An Ovine Model of Chronic Heart Failure: Echocardiographic and Tissue Doppler Imaging Characterization

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Abstract ***Background and aim of the study:*** **Heart failure in the western world is a major health-care issue. In order to validate novel surgical or pharmacological treatments, reproducible animal models of left ventricular dysfunction are necessary. In the current study, we report our data and experience with a model of toxin-induced heart failure in the sheep.** ***Methods:*** **Sequential intracoronary injections of doxorubicin (0.75 mg/kg) were carried out every 2 weeks until standard echocardiographic and tissue Doppler imaging detection of myocardial systolic dysfunction. The animals were assessed 1 month later and harvested. Indices of cardiac function from baseline to last day of protocol were recorded and their differences were evaluated by a Wilcoxon rank test for paired data.** ***Results:*** **Ten sheep received 2.5 $\pm$ 0.7 intracoronary injections of a cumulative dose of 88.8 $\pm$ 25 mg/m^2 doxorubicin. All available parameters demonstrated signs of severe cardiac dysfunction with statistical significance. All hearts demonstrated severe histological lesions, some of which were consistent with doxorubicin-induced toxicity.** ***Conclusions:*** **The present study shows that this ovine model is reproducible and stable. It can therefore be relevant to the study of chronic heart failure. It will be incorporated in our future studies concerning novel treatments (such as cell therapy) of nonischemic dilated cardiomyopathy.** doi: 10.1111/j.1540-8191.2006.00168.x *(J Card Surg 2006;21:50-56)*

Congestive heart failure (CHF) is a clinical syndrome including left ventricular dysfunction, remodeling, and increased neurohormonal activation. Heart failure in the western world is a major health-care issue. There are approximately 5 million U.S. citizens with heart failure and 400,000 to 600,000 new patients every year. The financial cost is estimated to be 1% to 2% of the total health-care budget.[1] Cardiac transplantation is currently limited by its long-term results, the side effects of immunosuppressive therapy, and above all by a critical shortage of donor organs. Despite improving medical therapy, mortality of chronic heart failure may reach 60% after 1 year for patients in New York Heart Association functional class IV.[1] Thus, new treatment modalities such as resynchronization therapy and cell transplantation are under consideration. In order to validate novel surgical or pharmacologic treatments, reproducible animal models of left ventricular dysfunction are necessary. In the current study, we report our data and experience with a model of toxic-induced heart failure in the sheep.

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MATERIALS AND METHODS

Animal model

The study was approved by the institutional ethics committee for animal research, and all animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996. Ten 53 to 73 kg 1-year-old Ile de France sheep (La Crezancy, France) were included in the protocol.

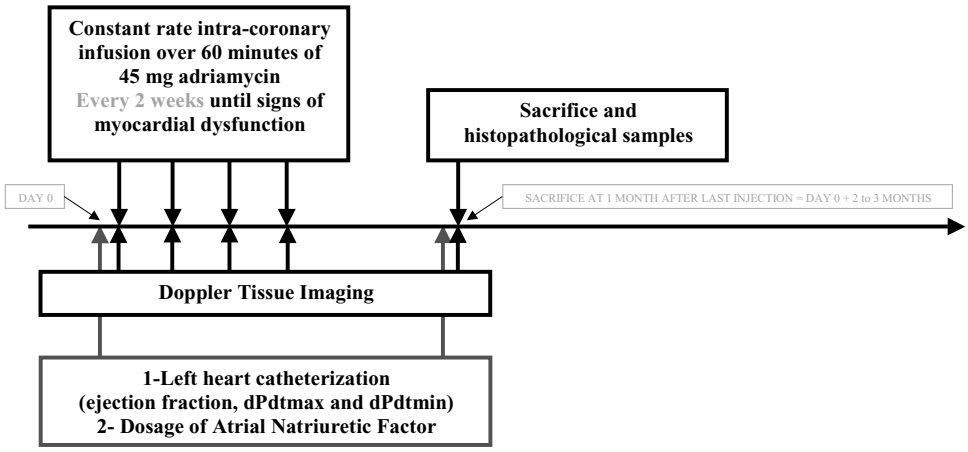

Figure 1. *Experimental design.*

Anesthesia

For left heart catheterization, animals were anesthetized with an IV injection of 0.5 mg/kg midazolam and then an IV injection of 0.5 mg/kg etomidate allowing endotracheal intubation and maintenance with isoflurane in 100% oxygen, delivered with a veterinary ventilator (HALLOWEL®, Pittsfield, MA). A constant rate infusion of lidocaine (50 μg/kg/min) was started at the same time as intracoronary injections of doxorubicin were carried out. Monitoring included invasive blood pressure (auricular artery), end tidal CO_2, oxymetry, and core body temperature.

After surgery the animals were left to recover with the required analgesic regimen (morphine 0.5 mg/kg IM BID, flunixin 1 mg/kg IM once) and the following day as needed.

Experimental design

The experimental design is outlined in Figure 1. Sequential intracoronary injections of doxorubicin (0.75 mg/kg) were carried out every 2 weeks until echocardiographic detection of signs of myocardial systolic dysfunction. The animals were assessed 1 month after the last injection and the hearts were harvested for histological evaluation.

To avoid the inflammatory pericardial effusion induced by the doxorubicin injections (observed in a pilot study), a small pericardial window was created prior to the first injection. For this purpose, the sheep were placed in left lateral recumbency and were clipped and prepared for standard thoracoscopy. One 10-mm cannula and two 5-mm cannulae were inserted into the thoracic cavity. A 0° 10-mm telescope connected to a video camera and monitor was inserted through the 10-mm cannula; atraumatic tissue forceps as well as scissors connected to cautery were inserted through the 5-mm cannula. A 3-cm window was created. The three portals were closed in two layers and a chest tube was left in place for 1 hour postoperatively. The sheep were then placed in dorsal recumbency for left ventricular catheterization.

The left or right femoral artery was percutaneously cannulated with a 5-French introducer. After 0.25 mg/kg of an IV bolus of heparin, a 5-French pigtail calibration catheter was advanced into the left ventricle (LV) under fluoroscopy and a standard one-plane cineventriculography at 25 frames per second was carried out, taking care not to include either ventricular premature beats or postextrasystolic beats. End-diastolic and end-systolic volumes were calculated by the area-length method[2] and used to calculate ejection fractions with the aid of a medical imaging software (Osiris 4.09).

After functional assessment, an Amplatz guiding catheter (AL 2, CORDIS®) was used to catheterize the left coronary ostium. Adequate placement of the catheter's tip was checked with small boluses of contrast media. A constant rate intracoronary infusion of 0.75 mg/kg doxorubicin (Adriblastine, Pharmacia & Upjohn®, St. Quentin en Yvelines, France) diluted in 50 mL of saline was started with a syringe pump and maintained over 60 minutes. Doses were determined in a pilot study. Animals were closely monitored in the immediate postoperative period for signs of arrhythmia or ventricular dysfunction.

In addition to echocardiographic examinations and left heart catheterization, a blood sample was collected and centrifuged for atrial natriuretic factor (ANF) as an indicator of atrial and ventricular dilation; plasma was stored at −20°C until the end of the study, when the whole batch was processed by radioimmunoassay.[3,4] The complete functional assessment (echocardiography, ANF, and left heart catheterization) was carried out at day 0 and before harvesting the hearts, 1 month after the last injection of doxorubicin.

Conventional echocardiography and tissue Doppler imaging examinations

Transthoracic conventional echocardiography and tissue Doppler imaging (TDI) examinations were performed by a single experienced operator, with continuous ECG monitoring, using a Vingmed system 5 (General Electric medical system, Waukesha, WI, USA) equipped with a 2.2 to 3.5 MHz phased-array

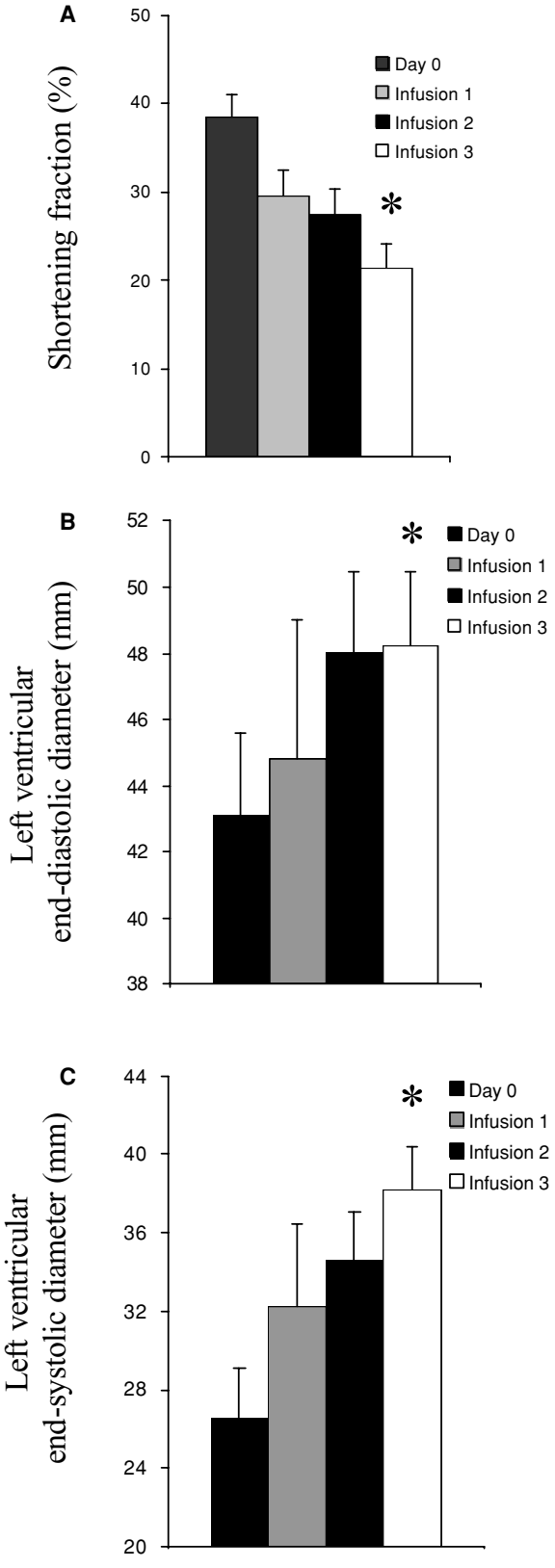

Figure 2. *Conventional echocardiographic parameters (mean ± SD, n = 10) recorded at day 0 and after sequential intracoronary infusions of doxorubicin (end of the protocol): shortening fraction (2A) systolic and diastolic left ventricular diameters (2B and 2C, respectively). Comparison between baseline (day 0) and after infusion 1, 2, and 3, *p < 0.001.*

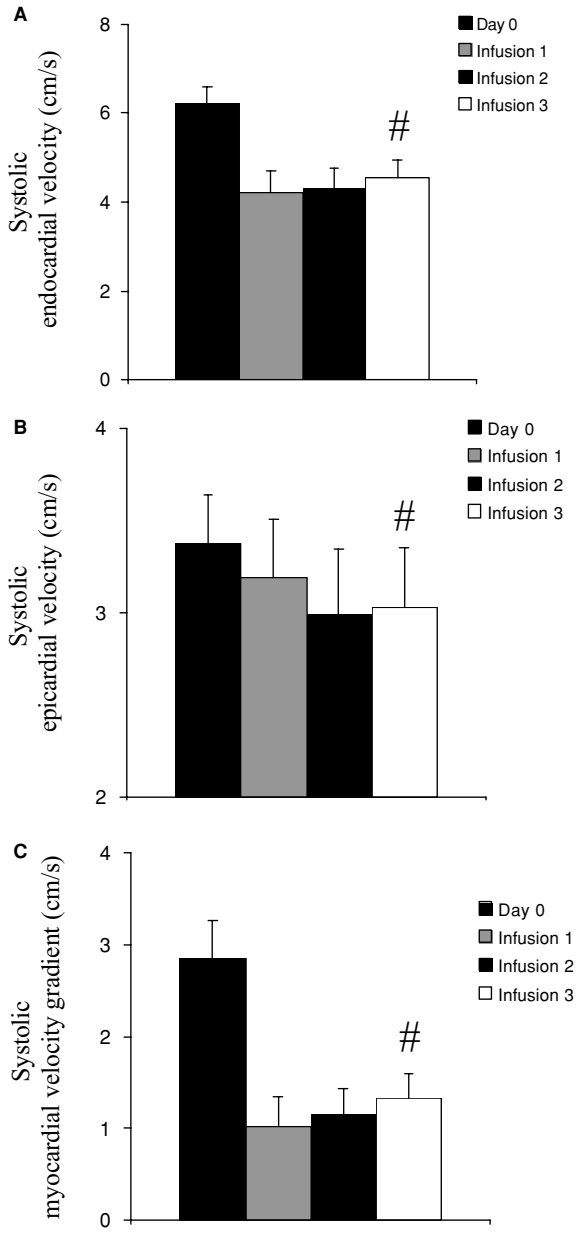

Figure 3. *Left ventricular TDI parameters (mean ± SD, n = 10) recorded at day 0 and after sequential intracoronary infusions of doxorubicin (end of the protocol): systolic endocardial (3A) and epicardial (3B) myocardial velocities, and systolic myocardial velocity gradients (3C). Comparison between baseline (day 0) and after infusion 1, 2 and 3, #p < 0.05.*

transducer. Animals were anesthetized with IV injections of 0.5 mg/kg midazolam and 10 mg/kg ketamine. Oxygen was supplied with a face mask.

The animals were placed in ventral recumbency and hair was clipped between the right fourth and seventh intercostal spaces. All transthoracic echocardiographic and TDI measurements included a mean of three consecutive beats.

Left ventricular dimension measurements were performed using 2D-guided M-mode on the right parasternal ventricular short-axis view,[5] according to the recommendations of the American Society of

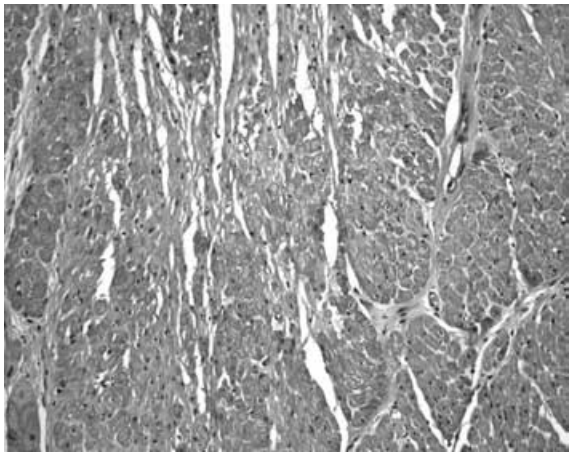

Figure 4. *Histological lesions. Note vast areas of replacement fibrosis.*

Echocardiography.[6] Left ventricular end-systolic and end-diastolic diameters (LVES, LVED) were measured and left ventricular shortening fractions (LVSF) were then calculated.

Two-dimensional color TDI was performed after each conventional echocardiographic examination. Measurement of myocardial velocities resulting from the radial left ventricular motion was carried out using the right parasternal ventricular short-axis view between the two papillary muscles. Real time color Doppler was superimposed on grayscale with a frame rate $\geq$100 frames per second. Doppler velocity range was set as low as possible to avoid occurrence of aliasing. Digital images were obtained and stored for later assessment using an offline measuring system (Echo Pac for System 5). Two-millimeter sampling was used and a tissue velocity profile was displayed in each sample location that is, the endocardial and epicardial segments of the left ventricular free wall. Endocardial and epicardial velocity profiles were obtained simultaneously during the offline analysis. The peak values of myocardial velocities were determined for each segment in systole (S) and the corresponding myocardial velocity gradient (MVG) was then calculated (difference between simultaneous endocardial and epicardial velocities).

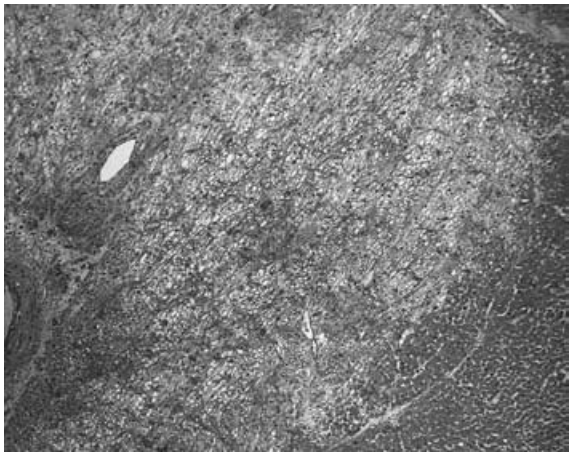

Figure 5. *Large subepicardial focus of degenerative myocardium made of vacuolated degenerative myocytes surrounded by some fibrosis.*

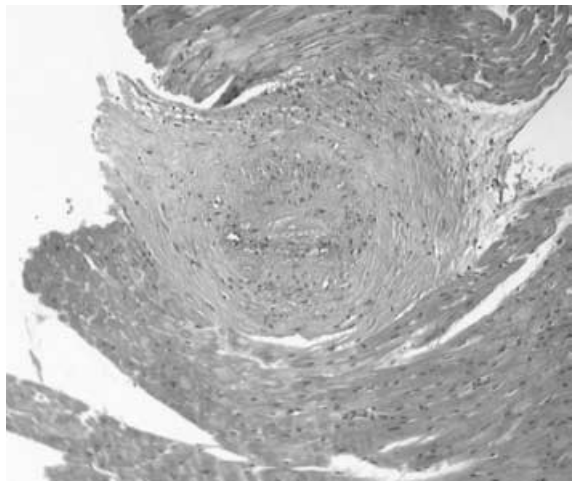

Figure 6. *Some vessels displayed lesions, such as intimal hyperplasia. Some rare vessels were also occluded.*

Histology

All sheep were euthanized 1 month after the last intracoronary injection. Heparin (10,000 IU) and 60 mg/kg of sodium pentobarbital were injected intravenously. The heart was harvested through a left thoracotomy and perfusion fixed with 3% formalin for histological evaluation.

Formalin-fixed, paraffin-embedded blocks from the LV were processed. Serial 5-μ sections from the harvested area were prepared for conventional HES staining. A pathologist assessed myocardial sections.

Statistics

Indices of cardiac function from baseline to last day of protocol were recorded. The data are presented as mean $\pm$ SD. Indices of cardiac function from baseline to last day of protocol were recorded and their differences were evaluated by a Wilcoxon rank test for paired data. A value below 0.05 was considered significant.

RESULTS

Ten sheep received 2.5 $\pm$ 0.7 intracoronary injections of a cumulative dose of 88.8 $\pm$ 25 mg/m^2 doxorubicin. Although the sheep did not show any clinical sign of overt heart failure all available parameters demonstrated signs of severe cardiac dysfunction.

Ejection fraction and ANF

Ejection fraction as assessed by cineventriculography decreased from 51 $\pm$ $-$3.5% preoperatively to 34.8 $\pm$ 6.1% at the end of the protocol, which was statistically significant ($p = 0.0156$). ANF increased markedly from 28 $\pm$ 15.7 pg/mL to 138.5 $\pm$ 121.2 ($p = 0.125$).

Echocardiography and TDI examinations

As expected, intracoronary infusions of doxorubicin resulted in statistically significant decrease in SF from day 0 (38.4 ± 5.7%) to the last injection (20.9 ± 7.1%) ($p = 0.008$), and increase in systolic (26.2 ± 4.5 mm vs. 41.5 ± 9.5 mm) ($p = 0.005$) and diastolic (42.2 ± 6.7 mm vs. 51.8 ± 8.7 mm) ($p = 0.008$) left ventricular diameters (Fig. 2).

TDI alterations occurred earlier and were observed after the first injection in some cases (data not shown). Systolic endocardial and epicardial velocities significantly decreased after the doxorubicin infusions ($p = 0.012$ and $p = 0.01$, respectively) (see Fig. 3). This severe impairment led to a decrease in systolic MVG ($p = 0.022$).

Histology

All hearts demonstrated severe histological lesions, some of which were consistent with doxorubicin-induced toxicity, including myocyte degeneration and severe interstitial and replacement fibrosis (see Figs. 4 and 5). Some of the vessels displayed intimal hyperplasia and abnormal smooth muscle cells. Some of these rare vessels were occluded (see Fig. 6).

CONCLUSIONS

Achieving a reliable large animal model of heart failure is a critical component of successful research on new CHF treatment modalities. Heart failure models in large animals have been achieved through many different modalities and in different species. Rapid-pacing does provide reproducible left ventricular dilation and signs of dilated cardiomyopathy but is known to be reversible and is therefore unfit for long-term studies.[7,8] Volume or pressure overload has commonly been used in the past but these methods are limited by the difficulty of controlling disease severity.[7]

Heart failure has been obtained through acute or chronic, complete or partial, surgical or interventional occlusion of the coronary arteries.[9-14] There are pros and cons for each of these models as regards technical ease, cost, reliability, and outcome, but they are mostly relevant for the study of ischemic disease. We wanted to concentrate on dilated cardiomyopathy. A spontaneous model of cardiomyopathy is well-known in the Syrian hamster but the size of the animals makes them unsuitable for the study of novel surgical modalities such as cardiomyoplasty, ventriculoplasty, or mechanical assist devices.

DCM is also a well recognized cause of spontaneous heart failure in large and giant breed dogs. Canine DCM bears a poor prognosis with a 1 and 2-year survival rate of 17.5% and 7.5%, respectively.[15,16] Clinical, hemodynamic, and histological findings have shown these large breed dogs to be a relevant clinical model for human cardiology.[17] However, canine DCM is a relatively rare condition and there is no readily available colony for CHF studies. We have previously reported the use of this model in a preliminary study on cell therapy for DCM.[18] Although the setting of the study was clinically relevant, animals had to take part in a veterinary clinical trial with the written consent of their owners, which made the logistic and ethical part of the study very difficult to carry out.

Doxorubicin has been widely used to induce heart failure in several animal models. Doxorubicin is one of the most widely prescribed and effective cytotoxic drugs used in oncology. It is a potent, broad spectrum chemotherapeutic agent effective against solid tumors and malignant hematological disease.[19] However, the use of doxorubicin is limited by cumulative, dose-related, progressive myocardial damage that may lead to irreversible CHF. In humans, a cumulative dose of 400 mg/m^2 of intravenous doxorubicin is known to be cardiotoxic in 3.5% to 5% of patients and 550 mg/m^2 is cardiotoxic in 7% to 26% of patients.[20,21] Several mechanisms are thought to be involved in doxorubicin-induced cardiac dysfunction, among which are DNA intercalation and oxidative stress.[19,22] Recent studies have indeed shown that doxorubicin induces apoptosis as well as necrosis in myocytes through generation of reactive oxygen species.[23,24] But there is growing evidence that cardiotoxicity may also be the consequence of endothelial cell apopotosis.[19] This could be consistent wih the occasional endothelial lesions we found in our model.

Rodents, rabbits, monkeys, dogs, and ruminants have been used in doxorubicin-induced heart failure studies.[25-37] Rodents and rabbits usually receive daily or weekly intraperitoneal or intravenous injections.[28] Dogs are also known to be a reproducible and useful large animal model for the study of doxorubicin toxicity.[26] Systemic effects can be devastating such as colitis, anemia, myelosuppression, lymphoid atrophy, and alopecia.[26] Several groups have addressed this problem using transcatheter infusion directly into the coronary artery, delivering higher peak concentrations to the myocardial cells while reducing the systemic effects.[29-33] Fatal arrhythmia remains a serious side effect of this model.[38] Goats and sheep have also been used as a doxorubicin-induced heart failure model.[34-36] Only intravenous methods have been reported so far. To our knowledge our study is the first to establish the feasibility and reliability of sequential intracoronary transcatheter injections of doxorubicin in the sheep. We have systematically obtained LV dilation, increased plasma levels of ANF, signs of global as well as regional contractile dysfunction.

The present study also underlines the use of TDI as a very sensitive tool for monitoring myocardial dysfunction. TDI is a new noninvasive ultrasound technique that enables quantification of regional myocardial velocities in real time.[39] TDI is a sensitive technique that can detect and quantify mild changes in regional wall motion that may occur during ischemia or reperfusion.[39] Its use has also been shown to be relevant for the detection of systolic and diastolic dysfunction in dilated cardiomyopathy and anthracycline-induced cardiotoxicity.[40]

One first limitation of the present model is that a pericardial window was necessary in order to avoid a possible tamponade due to the inflammatory pericardial

effusion. This complication was never reported in the dog. Thoracoscopic pericardial window opening is fairly simple and can be accomplished in 20 minutes. But it does require specific equipment and the presence of a trained surgeon. Because of several cases of tamponade and our early need to adjust the dosage of doxorubicin, mortality rate was high in the pilot study we carried out (survival rate: 33%). However, as regards doxorubicin-induced heart failure models, this mortality rate was in the general range of previously published studies.[30,33] Now that dosages are fine-tuned and pericardial window openings are performed, current survival rate is almost 90%. This drop in mortality reflects the learning curve of the investigators.

In conclusion, our data indicate that this ovine model is reproducible and stable. It can therefore be relevant to the study of chronic heart failure. It will be incorporated in our future studies concerning novel treatments (such as cell therapy) of nonischemic dilated cardiomyopathy.

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