

Pathological Findings of Latissimus Dorsi Muscle Grafts After Short and Long-Term Dynamic Cardiomyoplasty. Review of Published Autopsies and a Recent Post-Mortem Study of an Unconditioned Graft

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Abstract

Dynamic Cardiomyoplasty (DC) is a surgical procedure consisting of mobilization of the Latissimus Dorsi muscle (LDM) with its intact thoracodorsal neurovascular pedicle, followed by transposition into the thorax. The muscle is wrapped around the ventricles and electrically stimulated synchronously with cardiac contraction in order to assist a failing heart.

The morphological findings of the LDM specimens were analyzed in 13 published post-mortem cases in which the LDM graft was used for Dynamic Cardiomyoplasty (DC). The patients survived for 1 month to 8 years. Moreover muscle fibre and vascular changes are described after surgical deafferentation and transposition in an unconditioned LDM of a patient survived one month after DC. At this time post-operative 'degeneration of muscle fibres with interstitial oedema and extensive fibrous and fatty infiltration were observed. The epicardial-muscle interface showed signs of the recent surgery with inflammation and fibrous adhesions. Numerical reduction and necrosis of capillaries were detected mainly in the distal part of LDM graft.

At 1, 5 and 7 months after DC, the patients submitted to electric myostimulation showed mild muscular alterations and incomplete fibre type transformation. In long-term conditioned cases the electric stimulation induced an almost complete transformation of fibres into slow fatigue-resistant type 1 fibres.

Four cases were studied after 2 years DC. The LDM graft structure was preserved and variable fibrous and fatty infiltration of muscle mainly in the distal muscle was observed. In a case, LDM fibre atrophy with internal nuclei was seen at the periphery of muscle; fibre degeneration and moderate fibrosis was confined in the region between the electrodes. In a second case, the study of LDM vasculature showed a number of arteries 4 times higher than unstimulated contralateral LDM. In the long-term cardiomyoplasty, even after more than 8 years of electric stimulation, the LDM appeared to be thinner compared with that observed at the time of the surgery and showed some changes as a fibre atrophy and internal nuclei. In all cases variable fatty infiltration and connective tissue ingrowth were observed. These changes were not related to the distance from the electrodes. In the histochemically checked case, the fibre type transformation of LDM was consistent, with marked increase of type 1 fibres.

The authors conclude that surgical deafferentation of LDM mainly supporting the distal part of muscle caused ischemic changes in muscle fibres and that long-term electric stimulation induce a remodeling of the vascular bed and a progressive increase of intramuscular capillaries with discrete preservation of muscle fibres.

Key words: conditioned LDM, dynamic cardiomyoplasty, LD muscle grafts.

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Dynamic cardiomyoplasty (DC) is a surgical procedure based upon the use of conditioned Latissimus Dorsi Muscle (LDM) to support the cardiac ventricular function with the permanent electric stimulation of the muscle graft [1, 2].

In selected patients with chronic heart failure DC, improve the energetic efficiency of heart pump and the life quality of patients [1, 11, 18].

Yet DC induces a series of alterations affecting the integrity of the LDM graft. Muscle mobilisation is realized with deafferentation of the collateral circulation, mainly in the distal part of muscle, with consequent muscle ischemic damage limiting the muscular power during the phases of maximal work [7, 10]. Moreover the muscle re-configuration and electric stimulation pose a challenge to the long-term integrity of the muscle graft [7, 14].

In this review 12 published post-mortem cases in which the LDM was used for DC, were analyzed. The patients died at an interval of 1 month to 8 years after DC and the conditioned LDM graft morphology was studied with different techniques. Moreover we present a post-mortem morphological study of muscle fibres and microvasculature of an unconditioned LDM after 1 month DC.

Patients and Methods

The patients suffered from end-stage heart failure due to dilated cardiomyopathy, ischaemic cardiomyopathy or valvular pathology. At the time of surgery they were in NYHA functional class III or IV. The muscle was mobilized for transposition into the chest, the perforating vascular collaterals to the muscle were deafferentated by cauterization and the neuro-vascular pedicle was kept intact. The LDM graft was wrapped around the ventricles of a failing heart and then electrically stimulated by two intramuscular electrodes and by a myostimulator (Medtronic) according to published clinical protocols [5]. The patients survived for 1 month to 8 years.

About 3 patients had a limited clinical improvement, one had cardiac cachexia inducing atrophy and fatty infiltration of LDM graft, and the others had insufficient covering of a large heart by insufficient LDM length.

The remaining patients had variable clinical evolution with improvement from III or IV to I or II NYHA functional class. Almost all patients died suddenly, mostly of arrhythmias.

History, clinical evolution and main morphological changes in the muscle and in the intramuscular vascular bed of studied cases are reported in Table 1. In table 2 the results of the morphometric analysis in LDM capillaries from case 1 and 5 are reported.

On the death of patients, autopsies were performed after 24 hours. After gross examination, biopsy specimens were taken from the LDM graft overlying the left ventricle, which represents the mid and distal part of the muscle graft.

In all cases, LDM specimens were fixed in neutral formalin, embedded in paraffin and stained with hematoxylin and eosin.

In cases 1 and 9, fibre type composition and the percentage of type 1 muscle fibres were studied on cryostat transverse sections from specimens cooled in liquid nitrogen and treated for myosin ATP-ase pH 9.6 and 4.6 reactions [1, 8].

In cases 7 and 11, fibre typing was performed on paraffine-embedded material with immunohistochemical stains with mouse monoclonal antibodies raised against type 1 and 2 fibres. In these cases staining of tissue slices with elastine Van Gieson and Syrius Red were also performed to assess the amount of fatty and connective tissue, respectively [6].

In the case 5 [3], myosin heavy chains, myosin/actin ratio, total protein and collagen contents were analyzed according to Rizzi et al [13].

In the case 7 arteries with an inner diameter of at least mm 0.05 were counted and checked for intimal hyperplasia following elastin Van Gieson stain [6].

In patients 1 and 5, morphometry of LDM microvasculature was performed on transverse paraffine-embedded sections stained with Gomori' silver impregnation and reported as number of capillaries/muscle fibre (C/F) and capillary density for mm² (DC), as previously described [15]. The results of a contralateral normal LDM and of a post-mortem morphometric analysis of LDM in middle aged subjects [16] were used as control.

Results

Patient 1 (Scelsi et al, 1999)

One month after DC, histological changes were observed mainly in the distal portion of the unstimulated LDM. Histology revealed eosinophilic degeneration in 15% of muscle fibres, oedema of the interstitial connective tissues and dilatation of intramuscular capillaries and small vessels. Morphometric studies found that the number of capillaries related to the number of muscle fibres, i.e. the capillary-to-fibre ratio (CFR) decreased by 20% if compared with normal contralateral LDM. Electron microscopy showed degeneration and necrosis of wall of some capillaries, with nuclear preservation. In muscle fibres close to degenerating capillaries, the loss of subsarcolemmal and intermyofibrillar mitochondria, local disassembly of myofibrils and atrophy was observed. The muscle-epicardial surface was oedematous and showed inflammatory infiltrates composed by lymphocytes and neutrophils.

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Table 1.

Case	Author	Age	Death After DC	History	Death	Type 1 fibre %	Muscle morphology	Capillaries
1	Scelsi 1999	39	1 month	Congestive h. failure	Sudden	-	Degeneration Internal nuclei	Necrosis and reduction
2	Misawa 1997	40	1 month	Cardiac cachexia	Sudden	-	Atrophy, edema fat infiltration	-
3	Misawa 1997	58	5 months	Congestive h.failure	Sudden	60	Hypotrophy	Neoangiogenesis
4	Misawa 1997	62	7 months	Dilated cardiomyop	Sudden	-	Hypotrophy Fibrosis	-
5	Carraro 1996	63	15 months	Chronic h.failure	Sudden	55	Damage at needle inserction	Increase
6	Misawa 1997	60	18 months	Dilated cardiomyop	Sudden	90	Focal fibrosis	Normal
7	Davidse 1998	57	2 years	Dilated cardiomyop	End stage pump failure	-	Small fatty infiltration	-
8	Davidse 1998	66	2 years	Dilated cardiomyop	Sudden	68	Fibrosis Fatty infilt	Increase
9	Fontaliran 1997	18	2 years	Valvular disease	Sudden	-	Degeneration and atrophy	-
10	Hagege 1990	21	2 years	Valvular disease	Sudden	98	normal	-
11	Davidse 1998	-	5.5 years	Dilated cardiomyop	Hearth failure	76	Fatty infiltration	-
12	Misawa 1997	40	6 years	Dilated cardiomyop	Bowel necrosis	-	Atrophy necrosis, fibrosis	-
13	Carraro 1996	52	8.6 years	Ischemic cardiomyop	Heart failure	-	Atrophy Fibrosis	Normal

Table 2. Morphometric analysis of LDM capillaries. Capillary/fibre ratio (C/F) on normal muscle and on transposed LDM after Dynamic Cardiomyoplasty (DC).

Author	LDM	Time after surgery	Normal LDM	LDM after Cardiomyoplasty
Scelsi (1999)	Unconditioned	30 days	1.2±0.4	0.8±0.4
Carraro (1996)	Conditioned	15 months	1.2±0.1	1.6±0.1

Patient 2 (Misawa et al, 1997)

One month after DC and after initial starting of the LDM transformation protocol, histological studies showed muscle fibre atrophy, diffuse interstitial oedema and extensive fibrous and fatty infiltration of the muscle graft. In the epicardial-muscle interface fibrinous adhesions and fibrous-fatty infiltration were also observed.

Patient 3 (Misawa et al, 1997)

Five months after DC, the conditioned LDM wrap revealed minimal atrophy of muscle fibres and incomplete transformation to type 1 fibres (about 60%). The muscle-epicardium surface was thin, consisting of fibrous tissue and many blood vessels.

Patient 4 (Misawa et al, 1997)

Seven months after DC, the conditioned LDM wrap showed mild muscle fibre atrophy and fibrosis. In the epicardial-muscle interface no neovascularisation was observed.

Patient 5 (Carraro et al, 1996)

After 15 months DC, the conditioned LDM showed mild muscle atrophy and some fibres with internal nuclei. The percentage of fat tissue was 24% of the total cross-sectional area. The capillaries were frequently dilated and were increased if compared with the case 1, and with normal contralateral LDM. Main muscle alterations as a fibre degeneration, atrophy, presence of internal nuclei

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and interstitial fibrosis were seen near the electrodes. Fast to slow transformation of fibres (up to 60%) was observed in all muscle specimens after both enzyme-histochemical stains and electrophoretic analysis.

Patient 6 (Misawa et al, 1997)

After 18 months DC, the conditioned LDM showed normal findings. In the distal part of the muscle some interstitial fibrosis was seen. Fibre type transformation was almost complete (90% type 1 fibres). No neovascularisation was observed in the muscle-epicardial surface.

Patient 7 (Davidse et al, 1998)

After 2 years DC, the transposed LDM was preserved with only small amounts of fatty and connective tissues. The percentage of type 1 fibres was consistent over the entire muscle (80%). Intimal hyperplasia was detected in a muscle artery located in the middle portion of LDM. Moreover the number of blood vessels was significantly higher in comparison with the contralateral muscle (effect of electric stimulation). No studies on microcirculation were performed.

Patient 8 (Davidse et al, 1998)

After 2 years DC, the LDM graft was preserved in the proximal and middle portions. Fatty infiltration and fibrosis of muscle was evident in the distal part of LDM, with reduction of muscle fascicles. Fibre type transformation was evident with significant type 1 fibre increase (68%). No studies on intramuscular microcirculation were performed.

Patient 9 (Fontaliran et al, 1997)

After 2 years DC the left LDM graft showed discrete fibre degeneration mainly at the periphery of the muscle. Moderate interstitial fibrosis and fibre atrophy were seen near the electrodes. Type 1 fibre predominance by fibre transformation was observed. No studies on microvasculature were performed.

Patient 10 (Hagege et al, 1990)

After 2 years DC the LDM graft showed preservation of muscle structure without fibrosis. Fibre type transformation was almost complete (type 1 fibres: 98%).

No studies on muscle vasculature were performed.

Patient 11 (Davidse et al, 1998)

After 5,5 years DC, the LDM graft showed normal structure, but interstitial intrafascicular fatty infiltration and fibrosis were evident (20% fatty tissue).

Fibre type transformation was almost complete (type 1 fibres: 71%) in the distal portion of muscle graft. No studies on muscle vasculature were performed.

Patient 12 (Misawa et al, 1997)

After 6 years DC, some atrophy and interstitial fibrosis were observed mainly in the distal portion of the LDM graft. Acute inflammatory changes were seen in the muscle-epicardial interface as an expression of haematogenous spread of sepsis. No fibre typing nor studies on LDM vasculature were performed.

Patient 13 (Carraro et al, 1996)

After 8,6 years DC, the LDM graft showed discrete fibre degeneration and atrophy, and grouped fibres with centrally located nuclei. Some regenerating muscle fibres were observed and moderate interstitial fibrosis and fatty infiltration were confined in the distal part of the muscle. Small and large vessels were normal, but no morphometric analysis of capillaries nor fibre typing were performed.

Discussion

The results of almost all reviewed studies were limited by post-mortem autolysis of tissues and by the predominant utilisation of formalin-fixed material. Whereas the morphological study of LDM fibres and interstitial endomysial tissues appear partially exhaustive, very little is reported regarding structural aspects of the vascular bed of the graft and about the role of microcirculatory changes in the pathogenesis of the post-surgical muscle alterations [1, 5, 8]. In some patients, the utilisation of the automatic image analyzer permitted morphometric and statistical evaluations on the intramuscular microvasculature [1, 5]. In the case 1, the study of the intramuscular capillaries was also performed with electron microscopy [1].

The results of the fibre type characterisation by means of enzyme-histochemical or immuno-histochemical techniques were generally satisfactory, even if the published micrographs were not always of good quality. Good results have been obtained by means of the isomyosin analysis by SDS PAGE electrophoresis technique in the case 5 [4].

The objective of some reviewed studies was to study the LDM ischemic damage due to surgical deafferentation of collateral thoraco-dorsal vasculature and to the electric stimulation, especially to the possible muscular damage in the area of insertion of needle stimulators.

One month after DC, the 2 studied patients showed post-operative changes of muscle fibres with interstitial oedema and extensive fibrous and fatty infiltration. The epicardial-muscle interface also showed signs of the recent surgery with inflammatory and fibrinous adhesions [1, 2]. The recent disconnection of perforating collaterals of LDM induced numerical reduction and necrosis of capillaries in the distal part of the muscle graft [1].

At 5 and 7 months after DC, no evident muscular changes were observed and incomplete fibre type transformation (60%) was seen [12]. In almost all remaining

cases the electric stimulation induced an almost complete transformation of fibres into slow fatigue-resistant type 1 fibres [3, 12].

Four cases were studied after 2 years DC [6, 8, 9]. The LDM graft structure was generally well preserved and fibrous and fatty infiltration of muscle was variable mainly in the distal muscle. In a case, LDM fibre atrophy with internal nuclei was seen at the periphery of muscle; fibre degeneration and moderate fibrosis were confined in the region between the electrodes [8]. Concerning the possible damage to the LDM graft after DC procedure, Misawa's patients [12] had minor damage of muscle fibres and some interstitial fibrosis, in the distal part of LDM pedicle.

In the case 7, the increase in vascularisation of the long-term stimulated muscle may indicate an adaptation to the increase in type 1 fibres consequent to the electrically induced fibre type transformation [6]. The effects of the long-term cardiomyoplasty on LDM in 3 patients were described at 5, 6 and 8 years after DC [3, 6, 12]. The muscular morphology near to stimulation electrodes was studied to assess whether the electric stimulation itself was an additional cause of fibre damage. Even after more than 5 years of electric stimulation protocol, the LDM showed moderate fibre atrophy and some fibres with internal nuclei. The muscle appeared to be thinner compared with that observed at the time of the surgery. This may due in part to type 1 transformation, which may reduces the muscle mass by up to 40% [11]. In the case 11, the transformation of fibre types of LDM was consistent, with marked increase of type 1 fibres (76%). In all cases variable fatty infiltration and connective tissue ingrowth were also observed. These changes were not related to the distance from the electrodes. In cases 12 and 13, studies on fibre type transformation and on microvasculature were excluded because autoptic muscle specimens were obtained several hours after death [4, 12].

The comparison of the results between microvasculature of the LDM in the case 1 (unconditioned muscle 1 month after CD) and in the case 5 (conditioned muscle 15 months after DC) indicate the influence of the electric stimulation on muscle vasculature of the graft after DC.

The authors conclude that surgical deafferentation of LDM mainly supporting the distal part of muscle, caused morphological and ultrastructural changes of intramuscular blood vessels with decrease in the capillary-to-fibre ratio, with consequent ischemic changes in muscle fibres. After long-term electric stimulation of the LDM graft, a significant remodeling of the vascular bed with increase of the number of capillaries was observed, even in relation to fibre type conversion induced by electrical stimulation protocol.

Conclusions

In conclusion, in almost all reviewed cases the LDM graft utilized for DC show discrete preservation of muscle structure even after long term electrical stimulation. The most evident alterations of muscle seems to be the ascribed to ischemia and reduction of microvasculature in the distal part of LDM after surgical deafferentation. In the long term DC the microvascular impairment is modified through an evident vascular dilatation of the residual microcircle and by remodeling of the vascular bed induced by long-term electric stimulation of the muscle graft. Vascular delay procedures and new protocols of muscle conditioning (activity-rest stimulation in the demand dynamic cardiomyoplasty) have been recently proposed to improve the clinical outcome of patients with DC.

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