Effect of Cardiomyoplasty on Left Ventricular Diastolic Function

Edmundo I. Cabrera Fischer [(1)], Juan C. Chachques [(2)], Alberto Garcia [(1)], Eduardo de Fortezza [(1)], François Haab [(2)], Christophe Cron [(2)], Alain Carpentier [(2)]

(1) Research Department of Favaloro Foundation, Buenos Aires, Argentina, and (2) The Department of Cardiovascular Surgery, Broussais Hospital, Paris, France.

Abstract

The purpose of the present study was to determine the hemodynamic effects of dynamic cardiomyoplasty in an animal model of acute cardiac failure performed in 11 anesthetized dogs.

The statistical study showed that electrostimulation of latissimus dorsi produced a significant increase of systolic left ventricular pressure ($p < 0.05$), and a decrease of end diastolic and minimum value of diastolic pressure ($p < 0.01$ in both cases) before induction of heart failure. In dogs suffering cardiac failure induced by propranolol, electrostimulation of latissimus dorsi resulted in a significative increase of systolic left ventricular pressure ($p < 0.05$), cardiac output ($p < 0.01$) and cardiac index ($p < 0.01$). End diastolic left ventricular pressure was decreased significantly ($p < 0.01$).

We conclude that cardiac assistance by using dynamic cardiomyoplasty results in a significant improvement of hemodynamic parameters in the normal state and in induced cardiac failure, and this effect determines the decrease of left ventricular pressure during the diastolic period below physiological values.

Key words: cardiac failure, latissimus dorsi muscle, functional electrostimulation, cardiomyoplasty.

BAM 1 (3): 253-258, 1991

Cardiac failure is a clinical syndrome identified in 200.000 to 400.000 new cases per year in Europe. Independent of the etiology, this syndrome complicates the terminal stage of almost any heart disease [14].

Up to the present three different methods have been proposed in order to improve severe chronic heart failure: mechanical circulatory support [10], heart transplantation [13] and dynamic cardiomyoplasty [7].

Cardiomyoplasty utilizes an electrically stimulated latissimus dorsi muscle wrapped around the heart [5]. This skeletal muscle is stimulated in synchrony with normal heart contractions by using a burst of impulses delivered by a cardio-myostimulator [5]. Several studies have demonstrated that chronic electrical stimulation induces histological and biochemical changes in the latissimus dorsi flap in which the vascular and nerve supply is preserved [15].

Histological and biochemical studies of the chronically stimulated latissimus dorsi have demonstrated transformation of muscle fast myosin to slow myosin, similar to that found in heart muscle [15]. Thus way a skeletal muscle is turned by electrical stimulation into a fatigue-resistant muscle [6].

Postoperative studies performed in patients in whom cardiomyoplasty was performed as a treatment of severe cardiac failure suggest a long-term benefit, but although functional improvement was reported, hemodynamic augmentation could not be always demonstrated [16].

Since 1985 more than 150 patients have undergone cardiomyoplasty worldwide. The hospital survivors have improved their functional class for heart failure, but it is yet unclear how this procedure benefits these patients [21].

Our purpose was to study hemodynamic changes induced by latissimus dorsi cardiomyoplasty in dogs in which cardiac failure was induced to mimic as closely as possible the clinical situation.

Materials and Methods

Surgical Procedure

Eleven adult mongrel dogs (6 males and 5 females) weighing 21 ± 6 Kg were used in the study. Anesthesia was induced with sodium thiopentone (20 mg/kg, given intravenously). After intubation all dogs were ventilated

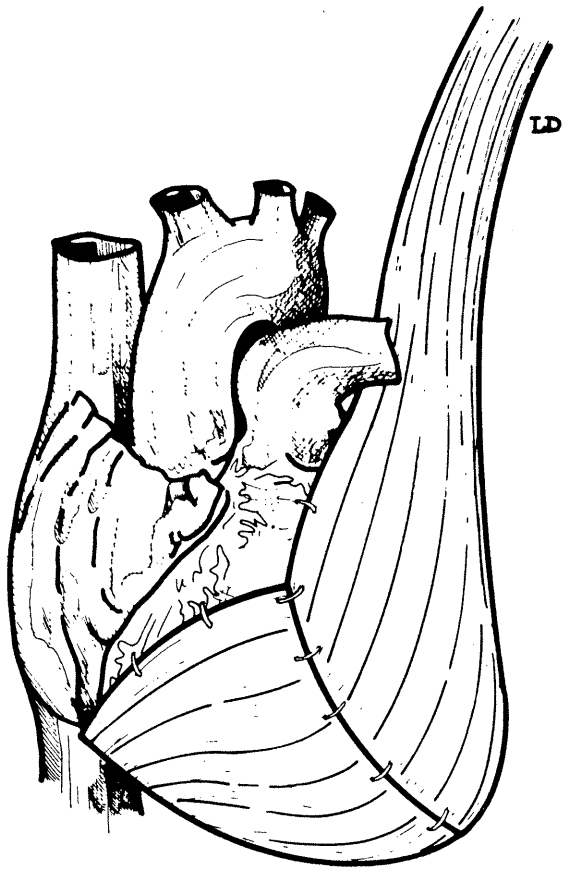

Figure 1. Latissimus dorsi wrapped around the heart.

with a respirator (Bird Mark 8) and anesthesia was maintained with halothane 1% carried in pure oxygen administered via a Bain tube.

A left lateral cutaneous thoracic incision was performed and the left latissimus dorsi flap was dissected, the thoracodorsal neurovascular bundle being kept intact. Two electrodes made in our laboratory were placed in the proximal part of the latissimus dorsi muscle flap according to a previously described technique [4].

The skeletal muscle flap and the leads were positioned in the thoracic cavity by way of a second rib resection. Afterwards, a thoracotomy was performed at the level of the fifth left lateral intercostal space. A third lead was placed in the right ventricular wall in order to detect the R wave.

The latissimus dorsi flap was then wrapped around the heart as shown in Figure 1, by fixing it with interrupted sutures.

Finally, a Swan-Ganz catheter was placed in the pulmonary artery, via the right atrial appendage, a 9 Fr. catheter in the left ventricle and a 9 Fr. catheter in the right atrium via the right atrial appendage. All catheters and flush solutions were heparinized. The animal temperature was maintained at 37 °C using an electric blanket.

Measurements

All electrodes were coupled to an external cardiomyostimulator manufactured in our laboratory, and capable of generating: pulse amplitude, 1-15 volts; pulse width, 210 μsec; burst rate, 2 to 30 Hertz; number of pulses, 1-9. The latissimus dorsi flap was stimulated in the present experiments by using a heart-muscle contraction ratio of 1/1, and trains of 6 pulses with a burst rate of 30 Hertz. Synchronization of latissimus dorsi stimulation with the cardiac rhythm was achieved by using the R wave of a surface electrocardiogram as seen in Figure 2.

Systolic, end-diastolic and minimum value of diastolic left ventricular pressures and mean right atrial pressure were monitored by using Gould-Statham transducers, Gould 4600 series preamplifiers, and a Gould multichannel recorder (Model 2600 S, Gould Inc, Cleveland, Ohio). The transducers were directly calibrated with water and mercury columns. The cardiac output was measured by the thermodilution technique using a cardiac output computer (Edwards 9520 A). The cardiac index was calculated by dividing cardiac output by body weight [17].

Hemodynamic parameters were measured during steady state under the following conditions: a-control state, that is to say before propranolol administration, and b-cardiac failure induced by using propranolol boluses (3 mg/kg, given intravenously). In both situations hemodynamic measurements were made with and without latissimus dorsi flap stimulation. This was achieved using the cardiomyostimulator functioning (stimulated values) and 10 minutes after the device was switched off (basal values) both in control state and in cardiac failure. The cardiomyostimulator was never utilized for more than 5 minutes in order to avoid muscular fatigue.

After the experiments were ended the animals were killed by injection of an overdose of thiopental sodium.

All animals received humane care in the preoperative period in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health (NIH Publications 35 80-23, revised 1978).

Statistical Treatment

All the results were analyzed by using one-way analysis of variance. To test differences between groups the Newman-Keuls test was applied.

Values reported are expressed as mean ± SD. Pressure values considered are the mean of five consecutive cardiac cycles; cardiac output values are the mean of three consecutive determinations.

The 95% confidence limit was chosen as the indicator of statistical significance ($p < 0.05$).

Results

From the initial 11 dogs operated, 4 were discarded due to technical mistakes made while the continuous recording was performed. No vascular accidents or deaths resulted during the experiments.

In the control state cardiac assistance was performed by stimulating the latissimus dorsi flap. Table 1 shows that this stimulation produced a significant increase of systolic left ventricular pressure ($p < 0.05$), with respect to basal values. The end-diastolic and the minimum diastolic value of left ventricular pressure decreased significantly ($p < 0.01$ in both cases), while the right atrial pressure values increased without reaching levels of statistical significance. Negative diastolic pressure values were observed in all cases during latissimus dorsi stimulation. No changes of heart rate due to latissimus dorsi flap stimulation were observed in any experiment.

Propranolol administration (Table 2) resulted in a non significant decrease of heart rate. Systolic left ventricular pressure, cardiac output and cardiac index showed significant decreases ($p < 0.05$, in all cases) after propranolol administration. End diastolic and the minimum value of diastolic left ventricular pressures increased after propranolol administration ($p < 0.01$ in both cases). Mean right atrial pressure showed a non significative increase.

Hemodynamic measurements during cardiac assistance in the cardiac failure state (Table 3) showed a significant increase of systolic left ventricular pressure ($p < 0.05$), cardiac output ($p < 0.01$) and cardiac index ($p < 0.01$). A noticeable and significative decrease of end diastolic and minimum value of diastolic pressures was observed ($p < 0.01$, in both cases). As in control situation latissimus dorsi stimulation determined negative values of the minimum diastolic left ventricular pressure in 6 of the 7 dogs (Figure 2). Mean right atrial pressure remained without significant changes.

With the object of checking the efficacy of the treatment, the unstimulated control state and the stimulated cardiac failure state were compared. There were no significant differences in terms of systolic and mean right atrial pressure. Cardiac output and cardiac index values were significantly lower in stimulated cardiac failure that in the basal control state ($p < 0.01$). Both end diastolic and the minimum value of diastolic left ventricular pressure showed a significant decrease with latissimus dorsi stimulation in the cardiac failure state with respect to the unstimulated values in the control state ($p < 0.01$ in both cases).

Table 1. Hemodynamic parameters in Control state (before propranolol administration) obtained whit and without latissimus dorsi flap stimulation. NS: Not Significant, SLVP: Systolic Left Ventricular Pressure, EDLVP: End Diastolic Left Ventricular Pressure, MRAP: Mean Right Atrial Pressure, MDLVP: Minimum Left Ventricular Pressure, CO: Cardiac Output, CI: Cardiac Index, HR: Heart Rate.

.	NON STIMULATED	STIMULATED	p
VALUE			
SLVP (mmHg) Mean ± SD	95.5 ± 24.4	110.1 ± 24.7	0.05
EDLVP (mmHg) Mean ± SD	5.28 ± 0.75	4.86 ± 1.46	0.01
MRAP (mmHg) Mean ± SD	3.90 ± 2.18	4.20 ± 1.80	NS
MDLVP (mmHg) Mean ± SD	1.29 ± 1.35	4.79 ± 2.67	0.01
CO (L/min) Mean ± SD	1.64 ± 0.32	1.77 ± 0.32	NS
CI (L/min/kg) Mean ± SD	0.074 ± 0.010	0.080 ± 0.009	NS
HR (beats/min) Mean ± SD	86 ± 23	86 ± 23	NS

Table 2. Hemodynamic parameters in seven dogs before and after cardiac failure production by using propranolol (3mg/Kg, iv). NS: Not Significant. SLVP: Systolic Left Ventricular Pressure, EDLVP: End Diastolic Left Ventricular Pressure, MRAP: Mean Right Atrial Pressure, MDLVP: Minimum Left Ventricular Pressure, CO: Cardiac Output, CI: Cardiac Index, HR: Heart Rate.

.	CONTROL GROUP	CARDIAC FAILURE	p
VALUE			
SLVP (mmHg) Mean ± SD	95.5 ± 24.4	74.4 ± 15.8	0.01
EDLVP (mmHg) Mean ± SD	5.28 ± 0.75	7.34 ± 2.18	0.05
MRAP (mmHg) Mean ± SD	3.90 ± 2.18	5.80 ± 3.4	NS
MDLVP (mmHg) Mean ± SD	1.29 ± 1.35	4.21 ± 1.47	0.05
CO (L/min) Mean ± SD	1.64 ± 0.32	0.84 ± 0.19	0.01
CI (L/min/kg) Mean ± SD	0.074 ± 0.010	0.038 ± 0.008	0.01
HR (beats/min) Mean ± SD	86 ± 23	74 ± 21	NS

Discussion

The development of an adequate technique for treating severe cardiac failure with the aid of skeletal muscle and an implantable stimulator is a better approach than one in which anticoagulation or imunosuppresive therapy must be utilized. At present, mechanical devices are only complementary methods for cardiac transplantation in spite of the fact that these devices have been shown to be appropi-

ate in the maintenance of systemic and pulmonary circulations [2, 11, 18]. However, cardiac anastomoses and cardiopulmonary bypass are required in most of these techniques. Other techniques such as intraaortic balloon pump counterpulsation are unable to provide adequate circulatory support in very severe stages of cardiac failure [19, 23].

The purpose of the present study was to investigate the effectiveness of latissimus dorsi dynamic cardiomyoplasty in an acute animal model of cardiac failure focusing our attention in the diastolic period in order to detect changes determined by the positioning and stimulation of this muscle.

The animal model of cardiac failure used in this study was chosen because it mimics closely heart failure due to myocardial depression observed in patients, and because it is a well known model utilized previously in experimental studies performed in dogs [8]. As we can see in Table 2 this objective was achieved and cardiac failure was maintained up to the end of the experiments in all animals.

In the present animal preparation the absence of a "trained" latissimus dorsi made it impossible to stimulate this skeletal muscle for a long period of time, the interval of stimulation being not more than five minutes. As previously reported, fatigue-resistant muscular fibers are the result of an electrical stimulation program of at least two months [7]. Untrained latissimus dorsi muscle were used in this study only for technical reasons and is not an alternative to trained muscle. For this reason recording of hemodynamic variables was performed in the steady state achieved within two or three minutes after beginning latissimus dorsi stimulation.

In our work the capability of the left ventricle to generate pressure and an adequate cardiac output was increased despite the use of a skeletal muscle without any previous conditioning: according to our observations the synchronized stimulation of a latissimus dorsi flap results in an improvement of hemodynamic parameters in dogs with or without cardiac failure.

Observation of negative pressures in the left ventricular filling period when latissimus dorsi stimulation was performed is an interesting phenomenon that in our opinion is closely related to the passive elastic properties of the ventricular wall. Intraventricular negative pressures determine a suction effect, which has been described since 1930 [20] and can be found in different hemodynamic situations.

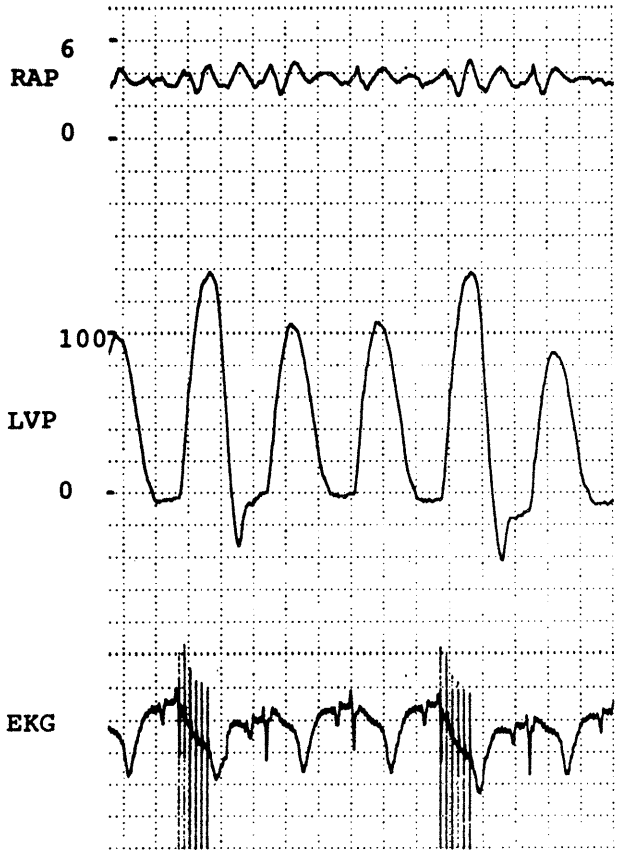

Figure 2. The negative values of diastolic left ventricular pressure were increased at the beginning of the diastolic period. RAP right atrial pressure. LVP left ventricular pressure. EKG electrocardiogram.

Table 3. Hemodynamic parameters recorded in dogs with cardiac failure in which lattissimus dorsi flap stimulation was performed. NS: Not Significant, SLVP: Systolic Left Ventricular Pressure, EDLVP: End Diastolic Left Ventricular Pressure, MRAP: Mean Right Atrial Pressure, MDLVP: Minimum Left Ventricular Pressure, CO: Cardiac Output, CI: Cardiac Index, HR: Heart Rate.

.	NON STIMULATED	STIMULATED	p
VALUE			
SLVP (mmHg) Mean ± SD	74.4± 15.8	87.9 ± 16.9	0.05
EDLVP (mmHg) Mean ± SD	7.34 ± 2.18	6.10 ± 1.47	0.01
MRAP (mmHg) Mean ± SD	5.8 ± 3.4	5.7 ± 3.3	NS
MDLVP (mmHg) Mean ± SD	4.21± 1.47	2.71± 2.43	0.01
CO (L/min) Mean ± SD	0.84± 0.19	1.20± 0.25	0.01
CI (L/min/kg) Mean ± SD	0.038± 0.008	0.054± 0.008	0.01
HR (beats/min) Mean ± SD	74± 21	74± 21	NS

Brecher in 1956 produced negative diastolic pressures by closing the mitral orifice [3], in the same year Bloom observed how the atrial wall was sucked into the mitral orifice in a beating rat heart immersed in a beaker of saline [1]. Fowler in 1957 observed that epinephrine and l-norepinephrine administration resulted in negative diastolic pressures in an animal preparation [12], and more recently negative diastolic pressures were obtained in conscious dogs with incremental changes in heart rate obtained by atrial pacing [9]. Similar results were obtained in patients with β-adrenergic stimulation with isoproterenol [24]. In hemodynamic studies performed in patients with mitral stenosis the diastolic pressures ranged between 6 and -7 mmHg [22]. According to these reports, they have several factors in common: low afterload, mitral occlusion and small end-systolic volumes. In the case of patients with latissimus dorsi cardiomyoplasty fluxometrical studies with the ultrasonic doppler method showed that muscle stimulation empties the left ventricle more than normally leaving a very small residual volume [7]. More experiments must be performed in order to clarify the reason or this finding.

We conclude that dynamic cardiomyoplasty results in a significant hemodynamic improvement in dogs with normal cardiac function and tends to recover the impaired hemodynamic variables in the model of cardiac failure utilized in this study. In addition changes in diastolic left ventricular function are involved in this improvements.

Acknowledgments

The authors wish to acknowledge the collaboration of Risk M.R., Cierto M. and Stutzbach P. for their technical assistance.

Address correspondence to:

Dr. J.C. Chachques, Department of Cardiovascular Surgery, Broussais Hospital, 96 rue Didot, 75014 Paris, France.

References

[1] Bloom WL, Ferris EB: Negative ventricular diastolic pressure in beating heart studied in vitro and in vivo. *Proc Soc Med Biol* 1956; 93: 451-54.

[2] Bolman R, Cox JL, Marshall W, Kouchoukos N, Spray TL, Cance C, Genton RE et al: Circulatory support with a centrifugal pump as a bridge to cardiac transplantation. *Ann Thorac Surg* 1989; 47: 108-12.

[3] Brecher GA: Experimental evidence of ventricular diastolic suction. *Circ Res* 1956; 4: 513-18.

[4] Chachques JC, Grandjean PA, Carpentier A: Latissimus dorsi dynamic cardiomyoplasty. *Ann Thorac Surg* 1989; 47: 600-04.

[5] Chachques JC, Grandjean PA, Carpentier A: Patient management and clinical follow-up after cardiomyoplasty. *J Cardiac Surg* 1991; 6: 89-99.

[6] Chachques JC, Grandjean PA, Perier P, Nataf P, Acar C, Mihaileanu S, Bensasson D, et al: Cardiomyoplastie. Bases experimentales, technique operatoire, indications. *Arch Mal Coeur* 1989; 82: 919-26.

[7] Chachques JC, Grandjean PA, Schwartz K, Mihaileanu S, Fardeau M, Swynghedauw B, Fontaliran F et al: Effect of Latissimus Dorsi Cardiomyoplasty on ventricular function. *Circulation* 1988; 78 (Suppl III): 203-16.

[8] Chagas ACP, Moreira LFP, da Luz PL, Camarano GP, Leirner A, Stolf NAG, Jatene AD: Stimulated preconditioned skeletal muscle cardiomyoplasty. An effective means of cardiac assist. *Circulation* 1989; 80 (Suppl III): 202-08.

[9] Cheng CP, Freeman GL, Santamore WP, Constantinescu MS, Little WC: Effect of loading conditions, contractile state, and heart rate on early diastolic left ventricular filling in conscious dogs. *Circ Res* 1990; 66: 814-23.

[10] Davis PK, Rosenberg G, Snyder AJ, Pierce WS: Current status of permanent total artificial hearts. *Ann Thorac Surg* 1989; 47: 172-78.

[11] Fischer EIC, Willshaw P, Armentano R, Delbo MIB, Pichel R, Favaloro RG: Experimental acute right ventricular failure and right ventricular assist in the dog. *J Cardiovasc Surg* 1985; 90: 580-85.

[12] Fowler NO, Bloom WL, Ferris EB: Systolic and diastolic pressure relationships in the isolated rat heart. *Circ Res* 1957; 5: 485-88.

[13] Fragomeni LS, Kaye MP: The registry of the International Society for Heart Transplantation: Fifth official report-1988. *J Heart Transplant* 1988; 7: 259-53.

[14] Franciosa JA, Wilen M, Ziesche S, Cohn JN: Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983; 51: 831-36.

[15] Goldspink DF, Easton J, Winterburn SK, Williams PE, Goldspink GE: The role of passive stretch and repetitive electrical stimulation in preventing skeletal muscle atrophy while reprogramming gene expression to improve fatigue resistance. *J Cardiac Surg* 1991; 6: 218-24.

[16] Grandjean PA, Austin L, Chan S, Terpstra B, Bourgeois IM: Dynamic cardiomyoplasty: clinical follow-up results. *J Cardiac Surg* 1991; 6: 80-88.

[17] Jett GK, Siwek LG, Picone AL, Applebaum RE, Jones M: Pulmonary artery balloon counterpulsation for right ventricular failure. *J Cardiovasc Surg* 1983; 86: 364-72.

[18] Joyce LP, Johnson KE, Toninato CJ, Cabrol C, Friffith B, Copeland JG, Keon WJ, et al: Results of the first 100 patients who received Symbion total artificial hearts as a bridge to cardiac transplantation. *Circulation* 1989; 89 (Suppl III): 192-201.

[19] Kantrowitz A, Kantrowitz A: Experimental augmentation of coronary flow by retardation of the arterial pressure pulse. *Surgery* 1953; 34: 678-687.

[20] Katz LN: The role played by the ventricular relaxation process in filling the ventricle. *Am J Physiol* 1930; 95: 542-53.

[21] Lee KF, Dyke CM, Wechsler AS: Theoretical considerations in the use of dynamic cardiomyoplasty to treat dilated cardiomyopathy. *J Cardiac Surg* 1991; 6: 119-23.

[22] Sabbah HN, Anbe DT, Stein PD: Negative intraventricular diastolic pressure in patients with mitral stenosis: evidence of left ventricular diastolic suction. *Am J Cardiol* 1980; 45562-66.

[23] Turina M: Surgical and mechanical support of the failing heart. *Europ Heart J* 1983; 4: 211-217.

[24] Udelson JE, Bacharach SL, Cannon RO, Bonow RO: Minimum left ventricular pressure during β-adrenergic stimulation in human subjects. Evidence for elastic recoil and diastolic suction in the normal heart. *Circulation* 1990; 82: 1174-82.