Is Injury to the Thoracodorsal Nerve Present after Long Term Dynamic Cardiomyoplasty in Goats?

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Abstract

Long term dynamic cardiomyoplasty is associated with atrophy, fibrosis, and fatty infiltration of the latissimus dorsi muscle (LDM). Ischemia, decreased muscle preload and chronic electrical stimulation have been recognized as factors for muscle deterioration after cardiomyoplasty. Transposition of the LDM around the heart might be associated with damages to the thoracodorsal nerve that can contribute to LDM deterioration. The purpose of the study was to evaluate the neuromuscular function of the thoracodorsal nerve and LDM after dynamic cardiomyoplasty. We performed neuromuscular functional analysis and histology on the LDM and thoracodorsal nerve of 6 normal goats and 6 goats after 6 months of dynamic cardiomyoplasty. Electromyographic analysis showed positive sharp waves and fibrillation potentials in the LDM of 3 goats from the dynamic cardiomyoplasty group. Conduction velocity of the thoracodorsal nerve of goats from the dynamic cardiomyoplasty group (58.32±9.80m/s) was reduced compared to the goats from the control group (71.48±5.71m/s, p=0.02). Loss of myelin sheaths, collapse of endoneurial connective tissue, and solitary foci of axonophagia and myelinophagia further documented severe injury to the thoracodorsal nerve in goats from the dynamic cardiomyoplasty group. The LDM wrap was denervated after long term dynamic cardiomyoplasty.

Key words: cardiac assist, degeneration, electromyography, goat, skeletal muscle.

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Skeletal muscle degeneration is emerging as a limitation to long term dynamic cardiomyoplasty. Fibrosis, fatty infiltration, necrosis and atrophy have been observed in the latissimus dorsi muscle of patients after cardiomyoplasty and in experimental animals after chronic electrostimulation of the skeletal muscle [1-5, 8, 11, 14-20, 22, 23].

El Oakley et al [11] showed that chronic electrical stimulation, decrease muscular preload, and ischemia are reasons for the muscle injury after in-situ skeletal muscle stimulation. Ianuzzo et al [15] demonstrated in a study on goats that surgical dissection exacerbates the muscle degeneration after in-situ chronic electrical stimulation. Chronic electrical stimulation of in-situ skeletal muscle does not necessarily reproduce the physiologic and anatomic conditions of the skeletal muscle flap during dynamic cardiomyoplasty. Transposition of the latissimus dorsi muscle on its neurovascular pedicle in the thoracic cavity results in modifications of the orientation of the neurovascular pedicle and forces of traction of the latissimus dorsi muscle on its neurovascular pedicle. These modifications might induce some damages to the thoracodorsal nerve during dynamic cardiomyoplasty. In a study on goats, Lucas et al [20] reported a difference in skeletal muscle deterioration between in situ skeletal muscle and wrapped skeletal muscle after chronic electrical stimulation. Indications of muscle denervation such as augmentation of endoneural tissue and spreading of acetylcholinesterase enzyme activity were only present in the wrapped skeletal muscle [13, 20].

Since dynamic cardiomyoplasty requires transposition of the skeletal muscle in the thoracic cavity and wrapping of the skeletal muscle flap around the heart, it is necessary to evaluate the skeletal muscle degeneration after chronic electrical stimulation with a wrapped skeletal muscle. To further define the muscle degeneration

after dynamic cardiomyoplasty we performed electromyographic evaluation of the skeletal muscle and nerve velocity analysis of the thoracodorsal nerve after long term dynamic cardiomyoplasty. We also performed histologic analysis of the latissimus dorsi muscle and thoracodorsal nerve after long term dynamic cardiomyoplasty

Materials and Methods

This study was performed according to "The Guide for the Use and Care of Laboratory Animals". Twelve goats were divided into 2 groups: a control group (n=6), and a cardiomyoplasty group (n=6). Goats in the control group received no treatment and were studied to establish reference values for electromyography (EMG), nerve conduction velocity, and histology. Goats in the cardiomyoplasty group had a dynamic cardiomyoplasty performed and were stimulated for 6 months according to a standard clinically-relevant protocol. At the end of the study period, EMG, nerve conduction velocity, gross anatomical, skeletal muscle fiber typing, and histopathologic studies were performed.

Surgery and anesthesia protocol

General anesthesia was induced by intravenous injection of propofol (4mg/kg). After endotracheal intubation, goats were maintained under anesthesia by inhalation of oxygen and isoflurane. Positive pressure ventilation was maintained with a volume-cycle ventilator. Each goat was monitored with ECG, direct arterial pressure, central venous pressure, end tidal CO_2, arterial oxygen saturation, and arterial blood gases. Ceftiofur was administered intravenously (2mg/kg) at the time of anesthesia induction and repeated every 2 hours. Penicillin G procaine was administered intramuscularly 1 hour before induction (22,000 UI/Kg) and daily thereafter until drains were removed.

Goats were placed in left lateral recumbency with the right forelimb extended and abducted. An incision was made on the right lateral thorax from the distal third of the humerus to the dorsal third of the last rib. The subcutaneous and costal surfaces of the right latissimus dorsi muscle were surgically isolated as was the thoracodorsal neurovascular pedicle. Goats in the control group were studied without further surgery. EMG and nerve conduction studies were performed on the in situ latissimus dorsi muscle. Tissue samples were collected for muscle fiber typing and histology according to the protocol outlined below.

Goats in the cardiomyoplasty group underwent cardiomyoplasty surgery at this time. A cranial (anterior) cardio-subcutaneous muscle wrap was performed with the right latissimus dorsi muscle according to a standard surgical procedure [12, 21]. Standard bipolar intramuscular leads (Telectronics Pacing Systems, Inc, 7400 Sth Tucson Way, Englewood, CO 80112) were implanted in the proximal latissimus dorsi muscle of goats in the cardiomyoplasty group. The cathode was placed just distal to the trifurcation of the thoracodorsal nerve, and the anode was placed 4 to 5 cm distal to the cathode. The latissimus dorsi muscle was introduced in the thoracic cavity and two mattress sutures were placed to secure the latissimus dorsi insertion to the costal periosteum and intercostal muscles. Two electrodes (Myocardial Screw-In unipolar VS-1 Silicone pacing lead, Telectronics Pacing Systems, Inc, 7400 Sth Tucson Way, Englewood, CO 80112) were implanted into the lateral wall of the right ventricle and connected with a Y-adapter for bipolar cardiac sensing. The muscle wrap was secured to the pericardium with 3-0 mattress sutures placed from the inside of the pericardium. The sensing and myostimulating electrodes were exteriorized through the thoracic wall, and connected to a myostimulator (Model 7220, Telectronics Pacing Systems, Inc, 7400 Sth Tucson Way, Englewood, CO 80112) implanted in a pouch between the external and internal oblique muscles.

Cardiomyoplasty stimulation protocol

The latissimus dorsi muscle flap was rested for 2 weeks to allow for revascularization of the flap and adhesion of the flap to the epicardium. The muscle was initially stimulated with one pulse for 14 days. Pulse number was increased to 2, 4, and then 6 pulses every 14 days. Pulses were delivered at a frequency of 35 Hz with a delay of 50.8 ms after the R wave was sensed. The heart muscle synchronization ratio was set at 1:1 for heart rates below 60 bpm, 2:1 for heart rates between 60 and 120 bpm, and 3:1 for heart rates over 120 bpm. After the training protocol was complete, goats were stimulated continuously with a 6-pulses burst for six months after the initial surgery. During this period, each goat was palpated and auscultated weekly to ensure that active muscle contraction could still be detected. If muscle contractions could not be detected, then pulse voltage or width was increased until muscle contraction could be detected.

Electromyography and nerve conduction velocity

EMG and nerve conduction velocity studies were performed on in situ unwrapped latissimus dorsi muscle of goats in the control group. Six months after cardiomyoplasty surgery, goats in the cardiomyoplasty group were anesthetized with the same protocol described above and the right thoracic wall was surgically resected leaving the neurovascular pedicle and cardiomyoplasty wrap intact. EMG and nerve conduction velocity studies were performed on the in situ wrapped latissimus dorsi muscle and thoracodorsal nerve with the myostimulator OFF.

Electromyography was performed with concentric electrodes (Disa Concentric Electrode Denmark) connected to an electromyograph (Disa Neuromatic 2000C Den-

mark). A ground electrode was placed in a subcutaneous area close to the muscle. Electromyographic activity was recorded in the proximal, middle and distal third of the latissimus dorsi muscle with a continuous sweep speed of 50 msec per screen. Electrical activity other than normal electrode insertion activity was recorded as abnormal insertional activity, end plate noise, motor unit potentials, positive sharp waves, and fibrillation potentials. The electromyographic results were reported as normal or abnormal for each site.

Motor nerve conduction velocities were determined by placing a recording electrode in the distal latissimus dorsi muscle and two stimulating electrodes on the thoracodorsal nerve (Teca Teflon Coated Needle). The stimulating electrodes were bipolar with the anode 5 mm proximal to the cathode. The distance between the two stimulating electrode sites was precisely measured. Latency (sec) was measured for each stimulating site. The motor nerve conduction velocity (MNCV) was calculated as follows:

MNCV = (Distance between site 1 and 2)/(Stimulation site 1 latency-Stimulation site 2 latency) m/sec

Muscle temperature was recorded during the procedure.

Histopathology

Tissue samples were taken from proximal, middle, and distal third of the right latissimus dorsi muscle of each goat. Muscle tissue was gently mounted on a board of wood and fixed in 10% neutral buffered formalin. Specimens were dehydrated, embedded in paraffin, and sectioned at 4-6 microns transversely, and mounted on microscopic slides and stained with hematoxylin and eosin. Both transverse and longitudinally oriented sections were evaluated. Morphometric analysis was performed to determine the percent cross-sectional area of fat in the muscle sample.

Tissue samples (2 mm x 2 mm x 2 mm) also were frozen in isopentane carefully positioned for transverse sectioning, and stained for myosin ATPase activity with acid (pH: 4.3) and alkaline (pH: 10.4) preincubation.(27) At pH:4.3, type I fibers are black and type 2 fibers are pale. At pH:10.4, type 1 fibers are pale and type 2 fibers are dark. Percentage of muscle fiber type I, and type II were determined by morphometric analysis with light microscopy (10 X).

Tissue samples of the thoracodorsal nerve in the proximal portion of the nerve outside of the thoracic cavity was collected. Nerve biopsies were gently mounted on a board of wood and fixed in 10% neutral buffered formalin. Specimens were prepared for histologic analysis as described above.

Statistical analysis

A one-way analysis of variance was used to evaluate the effect of treatment (control vs cardiomyoplasty) on nerve conduction velocity. A two-way analysis of variance was used to evaluate the effects of treatment, location of the muscle biopsy and interaction between treatment and location on morphometric measurement of fat infiltration and the percentage of Type I myofibers. A Fisher's protected least significant difference was used as the post hoc test. A Fisher exact test was used to evaluate the effect of treatment on electromyography results. Significance level was set at $p<0.05$.

Results

According to the protocol, all goats in the dynamic cardiomyoplasty group were anesthetized 6 months after the original procedure to expose the right hemithorax and performed electromyographic evaluation and nerve conduction velocity measurement. Fibrous tissue and bone proliferations were present around the thoracodorsal neuro-vascular pedicle at the 2nd rib space in each goat 6 months after dynamic cardiomyoplasty (Figure 1). The fibrous tissue and bone proliferations were compressing the neuro-vascular pedicle. The neurovascular pedicle in one goat was accidentally severed during surgical dissection because of the amount of fibrous tissue present. Nerve conduction velocity and electromyographic evaluation could not then be performed on this goat.

Electromyographic and nerve conduction data

Three of 5 goats in the dynamic cardiomyoplasty group had positive sharp waves or fibrillation potentials, or both, on electromyography versus none of 6 goats in the control group ($p=0.034$). Abnormal electromyographic changes were observed in the proximal part of the latissimus dorsi muscle in 3 goats, and abnormal electromyographic changes were observed in the middle part of the latissimus dorsi muscle in 1 goat. None of the goats in the cardiomyoplasty group had abnormal electromyographic changes in the distal part of the latissimus dorsi muscle. Nerve conduction velocities were slower ($p=0.02$) in the cardiomyoplasty group compared

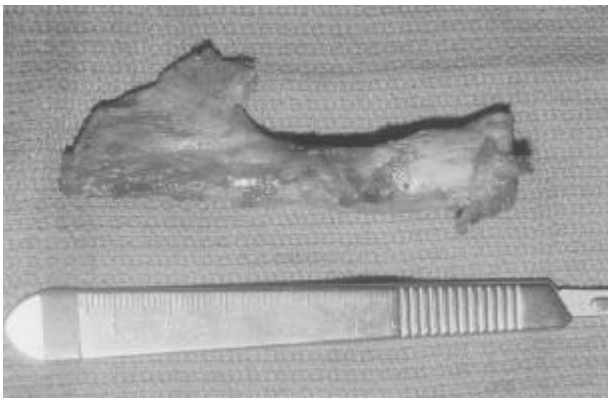

Figure 1. Fibrous tissue and bone proliferations present at the 2nd rib space 6 months after dynamic cardiomyoplasty.

to velocities in the control group (Table 1). Peak voltage amplitudes were decreased (p=0.002) in the cardiomyoplasty group compared to amplitudes in the control group. Muscle temperature at the time of the studies was not significantly different between the two groups.

Histologic data

Latissimus dorsi muscles from control goats were grossly and microscopically normal (Figure 2A; 3A). The latissimus dorsi muscles were discolored, thin, and fibrotic on gross examination in all goats from the cardiomyoplasty group. Microscopic examination revealed infiltration of muscle fibers with fatty and fibrous tissue associated with moderate myofiber atrophy in goats from the cardiomyoplasty group (Figure 2B; 3B). Degenerative myofibers were present in latissimus dorsi muscles from all goats in the dynamic cardiomyoplasty group and were characterized by swollen eosinophilic sarcoplasma with loss of striations. Mild proliferation of myocytes and satellite cell nuclei was present along the sarcolemmal membrane in latissimus dorsi muscle of goats in the cardiomyoplasty group. Chronic electrical stimulation for 6 months resulted in a significant fat infiltration of the latissimus dorsi muscle (Table 2). Electrical stimulation resulted in pronounced transformation to the fatigue resistance type 1 fibers in all examined latissimus dorsi muscles (Table 3).

The thoracodorsal nerves from control goats were grossly and microscopically normal (Figure 4A). Four of 5 goats in the cardiomyoplasty group showed marked loss of myelin sheaths with collapse of endoneural connective tissues in the thoracodorsal nerve. An increase in endoneural connective tissue was present in the thoracodorsal nerve of the goats in the dynamic cardiomyoplasty group (Figure 4B). Solitary foci of axonophagia and myelinophagia also were present in these histologic sections of the thoracodorsal nerve .

Discussion

Severe degenerative changes in the latissimus dorsi muscle structure were present in all the goats after wrapping and chronic electrical stimulation for 6 months.

Table 1. Nerve conduction data of the thoracodorsal nerve muscle in the cardiomyoplasty group (n=5) and the control group (n=6) at 6 months.

Group	Nerve Conduction Velocity (m/s)	Peak amplitude (mV)	
		First	Second
Cardiomyoplasty	58.32±9.80*	1.65±1.17*	1.78±1.29
Control	71.48±5.71	27.10±9.21	23.30±8.3

All data are expressed as mean ± standard deviation. * Significant difference between the latissimus dorsi muscle in the cardiomyoplasty group and the control group ($p<0.05$).

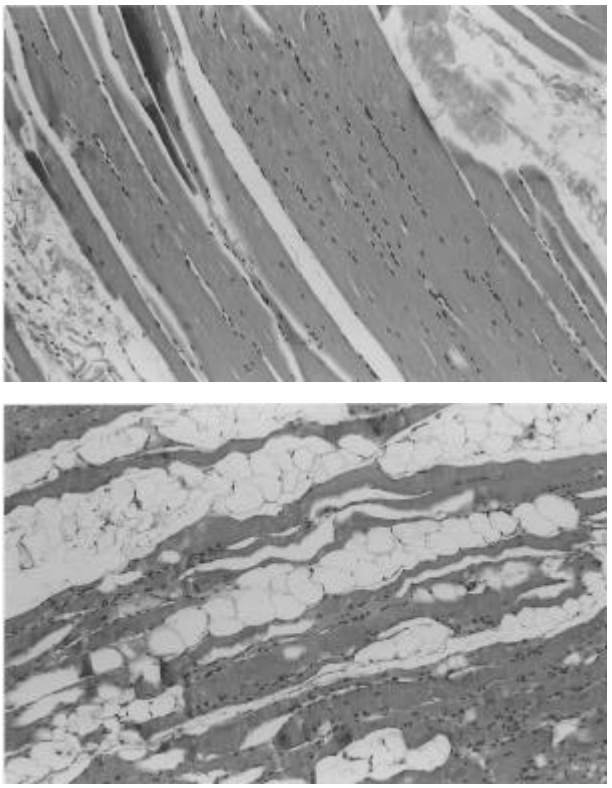

Figure 2. A: Photograph of a unwrapped and non stimulated latissimus dorsi muscle (Hematoxylin and Eosin stain, X 125). B: Photograph of a wrapped and long term stimulated latissimus dorsi muscle demonstrating the severe fat infiltration (Hematoxylin and Eosin stain, X 125).

Fat cells and fibrous tissue replaced muscle fibers. The orientation of the muscle fibers was not preserved. Histologic changes in this study are similar to those reported after long term cardiac assist in human patients as well as in experimental models [1, 14-16, 18, 22].

Presence of fibrillation potentials during the electromyography evaluation of the latissimus dorsi muscle and reduction of the nerve conduction velocity of the thoracodorsal nerve are two indications of latissimus dorsi muscle denervation after long term dynamic cardiomyoplasty. Collapse of endoneural connective tissue of residual axons, increase in endoneural connective tissue, axonophagia, and myelinophagia observed on nerve histology further support this conclusion. These changes are compatible with, but not specific for, partial or complete denervation of skeletal muscle [2, 13]. Lucas et al [20] showed spreading of the acethycholinesterase enzyme activity on the surface of the latissimus dorsi muscle and direct trauma to the large nerve branches in the pedicle near the intramuscular electrodes after dynamic cardiomyoplasty. Spreading of acethycholinesterase enzyme activity is considered an early sign of skeletal muscle denervation [13]. Lucas et al [20] did not perform electrophysiologic analysis of the latissimus dorsi muscle and thoracodorsal nerve to further document the

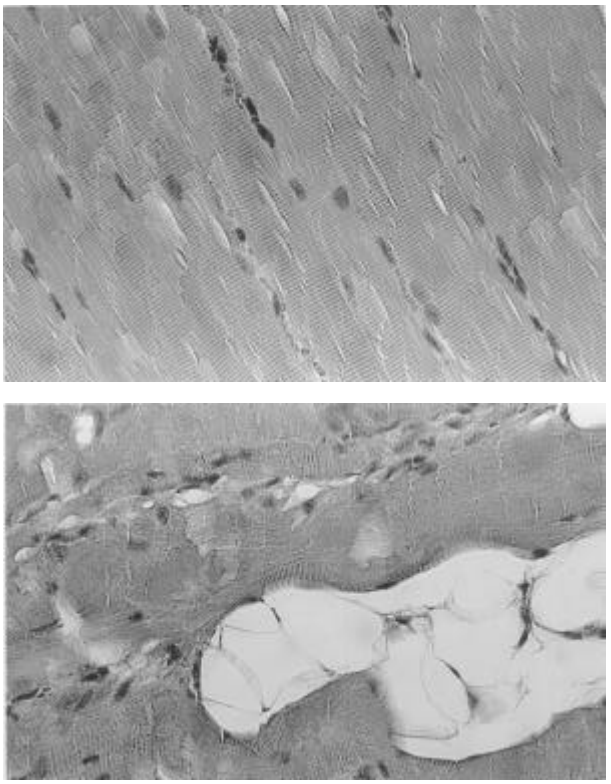

Figure 3. A: Photograph of a unwrapped and non stimulated latissimus dorsi muscle (Hematoxylin and Eosin stain, X 500). B: Photograph of a wrapped and long term stimulated latissimus dorsi muscle demonstrating the loss of skeletal muscle striation, and the disorganization of the myofibers (Hematoxylin and Eosin stain, X 500).

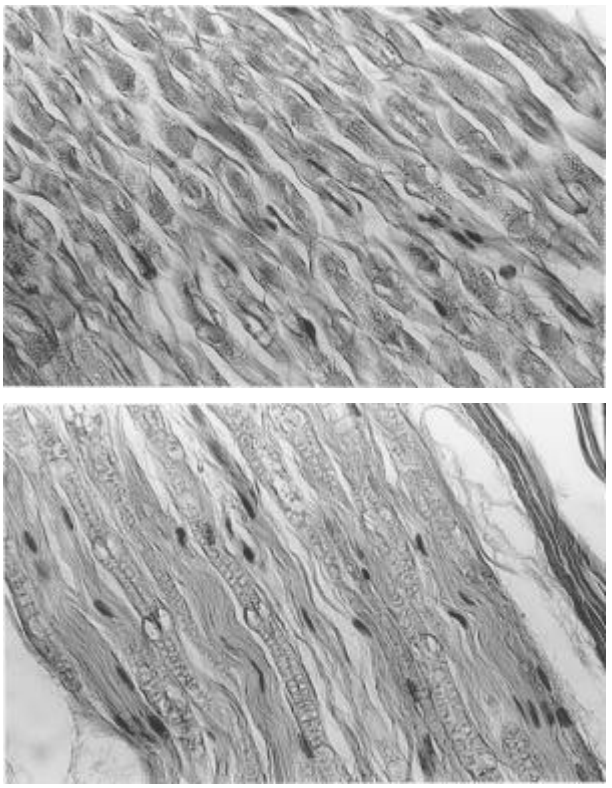

Figure 4. A: Photograph of a thoracodorsal nerve from a control goat. (Hematoxylin and Eosin stain, X 500). B: Photograph of a thoracodorsal nerve from a goat in the cardiomyoplasty group demonstrating marked reduction of axons and loss of myelin sheaths with collapse of endoneural connective tissues in the thoracodorsal nerve group after 6 months of electrical stimulation. An increase in endoneural connective tissue was also present in the thoracodorsal nerve between the remaining axons. The remaining axons were smaller than in the nerve of control goats (Hematoxylin and Eosin stain, X 500).

physiologic importance of the lesions they reported. Denervation could lead to the decay of a large number of muscle fibers, with subsequent replacement with fat cells [2, 13]. Denervation injury in our model is most likely contributing to the muscle degenerative changes observed after dynamic cardiomyoplasty.

Chronic electrical stimulation, decreased muscular stretch or preload, and ischemia all have been suggested in situ skeletal muscle and no evidence of muscle den-

Table 2. Histologic data concerning changes in the latissimus dorsi muscle in the cardiomyoplasty group (n=6) and the control group (n=6).

Group	Fat tissue infiltration (%)		
	Proximal	Middle	Distal
Cardiomyoplasty	46.40±27.66*	71.24±33.77*	45.65±24.18*
Control	1.14±2.20	1.05±0.91	1.42±1.43

All data are expressed as mean ± standard deviation. * Significant difference between the latissimus dorsi muscle in the cardiomyoplasty group and the control group ($p<0.05$).

Table 3. Percent of fiber type 1 in the latissimus dorsi muscle in the cardiomyoplasty group (n=6) and the control group (n=6) at 6 months.

Group	Type 1 fibers (%)	
	Acid	Alkaline
Cardiomyoplasty	85.11±27.97*	43.11±21.41*
Control	28.87±16.61	0.17±0.51

All data are expressed as mean ± standard deviation. * Significant difference between the latissimus dorsi muscle in the cardiomyoplasty group and the control group ($p<0.05$).

muscle changes were also more severe in the wrapped and electrically stimulated latissimus dorsi muscle than in the in situ electrically stimulated latissimus dorsi muscle [20]. Transposition in the thoracic cavity and wrapping of the skeletal muscle flap around the heart are more likely inducing a denervation of the skeletal muscle after dynamic cardiomyoplasty.

Fibrosis, changes in pH, corrosion, and heat production all have been identified as possible causes of nerve injury close to intramuscular electrodes during chronic electrical stimulation of skeletal muscle [24-26]. Lucas et al [20] attributed the denervation of the wrapped skeletal muscle after chronic electrical stimulation to ischemia of the thoracodorsal nerve, direct trauma to the thoracodorsal nerve from the intra-muscular electrodes, and the voltage of the electrical impulses. Since the nerve injury observed in this study was cranial to the electrode site, another mechanism seems more likely responsible for the observed injury. Muscle atrophy could be the primary cause of distal axonopathy or "dying back neuropathy" [6, 7]. Distal axonopathy is characterized by axonal atrophy, myelin remodeling and axonal degeneration [9]. A study in cats by de la Cruz et al [7] showed that muscle degeneration induced a transient distal axonopathy. One month after suppression of the target muscle the nerve recovered a normal function [6]. Since in our study the nerve function was abnormal 6 months after the initial surgery it is more likely that muscle atrophy was not the main reason for the distal axonopathy. However, our experiment could not completely eliminate this cause of distal axonopathy. Repeated traction on the neurovascular pedicle with each heart beat and muscle contraction may induce a neuropraxia to the thoracodorsal nerve. In this study, the latissimus dorsi insertion was secured to the costal periosteum and intercostal muscles, however, this fixation may not protect the thoracodorsal nerve from neuropraxia or more severe axonal injury. Continuous abrasion of the thoracodorsal neurovascular pedicle against the periosteum from the second rib resection might also contribute to the observed nerve injury. Finally, compression of the thoracodorsal neurovascular pedicle by scar tissue from the second rib resection might induce the nerve lesions observed in this study.

The importance of denervation as a contributing cause of skeletal muscle degeneration in clinical patients after dynamic cardiomyoplasty is unclear, however this issue is paramount to the optimization of muscle function and long term skeletal muscle cardiac assist. Direct trauma due to surgical dissection thoracodorsal neurovascular pedicle, ischemia of the nerve after dissection, repetitive traction on the neurovascular pedicle by the muscle wrap, and compression of the nerve by scar tissue at the entrance to the thoracic cavity are potential causes for the nerve injury and muscle denervation that will require further investigation. Identification of the cause of nerve injury might lead to strategies that prevent this injury.

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