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Topics

Minimally invasive videoassisted Cardiomyoplasty - Vascular delay - Monitoring of cardiac function - Conditioning and regime stimulation protocols - LD flap monitoring - Demand Dynamic Cardiomyoplasty

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ABSTRACTS

THIRTEEN YEARS OF DYNAMIC CARDIOMYOPLASTY

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Thirteen years have passed since the first world Cardiomyoplasty clinical case. New techniques have emerged and new data accumulated. World-wide, the total number of operations, exceeds 1,000 cases (100 cases at Broussais). After many years of questions and doubts on the efficacy of this operation, the general consensus drawn from the experience of the leading groups is that significant functional improvements were observed in most cases. Evaluation by ventricular pressure-volume loops analysis, Doppler tissue imaging, ultrafast CT scan, and radioisotopic studies has provided objective data underlining the mechanism of these functional improvements.

Future perspectives for Cardiomyoplasty include the use of minimally invasive video-assisted techniques, the evaluation of a vascular delay between latissimus dorsi muscle dissection and cardiac wrapping, the modification of the post-operative electrostimulation protocol (using an intermittent LDM pacing: "demand Cardiomyoplasty"), and the use of anabolic steroids and growth factors to improve muscle function. There is a new tendency to associate Cardiomyoplasty with electrophysiological therapy. These therapies include the implantation of ventricular defibrillators, cardiac multiple pacing, and the induction of a permanent AV block and subsequent cardiac pacing in Cardiomyoplasty patients suffering from atrial fibrillation.
The clinical use of aortomyoplasty is under investigation; muscle-powered artificial ventricle is progressing and a new promising technique, cellular and molecular Cardiomyoplasty, is emerging.

IMPROVING CARDIOMYOPLASTY RESULTS: INTRODUCTION OF AN INTEGRATED FIVE-STEP APPROACH FOR OVERCOMING WEAK POINTS

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In a previous clinical study (Russia 1988-1993), 35 patients underwent dynamic Cardiomyoplasty (CMP) and 2-5 years follow-up. Immediate and long-term results revealed several points which must be addressed in order to improve CMP results: acute postoperative heart failure from the inability to begin cardiac assistance immediately after CMP (3 patients); sudden cardiac death due to ventricular tachycardia (3 patients); recurrent myocardial infarction due to poor angiogenesis and myocardial revascularization (2 patients); unsatisfactory hemodynamic response due to the initial weakness of the latissimus dorsi muscle (LDM) or extreme postmobilization ischemia (6 patients). The loss of CMP benefits may be due to the incurable state of the myocardium or the weak condition of the LDM. We concentrated our efforts on the state of the LDM and utilized an integrated five-step approach for improving its premobilization, postmobilization and long-term performance. The following summarizes the findings of five experimental studies in adult sheep.
1. In order to increase the force of the LDM contraction (specifically for patients with prolonged preoperative immobilization, and thus an initially weak and thin LDM), an anabolic steroid (nandrolone decanoate) was administered locally (via osmotic pump) into electrically stimulated LDM. After 8 weeks of treatment, contractile force increased to 130±15% compared to baseline. In the control series, contractile force decreased to 78±8% compared to baseline.
2. In order to prevent ischemia-reperfusion damage, the LDM after subtotal mobilization was treated with autologous biological glue with added pharmaceuticals (aprotinin or pyrrolostatin). A significant increase in muscle revascularization and a decrease in fat degeneration was noted in the peripheral portion of the LDM. After 56 days, the percent of capillaries per area was 5.5±0.2% (glue only); 8.5±1.1% (glue + aprotinin); 9.4±1.2% (glue + pyrrolostatin) compared

to 3.6±0.7% (untreated ischemic LDM) and 4.1±0.3% (control).
3. In order to avoid the typical disuse atrophy of the LDM seen during the two week delay period, a cautious electrical stimulation was begun two hours after subtotal LDM mobilization (single impulses, 15 contractions per minute). After 16 days, during a one hour fatigue test (10 V, 30 Hz, 20 g/kg preload, 6 impulses per burst, 1 minute work followed by one minute rest) contractile force decreased to 85±6% (compared to 72±9% in control animals) and returned to baseline after 45 minutes (100 minutes in control animals).
4. In order to implement cardiac assistance immediately after CMP, a new work-rest regimen of electrical stimulation was tested (30 minutes two times daily for 16 days). On day 16, after 30 minutes of fatigue testing, contractile force did not change (104±2%). The percent area occupied by capillaries increased to 5.04+0.33% (compared to 3.02±0.6% in control muscle).
5. In order to accelerate angiogenesis and myocardial revascularization, autologous biological glue with added endothelial cells was administered between the myocardium and LDM during CMP. A model of ischemic heart disease was created previously. Capillary ingrowth was seen as early as two months postoperatively (no capillary ingrowth in control animals).

DYNAMIC CARDIOMYOPLASTY: INDICATIONS, RISK FACTORS AND CLINICAL OUTCOME

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Dynamic Cardiomyoplasty (DCMP) is a surgical procedure to treat end-stage failure in patients (P) with cardiomyopathy (C) in NYHA classification III despite of optimal drug treatment. Between 4/93 and 4/97 DCMP was performed in 21 P, aged between 33 and 67 years. Two of them suffered from ischemic C (1C), 15 from dilated C (DC).

The preoperative hemodynamic mean values are shown in the following table.

LVEF %	LVEDP mmHg	CI l/min/mm2	PAPsys mmHg
21.1 +/-9.0	22.2 +/-11.9	2.2 +:-0.5	43.7 +/-16.1

PCWP mmHg	VO2max ml/kg/min	LVEDD mm
21.3 +/-10.0	15.4 +/-3.8	68.7 +/-6.0

16 P were in sinus rhythm, 5 P had atrial fibrillation. 2 P had sustained ventricular tachycardia and 2 P had ventricular fibrillation (VF) with successful reanimation. Therefore all of these 4 P had an indication for an implantation of an internal cardioverter- defibrillator (ICD). Alcoholic and drug addiction consisted by 6 respectively 1 P and 5 P lived in obscure psycosocial conditions.
DCMP was performed according to the technique described by Carpentier and Chachques. The wrapping procedure was performed without use of extracorporal circulation. The mean operating time amounted to 290 min (220-380 min). Electrical stimulation started two weeks after operation with one impulse and ended 7 weeks later with a burst of 6 impulses and a synchronisation ratio 1:2. Left and right heart catheterization were performed after 6 months, 1 year and every following year. Hemodynamic parameters were measured with muscle stimulation (+CS) and without stimulation (-CS) for 15 min and results were compared with the preoperative values, as shown in the following table, n = 8:

	LVEF %	CI l/min/m2	PAPsys mmHg	PCWP mmHg
preop	29 +/_4.6	2.3 +/-0.5	34.5 +/-11.8	18.0 +/-7.4
postop (+CS)	33 +/-13.9	2.5 +/-0.7	34.7 +/-19.2	14.0 +/-9.3
postop (-CS)	27 +/-13.3	2.3 +/-0.6	34.7 +/-21.2	14.0 +/-10.9

Our data show a slide improvement of LVEF and CI, a decrease of PCWP and no change of PAP. Without myostimulation LVEF and CI reached preoperative values. Although only moderate changes of hemodynamics are observed, there is a significant improvement of clinical status (mean NYHA 1,3). One P with 1C died immediately postoperatively because of myocardial infarction. 1 P with 1C and 1 P with DC died because of heart failure, 1 P because of VF and 1 P because of non cardiac disease. All of the cardiac deaths were in the alcoholic and psychosocial risk group. DCMP reduces symptoms of heart failure and is a sufficient therapy for P with C which are on an optimized drug treatment in NYHA classification III. In our opinion, beside the known hemodynamic risk factors, malignant ventricular arrhythmias, alcohol and drug abuse, adverse psychosocial factors and ischemic cardiomyopathy are predictors for unfavourable outcome. For these reasons, in the presence of VF or sustained VT we implant an ICD before DCMP, we insist on a successful alcohol and drug withdrawal before DCMP and prefer P with dilated cardiomyopathy.

CONSIDERATIONS IN THE USE OF DYNAMIC CARDIOMYOPLASTY AND AORTOMYOPLASTY. CLINICAL EXPERIENCE

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Dynamic Cardiomyoplasty (DC) has been proposed in the treatment of severe cardiomyopathies, being its results acceptable. The aim of this study was to evaluate ventricular function and functional capacity two years post DC in a group of patients (p) in NYHA functional class III, IV that did not respond to medical treatment. Fifteen p were included (11

men). Mean age was 55.2 +/- 6.4 years (46-74). The ethiology was idiopathic dilalcd cardiomyopathy in 8 p, necrotic iscliemic cardiomyopathy in 6 p and Chagas's disease in the other. One p died one-day after surgery and an ofher one two months post DC. Mean follow-up of the rest of the p was 31.3 months.
Results of radionuclide left ventricular (LV) ejection fraction (EF), LV end diastolic diameter (LVEDD), fractional shortening (FS), left atrial diameter (LAD), NYHA functional class, 6 min walking test, hospitalizations/p/year, and oxygen consumption were analyzed for the 12 p that completed two years post DC.

	Preop	Post-DC	p
LVEF (%)	23.6+/-S	29.7+/-5	=0.001
LVEDD (mm)	72J+/-7	72.3+/-S	NS
FS (mm)	1 S.6+/-4	20.6+/-5	= 0.003
LAD (mm) .	55.5+AIO	53.2+/-10	NS*
Functional Class	3.06+/-0.2	I.7+A0.6	<0.0001
6 min walking test (m)	332+/-127	42I+/-102	=0.019
Hospitalizations/p/year	2+/-0.7	0.4+/-0.5	=0.002
Oxygen consumption (ml/min/kg)	13.3+/-3	14+/-3	NS

* p=0.07 NS Trend

Conclusions: DC improves LV systolic function, functional capacity and quality of life at 2-year follow-up. This improvements occurred without changes in oxygen consumption or LVEDD.

AORTOMYOPLASTY Four p were included with mean age of 50 years and a functional class (FC) III-IV. One p died two months later (ventricular arrhythmia) before completing the stimulation protocol. The others three p improve the FC with a value of I-II at 4, 17 and 24 months post-op. Apparently, aortomyoplasty is a potential efficient technique to assist selected patients with refractory cardiac failure.

THE FIRST CLINICAL CASES OF DYNAMIC CARDIOMYOPLASTY IN POLAND

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The first two clinical successfully cases of Dynamic Cardiomyoplasly (DCM) in Poland were performed at Institute of Cardiology in Cracow on December 1996. DCM was normally performed without cardiopulmonary bypass and the left latissiinus dorsi muscle was used according to the technique described by Carpentier and Chachques. The indications for this procedure were; ischaemjc cardiomyopathy in [he first case and dilated idiopathic cardio-myoplasty in the second case. The skeletal muscle flap stimulation started two weeks after the operation with protocol Clinical Research Study evaluating the Medtronic SP 1005 hurst cardio-myostimulator. Preoperalively, the first patient was in NYHA class IV, LVEF 16%, EDV 310+/- 30 ml. Peak V02 10,4 ml.min.kg. The average data obtained 3, 6, 12 months after operation were as follow: LVEF (%) 23, (3 months); 18 (6 months); 20 (12 months). EDV (ml) 220+/-30 (3 months); 260+/-33 (6 months); 240+/-32 (3 2 months), Peak VO2 (mlmin.kg) 16.6 (3 months); 14.4 (6 months); 15.2 (12 months). Now the patient is in NYHA class II/III. Pre-op, the second patient was in NYHA class III/IV, LVEF 15%, EDV 390+/- 36 ml, Peak VO2 11.2 ml.min.kg. The average data reached 3, 6, 12 months after dynamic cardiomyoplasty were as follow: LVEF (%) 22, (3 months); 20 (6 months); 20 (12 months), EDV (ml) 260+/-40 (3 months); 280+/-36 (6 months); 300 +/-32 (12 months). Peak VO2 (ml.min.kg) 16.4 (3 months); 14.4 (6 months); 15.1 (12 months). Now the patient is in NYHA class II/1II. In both of them improvement and stability of the circulation were achieved.

MINIMALLY INVASIVE VIDEO-ASSISTED CARDIOMYOPLASTY

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Following the first clinical case of cardiomyoplasty, performed at the Broussais Hospital in 1985, more than 1000 patients have undergone this procedure world-wide. Recent developments in the field of cardiomyoplasty include the use of a new minimally invasive video-assisted surgical technique. This procedure is performed through a small lateral thoracotomy. Hour patients at the Broussais Hospital have since benefited from this new technique. Technically, the operation consisted of dissecting the left latissimus dorsi muscle (LDM) through a small 10 cm transverse thoracic incision performed at the level of Ihc 5th intercostal space. Another 5 cm incision is performed at the level of the second rib. Through this incision, the rib is resected, the pacing electrodes are implanted and the LDM is transposed directly into the chest. A thoracotomy is then performed through the ilii intercostal space to expose and wrap the heart with the LDM.
The use of the minimally invasive approach for cardiomyoplasty has shown the following advantages;

1) The chest wall structures were better preserved, maintaining Ihe normal architecture of Ihe chest (sternotomy was avoided)
2) The left lung re-expansion was directly controlled
3) Postoperatively, there was only minimal impairment in respiratory function
4) The left ventricle was exposed better allowing a complete LDM wrapping
5) There was less postoperative bleeding
6) The small skin incision avoids wound complications, such as skin necrosis and infection
7) Cosmetic advantages are obvious (the total length of the new incision was 15 cm vs. 60 cm for the classic cardiomyoplasty incision)
8) Quicker patient rehabilitation
9) Video-assist system (e.g. Vista) seems to be very useful in the LDM dissection and cardiac wrapping

We believe that Cardiomyoplasty could be significantly improved with this new and appealing approach.

DEVELOPMENT OF VASCULAR DELAY FOR USE IN CARDIOMYOPLASTY

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Vascular delay is a well known reconstructive surgery procedure utilized to enhance blood perfusion in tissue flaps. This report describes our development of vascular delay of the latissimus dorsi muscle (LDM) from anatomical cadaver studies, to acute animal studies, to chronic animal applications in Cardiomyoplasty (CMP), to the clinical application of vascular delay in human CMP. We developed the technique of vascular delay of the LDM based upon anatomical studies of human cadavers, dogs, and other species. Acutely lifting the LDM results in ftbrosis/necrosis of the distai part of the muscle, as much as a third of the LDM is at risk following acute mobilization. Vascular delay alters the vascular architecture of the LDM and thus minimizes this necrosis, improves perfusion, and enhances contractile properties of the distal muscle. The beneficial effects of vascular delay were optimal between 10-14 days. We have also investigated the effects of vascular delay of the LDM during dynamic CMP in a dog model. After a two week vascular delay period, CMP was performed and LDM training initiated. Two weeks after CMP, global cardiac dysfunction was induced by injection of intra-coronary microspheres. Over a period of several months, stimulation of the LDM resulted in significant and consistent improvement in aorlic flow, left ventricular and aortic flow and pressures, and dP/dt. These improvements were not evident following a single-stage, non-delayed CMP. Based on these findings, we incorporated vascular delay into clinical Cardiomyoplasty. On August 7, 1997, vascular delay of the LDM was performed on a 60-yr. old male with idiopathic dilated cardiomyopaihy, NYHA class III, a LVEF of 18% and a history of cardiac arrest. After obtaining informed consent, the vascular delay and implantation of an AICD was performed. Vascular delay was accomplished by identifying and ligating all intercostal perforators (approx. 27) of the LDM. The paravertebral perforators and thoracodorsal neuro-vascular pedicle were left undisturbed. Two weeks following this procedure, a standard FDA-approvcd Cardiomyoplasty procedure was performed. During the CMP procedure, the delayed LDM appeared bciter perfused (biopsies were taken) and more oedematous than its historical controls. The laller feature necessitated the removal of parts of 2 ribs to allow passage of the LDM into the thorax. The postoperative recovery and training period were uneventful. The patient has returned to many normal daily activities (e.g., bicycle riding) a

on the promising results of our rigorous experimental research and the excellent early progress of our first clinical case, we believe that vascular delay constitutes a significant improvement over the conventional CMP technique. We believe that using vascular delay as an adjunct will significantly improve clinical outcomes in CMP.

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ANESTHETIC AND ICU MANAGEMENT OF CARDIOMYOPLASTY PATIENTS

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Advances in surgical and anesthetic techniques coupled with the acquired past experience gained in patients undergoing dynamic cardiornyoplasty have led ro a better understanding of the critical points and pitfalls in the management of such patients. The following abstract will deal with the major systems involved and corresponding therapeutic maneuvers necesssary to avoid rather than treat complications following a Cardiomyoplasty are: 1) cardiovascular 2) renal and 3) respiratory.

The cardiovascular system is of course central in determining outcome and must benefit from our entire attention throughout the procedure. All patients undergoing a CMP have been or risk being in cardiac failure and one should not hesitate with the use of inotropic support if the need arises (SvO2 CO). The choice of inotropcs is fundamental and should of preference be dobutaminc or a phophodicsterase inhibitor and one should avoid such drugs sucli as epinephrine and norepinephrine (which may cause alterations with LDM flap vascularization). The use of an intra-aortic balloon pump is in our current opinion gaining favorable mention in that with the recent surgical progress of minimally invasive CMP, patients are placed in right lateral dccubints (hcmodynamically unstable) for longer periods and seem to benefit from IABP assistance. The advent of ventricular arrhythmias during LDM wrapping is recognized and the use of topical lidocainc should be intrapericardium an adjunct to that of prophylactic continuous intravenous lidocaine.

Renal insufficiency after major cardiac surgery still carries a 50% mortality rate. LDM flap mobilization, manipulation and placement cause increases in circulating myoglobin and myoglobinuria which may, after precipitation in the renal tubules, lead to renal failure. Prophylactic treatment is warranted during the procedure and should consist in the dilution of renal tubule myoblobin concentrations by increasing diuresis. Patients should be placed on continuous intravenous diuretics during and following the procedure and replenished accordingly as to maintain adequate volume status.

The respiratory system is also cause of major concern in that LDM flap positioning and lung manipulation often result in compression atelectasis which may delay return to normal pulmonary function. The use of double - lumen endotracheal tubes during recent minimally invasive CMP through left mini-thoracotomy has proven beneficial. Deflation of the lung

causes less direct damage and complete visual re-expansion is possible at the end of the procedure. Furthermore, the recent use of anesthetic techniques permitting the return to earlier spontaneous ventilation appears to increase liemodynamic stability and decrease pulmonary complications during the postoperative period.

In conclusion, although cardiornyoplasty procedures arc performed on critically ill palients the use of a learned and reasoned approach can simplify outcome. The dichotomy between anesthesia and intensive care should not exist with ICU management starting immediately after induction ot" anesthesia so as to benefit from the precious time available.

BEDSIDE MONITORING OF DYNAMIC CONTRACTILE CHARACTERISTICS OF HUMAN LD FLAP IN LONG-TERM DYNAMIC CARDIOMYOPLASTY IN ITALY

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In dynamic Cardiomyoplasty, load-independent measurements of cardiac function demonstrate a real improvement of heart energetics when preoperative and postoperative analyses are compared. In order to improve a patient's quality of life, LD activation should optimally be delayed after the sensed QRS complex in order to avoid mitral valve regurgitation. To achieve greater systolic augmentation, it is essential to be able to monitor the LD flap contractile character! sties. Having a technique to non-invasively monitor the LD contraction and relaxation would facilitate the evaluation of new stimulation regimes or other techniques for improving LD function. We developed a new method for non-invasive, bedside monitoring ot" LD function using a standard polygraph, previously used for monitoring cardiac apical motion and heart sounds. ECG and heart tones arc registered simultaneously with the pressure changes due to LD flap contraction and relaxation which are measured near the rib window using the probe normally used for recording an apicocardiogram. From the LD •'mechanogram". we can determine: I) LD activation threshold, 2) optimal synchronization delay between cardiac events and the actual contraction of the LD flap, 3) the duration of the fttll LD contraction-relaxation cycle, and 4) (he dynamic contractile characteristics of the LD flap based on the determination of the tetanic fusion frequency. In a cohort of patients, we have shown that the LD flap becomes fatigue resistant and slow contracting by the end of the conditioning period, that is within two months after the operation, and can remain viable at least up to fifty months (the longest patient follow-up in this series). The extent of fast-lo-slow transformation of contractile characteristics of the LD flap can be related to the stimulation protocols used, *i.e.* the amount of impulses delivered per day. Optimal synchronization of the LD flap was determined in a subset of patients by catheterization and pressure-volume analysis. The optimal setting induces LD contraction during the systolic ejection phase which can also be assessed non-invasively in the same subjects using echo Dopplcr imaging of the aortic outflow tract.

References

Arpesella G, Mikus P, Giannoni A, et al. Daily work-rest stimulation regimen of sheep LD for eardiomyoplasty: rationale and results up to six months. Basic Appl Myol 1996;G:341-350.

Carraro U, Barbiero M, Docali G, Brunazzi C, Lorusso R, Rinaldi M, Gazzoli F, Vigano M, Gerometta PS , Barbier P, Biglioli P, Casarotto D, Muneretto C: Dynamic Cardiomyoplasty: Long-term viability demonstrated by non-invasive on-line analysis of dynamic contractile characteristics of human LD flap in Italian subjects. J Cardiovasc Diagn P, in press.

Carraro U, Docali G, Barbiero M, Brunazzi C, Lorusso R, Muneretto C: Dynamic Cardiomyoplasty: Implement a basic concept to allow non invasive monitoring of dynamic characteristics of the LD flap, in D. Popovic (ed): *Proceedings of the IFESS97 Conference,* (Burnaby, British Columbia, Canada, August 16-21) 1997,51-52.

Duan C , Trumble DR , Chrisllieb IY, Magovern JA, and Magovern GJ Sr Improved function in muscles trained via JDterval stimulation, Basic Appl Myol 1998, in press

OPTIMIZATION OF PROGRAMMING: THE DILEMMA OF SYNCHRONIZING MUSCLE AND VENTRICULAR CONTRACTION

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To obtain maximal benefit from dynamic Cardiomyoplasty, stimulation parameters of the cardiomyostimulator need to be optimized. The two components for optimization include the muscle channel and the synchronization channel. This study looks at the dilemma of timing muscle contraction to ventricular contraction. We looked al 2 methods to find optimal synchronization delay, 1) using the current clinical method of echocardiographic assessment of mitral valve closure with onset of burst stimulation, and 2) simultaneous open measurements of muscle and ventricular pressure generation. A left latissimus dorsi (LD) Cardiomyoplasty was performed in 4 dogs. Using a previously established protocol for muscle transformation, the LD muscle was continuously stimulated over 4 weeks with an epineural cuff and the Itrel II myostimulator. After the training period, a Cardio-myo-stitnulator #4710 was used for assist, and optimal synchronization timing was assessed. First, m-mode echo-cardiography was used (o optimize timing of burst stimulation spikes with closure of mitral valve. Second, a median sternotomy was performed, and Millar pressure measuring catheters were inserted into the left ventricle (LV) and the LD muscle. Optimization of synchronization delay was assessed with simultaneous measurement of ventricular pressure and

the LD intramuscular pressure. Comparison was made between optimal synchroni2atiou obtained by cchocardio-graphy and the open method.

All dogs survived the surgery without complication, and underwent the full period of muscle transformation, followed by optimization studies. One dog appeared to be in heart failure during the optimization study. Optimal synchronization delay for the two methods are shown in the following table:

Optimal Synchronization Delay (msec)

Dog	M-Mode Echo	Open Measurement
1	16	8
2	16	8
3	16	8
4	23	16

Of note, 1) optimal delay for the open method was determined by best overlap of peak pressures of muscle and ventricle. 2) peak pressure (Pmax) generation of muscle occurred 70-100 msec after LV Pmax i» 3 of 4 dogs (in one dog with failure, muscle P_{m}ax occurred 10 msec after LV P_{m}ax)> [ari]d 3) in 3 of 4 dogs, duration of muscle contraction exceeded ventricular contraction, making diasiolic overlap unavoidable. From our results, we conclude that optimal synchronization delay occurs at a shorter delay than as determined by ihe echocardio graphic method. Because muscle P_{ma}x occurs laier than LV Pmax' [an]^ duration of muscle contraction is longer than LV contraction a dilemma exists as to what is optimal timing for muscle contraction. Because peak LV wall stress occurs early in systole, and most LV filling occurs early in diastole, we suggest that muscle contraction should occur as early as possible even at the cost of some late diastolic interference.

INTERPRETATION OF CARDIOMYOPLASTY RESULTS: A CONTROVERSIAL MATTER

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The original concept behind cardiornyoplasty was the implementation of an autologous source of biomechanical assistance for the chronically failing heart. Device-evoked synchronized wrapped muscle contractions were meant (o support the systolic performance of the cardiac ventricles. Besides substantial changes in patient selection along the time, which concurred to made postoperative interpretation of hemodynamic data extremely difficult, recent clinical and experimental studies have provided new insights regarding mechanisms of action, clarified limitations of the current technique, and shown several methods to improve it. The use of cardiornyoplasty on experimental models of heart failure (rapid ventricular pacing) or of progressive heart dilatation (artero-venous fistula) undoubtedly has been shown to prevent progressive ventricular enlargement. The implementation of electrical stimulation was essential to "reverse" this tendency, restoring normal cardiac volumes: "passive card io myopia sty" is not at all sufficient to actively influence myocardial response. Additional studies, addressing the myocardial energetics, clearly documented reduced oxygen consumption s myocardial work. Our group thoroughly investigated these aspects in animals and in patients. Acute (beat-to-beat analysis) and chronic (prc versus postoperative) studies have been carried out showing that slight systolic contribution is indeed provided by Ihe wrapped muscle graft, but the main effect is exerted, on a long-term basis, acting on a progressive remodelling of the dilated heart. From the clinical standpoint, stabilization of the disease course has been shown to represent a significant achievement after cardiomyoplasly, and could be related io improved scgmenlal and overall conditions of myocardial performance. Still controversial appear the hypothetical myocardial revascularization by ncoangiogenesis ai the intcrmuscular level, even if experimenial and clinical findings seem to suppport this concept. In conclusion, current card iomy op tasty procedure appears to act mostly on a "dynamic reverse remodelling" with subtle, bui effective active muscle contribuiion. Cardiomyoplasty unfortunately shares with the other forms of surgical treatment of chronic heart failure the limited knowledge concerning the extent of myocardial damage, the potential for recovery of function, and the progression of the underlying disease. Patient selection has been claimed as fundamental facior for reduced mortality 10 be obtained, but still little is known regarding the type of myocardia! compromise which could benefil from chronic support. Heterogeneity of Cardiomyoplasty results arc certainly related to individual features of muscle structure and performance, but, additionally, to the individual type of myocytc impairment. Cardiomyoplasty seems to favor a recovery of wall motion synehronicily. with expected benefit on overall ventricular geometry, but the incidence of sudden cardiac death among cardiomyoplasly patients represents a major limitation regarding long-term outcome. The relation of myocardial impairment and arrhythmic death is still controversial, and so far only a combined use of implantable dcfibrillators and cardiomyostimulators may represent a potential option. Debate still persists on the fulurc improvements in terms of muscle performance and structural preservation, but direct relation between muscle structure preservation and tnechanical performance has been documented, suggesting that the most recent changes in muscle management may provide important changes and improvements in the procedural implementation. Step by step, Cardiomyoplasty has been showing that considerable progresses have been achieved, and that further improvements are possible, but apparently insufficient to eliminate the medical and, more recently, the industrial skepticism.

PRESERVING THE VIABILITY OF THE GRAFT S.

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The use of functional grafts of lalissimus dorsi (LD) muscle to provide cardiac assistance is based on two key elements: (a) skeletal muscle can be conditioned by chronic electrical stimulation to perform cardiac patterns of work, and (b) the LD muscle has a discrete blood supply from the thoracodorsal artery, entering close to its proximal insertion, and can

therefore be raised as *s* pedicled flap and transferred into the chest. However the LD muscle cannot be raised as a graft without dividing Ihe perforating arteries that enter its distal portion, and this results in ischacmic damage when the muscle is stimulated electrically.
To address this problem, we focused on anastomotic communications between branches of the thoracodorsal artery proxinmlly and the collateral vessels distally. These provide, in principle, a route whereby blood can be supplied to the distal part of the LD muscle via an existing vascular network, without the delays required for neovaseularization. Using a fluorescent microsphcre technique to measure regional blood flow in the sheep LD muscle, and fluorescence microscopy to image microsphercs in capillaries, we obtained the first definitive evidence that arterial anastomoses not only exist but are functional under physiological conditions of pressure, We went on to show that electrical stimulation of the muscle abolished the proximodistal gradient in blood flow derived from the thoracodorsal artery, enhancing flow to the distal portion of the graft after loss of the perforating arteries. This rendered the muscle resistant to the ischaemia associated with cooling, handling, elcctrocautery and loss of resting tension, all of which could contribute to collapse of the anastomotic channels during the normal clinical procedure. Thus an LD muscle stimulated prior to its use as a graft should be less susceptible to ischaemic damage and could, moreover, have undergone some degree of metabolic transformation. This would allow earlier introduction of cardiac assist, with the potential for extending the operation to patients who, on current protocols, would be considered a poor risk.

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References

Tang ATM, Jarvis JC, Salmons S. Arterial anastomoses in sheep latissimus dorsi muscle. J. Anat. (in press).
Tang ATM, Jarvis JC, Hooper TL, Salmons S. Observation and basis of improved blood flow to the distal latissimus dorsi muscle: a case for electrical stimulation prior to grafting. Cardiovasc. Res. (in press)

DEMAND DYNAMIC CARDIOMYOPLASTY: BASICS AND RATIONALE

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To many authors, cardiomyoplasty is a clinical reality, founded on the basis of its girdling effect which limits and/or reverses the progressive dilatation of a failing heart. Load-independent measurements of cardiac function demonstrate a real improvement of heart energetics when analyses are compared before and after cardiomyoplasty. One of the factors limiting the systolic assistance of cardiomyoplasty is m

dorsi (LD). Clinically, it is accepted that the LD benefits the patient's quality of life only if its activation is optimally delayed after the sensed QRS complex in order to avoid mitral regurgitation. Since maximum instantaneous power of a fully conditioned LD is smaller than the peak power of the left ventricle, the grafted muscle could assist the heart principally during mid and late systolic phases. Such a short time window requires a fast, powerful contraction which is not delivered by a fully transformed LD. Monitoring LD function is essential for evaluating and implementing new concepts aimed at improving LD function for greater systolic benefit. To perform this monitoring we have implemented the basic concept of tetanic fusion frequency analysis. Having a technique to non-invasively monitor the LD contraction and relaxation in dynamic cardiomyoplasry would facilitate the evaluation of new stimulation regimes or other techniques for improving LD function.
We developed the new method for non-invasive, bedside monitoring of LD function using a standard polygraph, previously used for monitoring cardiac apical motion and heart sounds. ECG and heart tones are registered together with the pressure changes due to LD flap contraction and relaxation which arc measured near the rib window with the probe normally used for recording the apicocardiogram. From LD "mcchanogram." we can determine: 1) LD activation threshold, 2) optimal synchronization delay between cardiac events and the actual contraction of the LD flap, 3) the duration of the full LD contraction-relaxation cycle, and 4) the dynamic contraetile characteristics of the LD flap based on the determination of the tetanic fusion frequency. The optimal setting induces LD contraction during the systolic ejection phase which can be assessed non-invasively in the same subjects using echo Doppler imaging of the aortic outflow tract. In a cohort of patients, we have shown that the LD flap becomes fatigue resistant by the end of the conditioning period, *i.e.,* within two months after the operation, and can remain viable at least up to fifty months. The extent of fast-to-slow transformation of contractile characteristics of the LD flap can be related to the stimulation protocols used, *i.e.* the amount of impulses delivered per day. Transformation is reversed by a "demand" stimulation, that is, with an activity-rest regime which rests LD several hours per day. By monitoring changes in fusion frequency over time, we hoped that it would be possible to adjust daily stimulation parameters in order to maintain a faster, more powerful muscle. Beside the sheep experiments of Arpesella team, corroborating results were recently presented in a rabbit model confirming that long-lenn daily stimulation increases blood flow but decreases muscle mass, while "interval stimulation", that is an activity-rest regime of stimulation, preserve muscle mass and force. In fact, this has now been achieved in Dynamic Cardiomyoplasty by implementing an activity-rest regime. After months of continuous daily stimulation it is possible to reverse the fast-to-slow transformation by a "demand" stimulation protocol which allows the LD flap to rest during periods of low-activity, both day and night. With this lighter stimulation regime, now used in patients at more than one-year of follow-up, substantial improvement in quality of life has occurred with a reduction in heart failure symptoms from NYHA Class III to I and improvements in peak V02. If these preliminary data can be substantiated by long-term results in these patients and in future patients in an Italian Trial of Demand Dynamic

Cardiomyoplasty (DDC), we are confident that DDC could offer long-standing benefits to manage pharmaco logic ally-intractable heart failure.

References
Arpesclla G, Mikus P, Giannoni A, et al. Daily work-rest stimulation regimen of sheep LD for Cardiomyoplasty: rationale and results up to six months. Basic Appl Myol 1996:6:341-350.
Carraro U, Barbicro M, Docali G, Brimazzi C, Lorusso R, Rinaldi M, Gazzoli F, Vigano M, Geromelta PS , Barbier P, Biglioli P, Casarotto D, Muneretto C: Dynamic Cardiomyoplasly: Long-term viability demonstrated by non-invasive on-line analysis of dynamic contractile characteristics of human LD flap in Italian subjects, J Cardiovasc Diagn P, in press.
Carraro U, Docali G, Barbiero M, Brunazzi C, Lorusso R, Muneretto C: Dynamic Cardiomyoplasty: Implement a basic concept to allow non invasive monitoring of dynamic characteristics of the LD flap, in D. Popovic (ed): *Proceedings of ihe IFESS97 Conference,* (Burnaby, British Columbia, Canada, August lfi-21) 1997,51-52.
Carraro U, Rizzi C, Catani C, Miracoli L, Arpesella G, Mikus P, Cirillo M, Parlapiano M, Pierangeli A: Basics on muscle-powered cardiac assist devices: Power output of sheep LD conditioned to fatigue resistance. IEEE-EMS 1991; 13: 936-937.
Duan C , Trumblc DR . Christlieb IY, Magovern JA, and Magovern GJ Sr: Improved function in muscles trained via interval stimulation. Basic Appl Myol 1998, in press

DEMAND DYNAMIC CARDIOMYOPLASTY: PRELIMINARY CLINICAL RESULTS

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Full transformation of latissimus dorsi muscle from a fast-fatigable to a slow faliguc-resistanl muscle has been considered until recently as Ihe key step in Dynamic Cardiomyoplasty. Unfortunalely muscle power has been showed to decrease with extent of fast to slow transformation. On the basis of the experimental data, we have developed a new clinical protocol based on activity-rest stimulation which provides resistance lo fatigue at higher muscle power. The extent of transformation of contractile characteristics of Ihe LD flap can be eclated to the stimulation protocols used, *i.e.* the amount of impulses delivered per day. Beside the sheep experiments of Arpesella team, corroborating results have been recently presented in a rabbit model confirming that long-term daily stimulation increases blood flow but decreases muscle mass, while "interval stimulation", that is an activiiy-rest regime of stimulation, preserves muscle mass and force. Indeed, transformation is reversed by a "demand" stimulation, i.e., wilh an activity-rest regime which rests LD several hours per day. The result is achieved with an activity-rest LD stimulation obtained by a heart frequency dependent stimulation cut-oil. Thus, in patients LD muscle is rested during low activity periods. Preliminary study included four patients with cardiac heart failure due to dilatative cardiomyopathy in NYHA class III with a mean preoperative peak VO2 of 12 inl/kg/min. There are no deaths and all patients are in NYHA class I after a mean follow up of 11 months. One year after Demand Dynamic Cardiomyoplasly peak VO2 increased up to 35% when compared with preoperative values. If these preliminary data will be confirmed in a larger cohort, Demand Dynamic Cardiomyoplasty could offer long-standing benefits to manage pharmaco logically-intractable heart failure.

References
Arpesella G, Mikus P, Giannoni A, ct al. Daily work-rest stimulation regimen of sheep LD for Cardiomyoplasty: rationale and results up lo six months. Basic Appl Myol 1996;6:34I-350.
Carraro U, Barbiero M, Docali G, Bruna77,i C, Lorusso R, Rinaldi M, Gazzoli F, Vigano M, Gcrometta PS , Barbier P, Biglioli P, Casarotto D, Munereito C; Dynamic Cardiomyoplasty: Long-term viability demonstrated by non-invasive on-line analysis of dynamic contractile characteristics of human LD flap in Italian subjects. J Cardiovasc Diagn P, in press.
Carraro U, Docali G, Barbiero M, Brunazzi C, Lorusso R, Muneretlo C: Dynamic Cardiomyoplasty: Implement a basic concept to allow non invasive monitoring of dynamic characteristics of the LD flap, in D. Popovic (ed): *Proceedings of the IFESS97 Conference,* (Burnaby, British Columbia, Canada, August 16-21) 1997,51-52.
Duan C , Trumble DR , Christlieb IY, Magovcrn JA, and Magovcrn GJ Sr: Improved function in muscles trained via interval stimulation. Basic Appl Myol 1998, in press

NEW METHOD FOR MONITORING THE FUNCTIONAL STATE OF DYNAMIC CARDIOMYOPLASTY

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In order to assess the impact of dynamic Cardiomyoplasty on failing hearts, it is essential to estimate the contraction force of the skeletal muscle and how its contraction is synchronized with the heart cycle.
In a six-months study a small fluid filled balloon mounted catheter was placed between the myocardium and the muscular wrap in five adult female Boor goats and two female domestic pigs. The catheter was connected to a subcutaneous measuring chamber whereby pressure monitoring could be accomplished. Distinct pressure signals due to function of the dynamic Cardiomyoplasly and the heart were detected initially in all animals. Maximal relalive pressure from DCMP was calculated as 336.2 +/-69.4% on day 24 +/- 6.1 (n= 7) and end

stage pressure as 59-8+/-9.7% on day 174-6+/- 13.1 (n=4). A functional loss of pressure signals from dynamic cardiovnyoplasty was correlated to severe histological muscle damage (n =3). Pressure signals transferred from the contracting myocardium to Ihe catheter showed defined segments of a contraction, ejection and filling period, allowing a mechanical synchronization of the dynamic card Jo myopia sty to the heart cycle.
This monitoring catheter enabled the assessment of the functional state of the dynamic Cardiornyoplasty and allowed a synchronization to the heart cycle. It will promote understanding and might help lo avoid muscle damage of dynamic Cardiornyoplasty for an improved outcome of the surgical treatment of end stage heart failure.

MICROVASCULAR ADAPTIVE MODIFICATIONS OF THE LATISSIMUS DORSI MUSCLE AFTER DYNAMIC CARDIOMYOPLASTY

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Dynamic cardiomyoplasty (DC) is a surgical procedure in which a pedicled Latisslmus Dorsi flap is transposed into the chest and wrapped around the ventricle of a failing heart. LDM fibres and microvasculature undergo an adaptation after surgery. Intraoperative deafferentation of intercostal and lateral thoraco-dorsal vaseulature of LDM, partially deprives the muscle of a portion of the afferent vaseulature. Postoperative protocol of chronic electric stimulation leads to modifications in the contractile properties of muscle fibres with adaptive modifications of microvasculature. At last, muscle fibres and capillaries are conditioned by training of a muscle now utilized as support of ventricular function. The present is a morphological and ultra-Structural study of microvasculature of LDM from 5 subjects that underwent DC. Contra lateral LDM specimens were utilized as control. Capillary vessels analysis was performed on paraffin-embedded transverse sections stained with Gomori' silver impregnation and on sections immuno-histochemically stained for cndothclial marker CO 34. The number of capillaries per mm^2 (capillary density CD) and the number of capillaries around each fibre (C/F) were evaluated as previously described (Scelsi, 1992). The ultrastmctural analysis of capillaries was performed on specimens fixed in Karnovsky fluid and then processed for transmission electron microscopy. Two patients underwent DC and the LDM was analyzed 10 and 25 days after surgery in absence of electric stimulation protocol. The unconditioned LDM showed decrease of C/F and CD and changes such as degeneration of cndothclial cells. Some capillaries showed cytoplasmic interdigitations between the endothelial cells and pcricytes as generally observed following active vascular proliferation (Wakui, 1993). These adaptive alterations might be due to the opening of existing shunts between the thoracodorsal artcrioles and the distal perforating arterial bed, or through neoangiogenesis. Three patients underwent DC and LDM specimens were studied at one, nine and fifteen months after electric stimulation, m comparison to c showed significant increase in capillary density and in number of capillaries per fibre. These aspects arc mainly related to electric muscle conditioning and training which induce modifications in the contractile properties of fibre types, with increase in mitochondria I volume and in mitochondria-bound oxidative enzyme activities (Ingjer, 1979, Pette, 1992) and consequently in the capillary density. The present findings further support the assumption that factors controlling the increase in mitochondria! content also take part in the adaptation of the capillary supply to muscle fibres following DC.

References

Ingjer F. Effects of endurance training on muscle fibres in man. J Physiol 1979; 294: 419-432.
Pettc D, Vrbova G. Adaptation of mammalian skeletal muscle fibres to chronic electrical stimulation. Rev Physiol Biochem Pharmaco! 1992; 120: 115-202.
Scelsi R. Morphometric analysis of skeletal muscle fibres and capillaries in mitochondria! myopathies. Path Res Pracl 1992; 188:607-611.
Wakui S, Furusato et al. Endothelial-pericyte interdigitations in rat cutaneous disc implanted angiogenesis. Microvasc Res 1993; 46: 19-27.

ICD IMPLANTATION TO SAFEGUARD AGAINST FATAL ARRHYTHMIAS

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Sudden cardiac death remains a major cause of attrition on long term survival in patients that have undergone cardiomyoplasly. Among the available therapeutic strategies for patients al high risk for sudden cardiac death, the implantablc cardioverter defibrillalor (ICD) is the most effective therapy. To date, at The Milwaukee Heart Institute, four patients have undergone cardiomyoplasty with concomitan! ICD implantation (both devices by Medtronic, Inc. Minneapolis, MN) in three operative scenarios. I. ICD implantation shortly after cardiomyoplasty. A 65 year old patient with advanced dysfunction related to coronary artery disease was evaluated for cardiomyoplasty. He suffered an out-of-hospital cardiac arrest from which he was successfully resuscitated. Monornorphic ventricular tachycardia was documented as the initial rhylhm. Cardiomyoplasty was performed with a posterior wrap through a medial sternotomy. ICD implantation was performed two weeks after cardiomyoplasty. During two years of follow-up, this patient had seven episodes of ventricular tachycardia that were detected by the ICD and appropriate therapy was delivered with consequent conversion lo sinus rhythm. Interrogation and analysis of the stored clectrograms revealed that no interaction between the cardiomyoplasty generator and the ICD were noted during the clinical events.
2. ICD implantation several months after cardiomyoplasty. A 44 year old patient with coronary artery disease, ischemic cardiomyopathy and severe left ventricular dysfunction was evaluated for cardiomyoplasty, Cardiomyoplasty with the left latissimus dorsi wrap was performed without any

complications. Three months after surgery, a Holler report showed n on sustained asymptomatic monomorphic ventricular tachycardia. This finding indicated a high risk for ventricular tachycardia and subsequent sudden cardiac death. For this reason, an I CD was placed three months after cardioniyoplasty. During the eight months subsequent of ICD implantation, there were no arrhythmic episodes requiring the discharge of the ICD.

3. Cardiomyoplasty after ICD implantation. A 38 year old patienl with advanced dilated cardiomyopathy and ventricular tachycardia history had irnplauled an ICD using a nonthoracotomy lead syslem. Two years later, a permanent dual chamber pacemaker was implanted to treat sinus bradycardia associated with symptomatic complete AV block. Five years after the ICD implantation, cardioniyoplasty was performed. During the postoperative hospilalizalion, four ICD discharges occurred as therapy for one episode of ventricular tachycardia. The patient is doing well eight months following the Cardiomyoplasty procedure.

The timing of ICD implantation in relationship to dynamic Cardiomyoplasty needs to be individualized. Cardiomyoplasty may be performed in patients who have already had ICD implantation. Alternatively. ICD implantation may be performed concornitantly or soon following cardioniyoplasty surgery. In some patients, ventricular tachycardia or cardiac arrest have not rcoccurrcd following Cardiomyoplasty, perhaps as a result of improvement in hernodynamics, ventricular stretch, or autonomic imbalance. Implantation should not be deterred in these individuals, since the antiarrhythmic effect of eardiomyoplasty cannot be accurately predicted. It is anticipated that the ICD utilized in conjunction with dynamic Cardiomyoplasty will favorably impact survival by reducing the risk of arrhythmic death in patients with advanced ventricular dysfunction.

TUTORIAL ON LD FLAP MECHANOGRAM MONITORING OF DYNAMIC CHARACTERISTICS OF WRAPPED LD AT BEDSIDE

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Dynamic Cardiomyoplasty was performed in selected subjects according the standard Carpentier and Chachqucs procedures. The conditioning period was shortened to one month. Beginning with one impulse, one-two week after surgery, an impulse was added each week for a toial of four impulses per burst. The pulse interval was 23 msec (43 Hz), and the LD was stimulated every third cardiac cycle. Each subject's LD flap was monitored bed-side using a standard polygraph (Siemens MegaCart or Mingophon).

Originally developed for monitoring cardiac apical motion (apicocardiogram) and heart sounds, we have used this technology to provide a simple, non-invasive way to monitor LD contraction. A signal registering the contraction and relaxation of the LD can be measured by placing the transducer normally used for recording the apicocardiogram o cavity. ECG and heart sounds are recorded simultaneously with the pressure changes due to LD flap contraction-relaxation. From this LD "mechanogram" the following parameters relating to LD contraction were determined:

1) the activation threshold, 2) the clinically acceptable LD activation amplitude, 3) the tetanic fusion frequency (TFF) of the LD, 4) the duration of the complete mechanical event (contraction and relaxation), and 5) the optimal synchronization timing between cardiac events and LD contraction. The activation threshold is easily determined by measuring the peak contraction at different amplitudes of stimulating voltage (from 1 to 8 Volts). The point at which the muscle is first activated is easily recognized, even in patients whose LD contraction is not readily identified through standard palpation of the axillary region. We chose a clinical stimulation amplitude at half the difference between the threshold and the maximal contraction accepted without discomfort for the patient. This is not the maximal activation of the LD, but in such a way the non-activated portion of the flap is "spare LD." available in case of long-term-activity muscle damage. The dynamic characteristics of the LD flap are also determined from the LD response to doublets of stimuli delivered at increasing frequency rate. The LD tetanic fusion frequency can be identified by delivering doublets at intervals ranging from 16 to 200 msec (63 to 5 Hz, respectively). The percent of relaxation between two stimuli delivered at a 100 to 200 msec interval could also be measured. Of course, the faster the LD flap the greater the extent of muscle relaxation between the two impulses. The duration of the complete mechanical event in response to four impulses delivered at 23 msec intervals was measured.

Finally, the optimal synchronization between the cardiac cycle and contraction of the LD flap was determined. This can be done using the mitral and aortic valve tones as measured on the phonocardiogram or, preferably, by connecting the mechanogram signal directly to echocardiography equipment. In this way, the LD mechanogram events can be directly and simultaneously compared to the high-resolution images of cardiac events, cither M-mode imaging of valve motion or Doppler imaging of the left ventricle outflow. Precise tuning based on the actual mechanical events of LD contraction and relaxation can be achieved rather than Liming based only on the electrical impulses delivered to the LD as observed on the ECG. The onset of LD contraction can be programmed to occur at the start of the isovolumic contraction phase of cardiac systole or just at the start ofcjcction. Patients were submitted to an activity-rest stimulation regime by special programming of the cardiomyostirnulator (Transform®, Model 47 iO, Medtronic. Inc., Minneapolis, MM, USA). These patients were operated in June 1996 (a 48-year-old man and a 46-year-old woman). They were submitted to an activity-rest regime after six to nine months of continuous daily stimulation. The patients' average heart rates during the day and night were first determined by 24-hour Ftoiter analysis. For both patients, the average heart rate at night was less than 80 bpm and greater than 80 bpm during Ihe day. The lower rate on the pacing channel of the cardiomyoslimulator was then programmed to 80 but with minimum values for pacing amplitude and pulse width. In this way, the device will be pacing most of the time during night or resting hours but at a very low, sub-capture level. By programming the muscle channel output to "Sense," rather than "Sense +• Pace," muscle stimulation will occur only when the heart rate goes above 80

bpm. When the heart rate decreases, indicating a period of low activity, the device begins to pace and muscle stimulation is inhibited most of the time, allowing (he muscle to rest. With the device programmed accordingly, repeat Holier studies have shown approximately 8 to 10 hours per day of reduced muscle stimulation; 7 to 8 hours at night plus I to 2 more hours during the day. This intermittent stimulation has been well tolerated by the patients with no sleeping disturbances.

References

Carraro U, Docali G, Barbiero M, Biimazzi C, Lomsso R, Muneretto C: Dynamic Cardiomyoplasty: Implement a basic concept to allow non invasive monitoring of dynamic characteristics of the LD flap, in D. Popovic (ed): *Proceedings of the 1FESS97 Conference,* (Bumaby, British Columbia, Canada, August 16-21) 1997, 51-52.

Carraro U, Muneretto C, Barbiero M, Biunazzi C, Docali G, Barbaresi F, Testolin L, Marcassa A, Casarotto D, Pieotti P, Bandello A, Marchi C: Cardiomioplastica Dinamica: come; sceglicre e preparate i pazienti. Medicus new.s 1997; 4: 22-25.

Carraro U, Barbiero M, Docali "G, Brunaxzi C, Lorusso R, Rinaldi M, Gazzoli F, Vigand M, Gerometta PS , Barbier P, Biglioli P, Casarotlo D, Muneretto C: Dynamic Cardiomyoplasfy: Long-term viability demonstrate! by non-invasive on-line analysis of dynamic contractile characteristics of human LD flap in Italian subjects. J Cardiovasc Diagn P, in press.

THE HYDRAULIC PERFORMANCE OF SKELETAL MUSCLE VENTRICLES

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The purpose of a skeletal muscle ventricle is to provide the additional hydraulic work needed by a failing cardiovascular system. Although the basis for this approach is now well established, it has not been possible to predict the performance of such pumps from a knowledge of the linear properties of the muscle and the geometry of the ventricles. We have therefore characterized the function of SMVs by measuring their ability to produce pressure in isovolumetric and ejecting contractions under carefully conn-oiled conditions. We have made SMVs from sheep LD muscle in three different configurations, with the fibres running (1) at 90 degrees to the long axis, (2) at 45 degrees to the long axis, and (3) at zero degrees to the long axis. We are now able to describe the function of these groups of SMVs in terms of a numerical analogue. This model has two functions: first, it allows us io make quantitative com par i sons between ventricles formed with different geometrical configurations or sizes. Second, the model can be incorporated into a numerical model of the complete cardiovascular system that can simulate both normal function and various pathological states. The composite model can then be used to perform virtual experiments to explore the effect of changes in the timing and in various parameters of the SMV model on clinically relevant indices such as mean diastolic pressure or endoeardial viability ratio.

By testing these predictions in the assisted circulation of anaesthetised pigs we will be able to evaluate the model critically and under a wide range of conditions. Necessary refinements will be built into the model, so that it becomes a reliable tool for predicting and optimizing the clinical benefits of SMV assistance.

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DEVELOPMENT OF A B1OMECHAN1CAL HEART - A MUSCULAR BLOOD PUMP TO BK TRAINED DYNAMICALLY WITHIN CIRCULATION.

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Dynamic training of skeletal muscle ventricles (SMVs) in growing animals resulted in blood pumps with increased muscular power. This training was to apply and optimise in SMVs of adult muscular tissue and to test within circulation. In 34 adult Boor goats SMVs of lalissimus dorsi muscle (LDM) were dynamically trained under chronic electrical Stimulation over 3 to 5 months. In group I (n=I4) SMVs pumped against an increasing filling pressure of an elastic training device. In group II (n=4) the same procedure was additionally supported by the beta-2-stimulalor Clenbuterol. In group III (n=4) SMVs contracted against a constant high devices filling pressure supported by Clenbuterol and in group IV (n=12) this high load training was applied Io a muscular wrap around a polyurethanc bladder within circulation. Dynamic training was successful in adult muscular tissue in 5 SMVs of group I (n= 5 successful) with 136 +/- 15 g pumping 479 +/- 83 ml/min as well as in combination with Clenbuterol (group II) up to 690 ml/min. Under high load conditions SMVs of 300 g and 330 g supported by Clenbuterol (group III) pumped 1.1 and 1.2 L/min continuously. One device of group IV with about 330 g muscle resulted in a blood pump shifting up to 1.4 L/min. This autologous blood pump with a stabilising inlay, performed in a one step operation and trained dynamically within circulation was defined as a biomcchanical heart. Biomechanical hearts are hemodynamic relevant. They are expected as clinical practicable and economic for the treatment of end stage heart failure.

ACTIVITY-REST STIMULATION REGIME FOR DYNAMIC CARDIOMYOPLASTY AND SKELETAL MUSCLE CARDIAC ASSIST

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In Dynamic Cardiomyoplasty chronic stimulation of the Latissimus Dorsi achieves full transformation of its myofibers,

so that slowness and consequent delimited power limits its systolic support. A daily activily-rcsl regimen of stimulation could maintain a partial transformation of LD and its power output. After surgical shortening in sheep, LD were burst-stimulated either 10 or 24 hr per day. Two weeks after surgery and two, four, six and twelve months after stimulation, fusion frequency of tetanus, power output, and fatigue resistance of LD were assessed. LDs were biopsied at six months of stimulation, and sheep sacrificed at twelve months. After one year of 10 hr/day stimulation LD was substantially conserved and contained large amounts of fast type myosin. From two-month up to one-year of stimulation the power per muscle of the daily rested LD was three to four times higher than in 24 hr/day stimulated LD and its sustained power was bigger than that of the lefl ventricle.
Corroborating results were recently presented in a rabbit model confirming that long-term daily stimulation increases blood flow but decreases muscle mass, while "interval stimulation", that is an activity-rest regime of stimulation, preserve muscle mass and force.
If these results will be confirmed and extended to human muscle, we are confident that they could be the experimental basis for a demand cardiomyostimulation, whose discontinuous activity could offer to cardiomyopiasty patients the long-standing advantage of a faster and powerful muscle contraction.

EVALUATION OF TWO DIFFERENT TRAINING REGIMENS BY IN SITU STIMULATION OF THE LATISSIMUS DORSI MUSCLE IN PIGS

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Carpentier's training concept has been the reference procedure for conversion of the latissimus dorsi muscle for cardiac assistance since the introduction of cardiomyopiasty in 19K5. Another (raining concept proposed by Guldner et al. has indicated better performance of the converted muscle. Therefore, we compared the characteristics of porcine latissimus dors! muscles after conversion with the two regimens in minipigs.
Six Gottingen mini pigs had bilateral in situ stimulation of latissimus dorsi muscle performed by either Carpentier's or Guldner's training procedure in prospective randomized fashion. Open muscle biopsies (5 x 5 mm) were cut from the muscle ever}' fourteen days during a twenty weeks study period. The biopsies were immediately frozen in isopentane and placed in a vial at -80_ C until bulk analysis of 1) Citrate synthase (CS), 2) 3-OI-I-acyl-CoA dehydrogenase (HAD), and 3) total lactate dehydrogenase (LDH) could be made on all specimens. These enzymes arc markers representing different metabolic pathways. The mean CS activity in the Carpentier and the Guldner group Increased from 3.0 to 10.9 and 3.9 10 14.4 j.imol/gram wet weight respectively. HAD activity increased from 2.9 to 15.6 a 2300 to 466 and 2677 to 968 respectively. The temporal course of these changes displayed a rapid initial incremental raise of CS and HAD and stagnation after six weeks using Carpentier's method, while no stagnation was seen within the observation period when implying Guldner's method. The CS and HAD activity showed no significant difference after 20 weeks between the two (raining concepts. LDH activity displayed an almost linear inverse course Tor both regimens throughout the study period and a significant difference of the two training regimes after Ihe 8th week of stimulation ($p<0.05$).
Both training concepts lead to significant enzymatic changes which Indicate equal degree of conversion by two different time courses. The biochemical markers for the conversion shall be related to the biomcchanical muscle performance in order to be used as monitoring tools in cardiomyopiasty.

CHANGES IN SKELETAL MUSCLE IN HEART FAILURE AS DETECTED BY MICROBIOPSIES

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Congestive Heart Failure is characterised y the occurrence of a specific myopathy with preferential synthesis of fast MHC2b more fatigable myosins and a decreased expression of the slow fatigue resistant aerobic MHC1. By means of a new electropheretic method developed in our laboratories we have been able to study the MHCs composition of the gastrocnemius in patients with CHF. We did that by taking 100-150 ug microbiopsies with a Mcnghini soft-tissue needle. We have found a strong correlation between indexes of severity of cardiac failure, such as NYHA class, diuretic consumption, ejection fraction and cardiopulmonary indexes of exercise tolerance (peak VO2, anaerobic threshold) and the MHCs composition suggesting that the impaired exercise capacity in patients with CHF is al least in part due to the shift of the skeletal muscle pattern toward fast fibres. We have also correlated the magnitude of the improvement in exercise tolerance in patients with CHF after 6 months treatment either wilh ACE inhibitors (Captopril 50 rng b.i.d.) or with All antagonist (Losarlan 50 mg once daily) with the net changes in skeletal muscle MHCs. We found that the improvement in peak V02 correlates significanlly with the change in MHC2a and 2b. We have therefore put forward the hypothesis that the increased exercise tolerance seen in patients with CHF with the pharmacological block of the angiotensin syslem can be in part explained by the favourable changes occurring in the skeletal muscle.
We are currently developing a method enabling us to detect apoptosis (by means of TUNEL method) on (he skeletal muscle microbiopsies. Preliminary results show that apoptosis occurs in CHF to a higher degree than in healthy subjects. Apoptosis is more pronounced in endothclial cells rather than in myofibers.

APOPTOSTS COULD OCCUR IN MYOCARDIUM, BUT NOT IN LD WRAP AFTER DYNAMIC CARDIOMYOPLASTY

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Apoptosis or programmed cell death is a process of cell death occurring in many tissues, in which dying cells display similar changes in morphology and chromosomal DNA degradation. The current view that apoptosis precedes necrosis in death of dy strop bin-deficient muscle fibers of mdx mouse is well advanced. Moreover we described a ten-time increase of apopiolie myonuclei in dystrophin-deficient mice two days after spontaneous exercise performed during a night in a cage with an exercise wheel. Apoptosis was assessed by the terminal deosynucleotidyl transferase assay and by elcctrophoretic detection of fragmented DNA. Whilst being absent in muscles of normal "sedentary" mice, apoptotic myonuclei together with DNA ladder peak in muscles of nonnal mice immediately after a night of spontaneous wheel-running; they then decrease in number but are present at least up to four days laler. Interestingly, the percent content of apoptotic myonuclei just after running is similar to lhat of myofibcrs displaying regeneration features four days later. Apoptosis of endothelial cells of intramuscular vessels also occurs, both immediately after the night of wheel-running and with a 2-fold increase four days later, suggesting a sequential nature of the pathogenic mechanisms of exercise-induced muscle damage/apoptosis.

We studied contribution of apoptosis to exercise-induced damage of muscle fibber which may or may not occur in the LD muscle of Dynamic Cardiomyoplasty in two autopsy cases. While frequently present in myocardiocytes, apoptolie features in myonuclei of muscle fibres of LD were absent. Only in severely a trophic myofibers focally present in one of [he control muscles (denervalion?) myonuclei were positive by the terminal deoxynuclcotidyl transferase assay. These preliminary results suggest that, if present, the burst of muscle apoptosis in exercise-induced damage is an early event peculiar of untrained muscle.

References

Carraro U (1995) Apoptotic death of dystrophic muscle fibers
after exercise: a new hypothesis on the early events of muscle
damage.
Basic Appl Myol 5:371-374.

Carraro U, Franceschi C (1997) Apoptosis of skeletal and cardiac muscles and physical exercise.
AgingClinExpRes9: 19-34, 1997.

Podhorska-Okolov M, Sandri M, Bruson A, Carraro U,
Massimino ML, Arslan P, Monti D, Cossarizza A, Franceschi
C (1995) Apoptotic myonuclei appear in aduli skeletal muscles of normal and *mdx* mice after a mild exercise.
Basic Appl Myol 5:87-90.

Sandri M, Carraro U, Podhorska-Okolow M, Rizzi C, Arslan
P, Monti M, Franceschi C (1995) Apoptosis, DNA damage and ubiquitin expression in normal and *mdx* muscle fibers after exercise.
FEES Lett 373:291-295.

Sandri M, Podhorska-Okolow M, Geromel V, Rizzi C, Arslan
P, Franceschi C, Carraro U (1997) Exercise induces
myonuclear ubiqnitinauon and apoptosis in dystrophin
deficient muscle of mice.
J Neuropath Exp Neurol, 56:45-57.

CELLULAR CARDIOMYOPLASTY: PRESENT AND FUTURE

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Cellular Cardiomyoplasty is an approach to implant cells and grow new muscle fibers in the damaged myocardium that potentially may contribute to the contractile performance of the heart. Frequently, ischcmic or degenerative diseases affect the myocardium. Since cardiomyocytes cannot regenerate, the injury is irreversible. Therefore, the aim of cellular cardiomyoplasty is the repair of injured myocardium by cell transplantation. Two types of cells have mainly been used for this purpose:

1. foetal cardiomyocytes, an approach which requires an immunosuppressive therapy
2. Auiologous myoblasts obtained from skeletal muscle cells of the same animal

In the research of cellular cardiomyoplasty there are many variables, which make a comparison between different studies almost impossible. These variables may include; the animal model used, the type of cells to be transplanted, the method of rnyocardial injury, how cells are transplanted and how long after myocardial injury, cell detection post-transplantation, and cell function.

At present, graft survival of transplanted cells has been established. Foetal cardiomyocytes seem to form gap junctions in the host, satellite cells are able to form intercalate disks and C2C12 cells even differentiate into myofibers *in vivo.* Cellular card io myopia sty has also been found to limit scar expansion. Furthermore, the first results on improved heart function have been published, although the actual mechanism involved remains unclear.

What does cellular cardiomyoplasty hold for the future? Is cellular cardiomyoplasty cell type specific? Do factors secreted by the cellular grafts improve heart function? Could clcctrostimulalion on the heart influence transplanted cells? Many questions are still unanswered.

Our group is currently working on a sheep model and our future aim is to combine fhe technique of cellular cardio-myoplasty with electrostimulation.

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