, LV, and RV tissues and in the plasma after 72 hours of intrapericardial infusion. The highest concentrations of these agents were observed in the left atrial tissues (all 3 groups). The lowest tissue concentrations were observed in the LV tissues in 2 of the 3 dosage

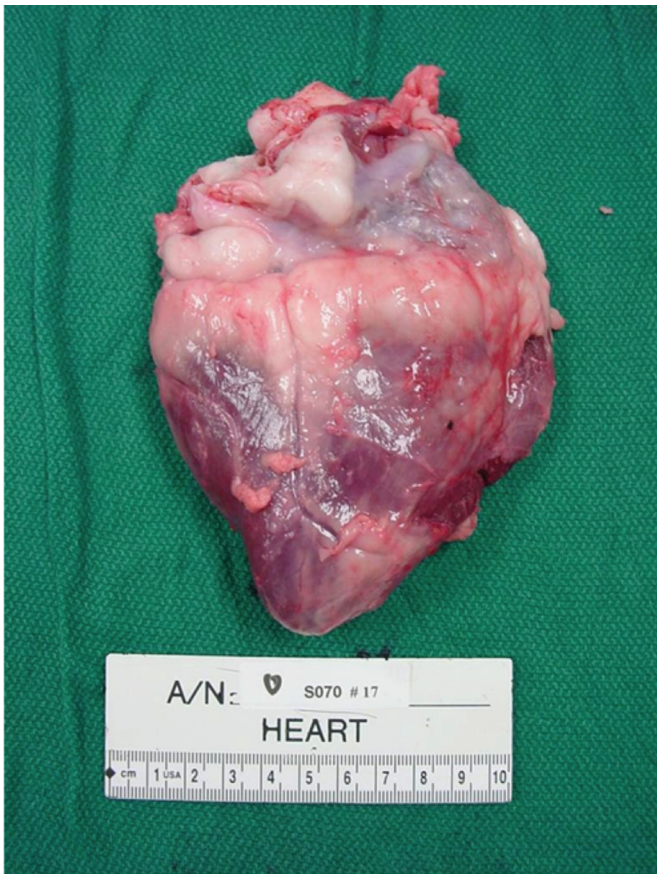

Figure 3. Epicardial fibrosis was observed in the anterior right and left ventricles of the heart of 1 sheep in the low-dosage group.

groups, but higher levels of amiodarone and DEA were seen in the LV tissue than in the RV tissue in the 2.0-mg/mL-dosage group. In each group, the plasma drug levels of amiodarone and DEA after 3 days of intrapericardial infusion were considerably lower than the corresponding tissue levels. In all 6 comparisons, the left atrial tissue levels were at least 100-fold (139–1487 times) higher than the plasma drug levels. The DEA concentration in the left atrial tissue ranged from 139 times higher (high-dosage) to 373 times higher (mid-dosage) than the comparable plasma level. The amiodarone concentration in the left atrial tissue ranged from 878 times higher (high-dosage) to 1487 times higher (mid-dosage) than the comparable plasma level. These extreme differences in the left-atrial tissue versus plasma concentrations show that clinically effective concentrations can easily be provided at the left atrial target site. This approach eliminates all the systemic side effects usually associated with amiodarone use, and this concentration effect holds for differing drug dosages.

Hematologic, Biochemistry, and Histopathologic Results at 90 Days

Laboratory Bloodwork Analysis. For almost all the laboratory tests evaluated at 90 days, hematologic and biochemical values were not significantly different from those observed at baseline, regardless of the drug concentration administered (Table 1). Elevations of an unknown origin were observed in the serum glutamic oxaloacetic transaminase and lactate dehydrogenase levels of 1 high-concentration sheep (to 548.0 IU/L and 1170.0 IU/L, respectively) at the study endpoint. Pathologic evaluation of this animal's heart revealed multifocal-to-confluent fibrosis with no ischemia or infarction, and all other end organs were within normal limits. Similarly, the creatine kinase level of 1 low-concentration sheep was also elevated (to 1661.0 IU/L) at the study endpoint. There is no known reason for this elevation, as the degree of epicardial fibrosis in this animal's heart was minimal compared to that seen in the other animals. Furthermore, an elevated baseline white blood cell count (to 22.4 10^3/μL) and plasma free hemoglobin level (to 16.57 mg/dL) were noted in 2 separate animals, both in the high-concentration group. Because these values significantly decreased to 3.7 10^3/μL and 2.11 mg/dL, respectively, 24 hours after surgery, the elevation in the initial baseline values was probably due to sampling errors. As indicated by the remaining laboratory values, liver and kidney function were not adversely affected during or after intrapericardial amiodarone infusion.

Gross Evaluation. Focal fibrin deposition and adhesions between the thoracotomy site and the epicardial/pericardial surface were typical of postoperative healing in sheep undergoing open-pericardium surgery, and pericardial amiodarone administration did not appear to increase fibrosis or inflammation. In the sheep from the low-dosage group, the right lung had patchy plum-colored mottling, and the anterior right and left ventricles had patchy irregular areas (1–3 cm) of epicardial fibrosis (Figure 3), but the posterior region was unremarkable. Cross-sections (perpendicular to the long axis of the heart) from apex to base showed unremarkable myocardial tissue except for 3 sections (Figure 4A-C) that had focal (<0.5-cm) irregular areas of fibrosis (midmural to subepicardial) in the anterior free wall of the left ventricle; a similar finding was noted in the anterior free wall of the right ventricle (Figure 4D). In the sheep from the high-dosage group, the lateral surface of the left, medial, and diaphragmatic lung lobes had multifocal-to-confluent areas of plural fibrosis (Figure 5), and the heart had patchy irregular areas (1–3 cm) of epicardial fibrosis in the anterior right and left ventricles, similar to those of the sheep in the low-dosage group. Cardiac cross-sections were unremarkable except for 3 sections (Figure 6A-C) that showed focal (<0.5-cm) irregular areas of midmural to subepicardial fibrosis.

The frequency and extent of the pulmonary and cardiac fibrosis described above is typical after any open-pericardium surgery in sheep.

Microscopic Evaluation. Postmortem histopathologic examinations revealed small, localized pulmonary and cardiac fibrosis in 2 of the 9 sheep: 1 from the low-dosage (2.5-mg/h) group and 1 from the high-dosage (50-mg/h) group. For the heart tissue samples, a semiquantitative assessment also was performed based on H&E slides from 7 regions (LV anterior, LV anterolateral, LV lateral, LV posterolateral, LV posterior, RV anterior, and RV posterior). Table 2 presents the results

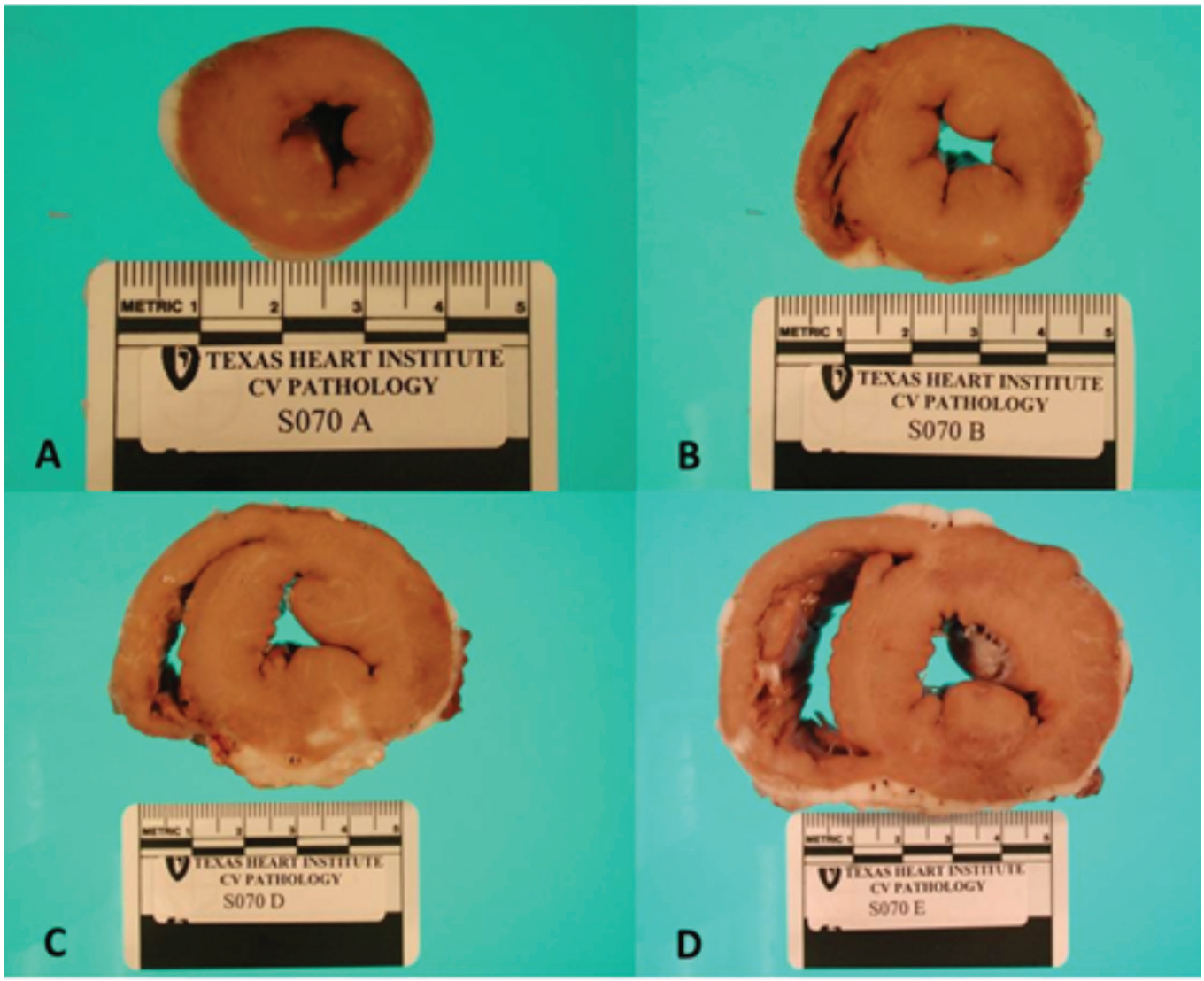

Figure 4. Same sheep heart as in Figure 3. Cross-sections of the heart, showing fibrosis in the anterior left ventricular free wall (A-C) and in the anterior right ventricular free wall (D).

of this assessment, which showed only a slight trend toward less epicardial fibrosis in the low-dosage amiodarone group than in the high-dosage group. Microscopic evaluation of the liver, kidneys, brain, and lungs did not reveal any evidence of abnormality.

DISCUSSION

In this study, we showed that 72-hour intrapericardial administration of amiodarone in postoperative sheep provided therapeutic drug levels in the left atrial and ventricular tissues, without causing any appreciable systemic distribution of the drug or its active metabolite. Further, we showed the safety of the intrapericardial delivery method, as measured by examination of end-organ damage after a follow-up period of 90 days. Pericardial infusion of our highest dosages of amiodarone resulted in high drug concentrations in myocardial tissue without causing any cardiac hemodynamic disturbances (tamponade, arrhythmias, etc) during or after drug infusions. The left atrial, LV, and RV tissue concentrations of amiodarone and DEA were similar to, or higher than, the atrial and ventricular tissue concentrations observed in patients taking long-term oral amiodarone [Marcus 1981; Adams 1985; Bandyopadhyay 1987; Brien 1987; Beder 1998; Bolderman 2009]. Thus, pericardial infusion should be at least as efficacious for preventing and controlling postsurgical atrial fibrillation as has been previously and widely reported for oral and intravenous therapy.

Table 2. Semiquantitative Histopathologic Assessment of Cardiac Tissue Samples.*

	Microscopic Region							
Study No.	LVA	LVAL	LVL	LVPL	LVP	RVA	RVP	Rx Group Amiodarone Concentration, mg/mL
1	3	3	3	2	2	3	3	0.5
2	3	3	3	3	3	3	3	10
3	3	2	2	2	2	2	2	2
4	2	2	2	2	2	2	2	0.5
5	2	0	2	3	3	3	3	2
6	2	3	2	2	2	3	3	10
7	2	3	3	3	2	3	3	0.5
8†	—	—	—	—	—	—	—	—
9	2	2	2	2	2	2	3	10

*This assessment was scored as follows: 0 = no epicardial fibrosis; 1 = focal covering of surface by connective tissue; 2 = multifocal covering of surface by connective tissue; 3 = multifocal to confluent covering of surface by connective tissue; 4 = diffuse covering of surface by connective tissue.

†Unscheduled death (ischemic bowel, 6 d postoperatively). Data not included."

LVA indicates left ventricle, anterior; LVAL, left ventricle, anterolateral; LVL, left ventricle, lateral; LVPL, left ventricle, posterolateral; LVP, left ventricle, posterior; RVA, right ventricle, anterior; RVP, right ventricle, posterior; Rx, treatment.

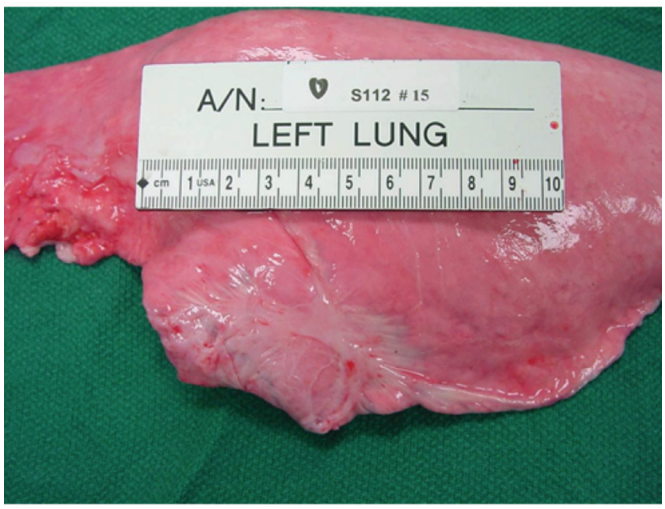

Figure 5. Fibrosis was also observed in the left lung of 1 sheep in the high-dosage group.

The plasma levels of both amiodarone and DEA remained negligible at the end of 72 hours of continuous intrapericardial drug administration. Even in the sheep that received the highest drug concentration, the plasma levels of amiodarone and DEA reached only 92 and 3.63 ng/mL, respectively. This plasma concentration of amiodarone is approximately 10^7 times lower than the therapeutic plasma concentration of 1 to 2.5 mg/L proposed as the target for clinical oral or IV amiodarone administration. Such low plasma drug levels are in distinct contrast to the high myocardial tissue drug levels achieved by using intrapericardial administration.

The systemic side effects of amiodarone administered orally or intravenously are related to its prolonged half-life, large volume of distribution, and low clearance rate, as documented in animal models [Beder 1998]. Also, several previous studies involving short-term infusions have shown that amiodarone and DEA levels are barely detectable in serum [Adams 1985; Bandyopadhyay 1987; Brien 1987; Ayers 1996; Bolderman 2009]. In our study, we observed only trace amounts of systemic plasma amiodarone and DEA; therefore, the intrapericardial route may be valuable for preventing systemic side effects of amiodarone, such as pulmonary fibrosis, thyroid dysfunction, hepatic toxicity, or nerve toxicity.

Supraventricular arrhythmias occur after open heart surgery in up to 40% of cases. Use of amiodarone to manage this complication improves patient outcomes. Postoperative

Figure 6. Same sheep lung as in Figure 5. (A-C) Cross-sections of the heart, showing fibrosis.

prophylactic administration of amiodarone by means of intrapericardial infusion appears to be a promising method for rapidly achieving therapeutic concentrations in myocardial tissues, eliminating the need for preloading with oral amiodarone and decreasing the risk of systemic side effects.

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