Biventricular Assist Device-Induced Right Ventricular Reverse Structural and Functional Remodeling

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Background: Support with a left ventricular assist device (LVAD) induces LV reverse structural and functional remodeling, evidenced by normalization of passive end-diastolic pressure–volume relationships (EDPVRs) and cardiomyocyte function. These changes are not evident in the right ventricle (RV), which remains dilated during LVAD support. However, studies on whether RV reverse remodeling could be induced by RV or biventricular assist support (BiVAD) have not been published.

Methods: Whole hearts from 16 patients with end-stage congestive heart failure (CHF) at the time of cardiac transplantation without LVAD support, 16 patients with LVAD support, and 3 patients with BiVAD support were used to study RV EDPVRs, with estimation of chamber stiffness. Perfused isolated myocardial trabeculae were used for functional studies. Furthermore, RV free wall samples were used for histology and collagen determination by hydroxyproline.

Results: The RV size, calculated from the ex vivo RV EDPVRs, RV mass, and myocyte diameter were significantly smaller in BiVAD-supported hearts than in non-supported or LVAD-supported hearts ($p < 0.05$) and reached normal levels. Furthermore, cardiomyocyte function demonstrated a normalized response to increased stimulation frequency and after perfusion with isoproterenol following BiVAD support. In addition, myocardial collagen content and chamber stiffness increased tremendously after BiVAD support ($p < 0.05$ vs CHF and LVAD).

Conclusion: BiVAD-induced hemodynamic unloading support resulted in significant reverse structural and functional remodeling of the right chamber. The lack of these findings during LVAD support alone provides additional support that diastolic pressure and volume unloading is an important mechanism underlying the process of reverse remodeling. J Heart Lung Transplant 2005;24:1195–201. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

The end-diastolic pressure–volume relationship (EDPVR) is a fundamental measure of passive ventricular properties. Understanding how this relationship changes in disease and in response to treatments has provided important insights into the pathophysiology of heart failure. In end-stage heart failure with systolic pump dysfunction, the left ventricular (LV) EDPVR is shifted toward higher volumes, synonymous with ventricular structural remodeling.[1] Such remodeling occurs in both idiopathic dilated and ischemic cardiomyopathies.

We have shown in previous studies that after left ventricular assist device (LVAD) support, the LV EDPVR is shifted leftward toward more normal volumes, a process we referred to as reverse structural remodeling.[2-4] This EDPVR shift toward normalization is a consequence of reduced LV mass, size, and myocyte diameter.[2-6] In addition, LV reverse functional remodeling, evidenced by improved cardiomyocyte function either in isolated cardiomyocytes or whole muscle strips, has been demonstrated following LVAD support.[5,7,8] Reversal of molecular, cellular, and neurohormonal abnormalities are also apparent during LVAD support.[6-8]

The right ventricle (RV) also remodels in chronic heart failure, with a rightward shift of its EDPVR. This may be due to an underlying abnormality of RV muscle (either because of ischemia/infarction or underlying myopathy) and/or to elevated RV preload and afterload associated with LV failure. In contrast to the LV, the RV does not exhibit significant reverse structural remodeling during LVAD support (i.e., the RV EDPVR does not shift toward normal and the myocyte size does not normalize)[9] despite reduced RV afterload, as evidenced by marked decreases in left atrial and pulmonary pressures during LVAD support. In addition, RV cardiomyocyte function is not restored, despite a normalized hemodynamic and neurohormonal milieu.[2]

We previously concluded that the persistent RV chamber enlargement and the limited recovery of RV cardiomyocyte function during LVAD support is caused

by the persistently elevated central venous pressure (high diastolic wall stress) and relative volume overload of the impaired RV.[10] In this study, we hypothesized that RV reverse structural and functional remodeling would be induced when diastolic pressure and volume unloading of the RV was provided by a RV assist device (RVAD). To test this hypothesis, we measured right ventricular EDPVRs and isolated trabeculae function of hearts of patients who underwent biventricular support until cardiac transplant. We compared these measurements with those from hearts that had been supported with an LVAD alone, with those of unsupported end-stage failing hearts, and with those of normal hearts.

METHODS

This study was performed according to the guidelines of the Declaration of Helsinki. The New York Presbyterian Medical Center Institutional Review Board approved all procedures involving human tissue use. Hearts were obtained at the time of cardiac transplantation from 3 groups:

- CHF Group: 16 patients with end-stage congestive heart failure (CHF) without LVAD support (average age, 49 ± 12 years).
- LVAD Group: 16 transplant patients after LVAD support (average age, 46 ± 12 years). The duration of LVAD support was 144.8 ± 33.1 days with a Heartmate LVAD (Thoratec Corp., Pleasanton, CA).
- BiVAD Group: 3 transplant patients after BiVAD support (Table 1). In this group, RV heart support was performed with a Thoratec RVAD (Thoratec Corp.) that was instituted 0, 13, and 28 days after LVAD implantation. The average time of biventricular support was 56 ± 27 days.

Five normal hearts, unsuitable for transplantation, were also available.

Passive End-Diastolic Pressure–Volume Relationship and Estimation of Chamber Stiffness

All hearts were perfused with cold, hypocalcemic, hyperkalemic cardioplegic solution at explantation. The RV passive EDPVR of each arrested heart was measured as described previously.[5] In brief, the pulmonary artery and, in case of RVAD-supported hearts, the RVAD inflow cannula were clamped. A metal adapter was attached to the tricuspid annulus, and a compliant water-filled latex balloon was placed within the chamber. The pressure within each balloon was measured with a high-fidelity micromanometer as volume was progressively increased. The pressure was then plotted as a function of volume at each step, resulting in an EDPVR that was similar to the EDPV relationship of a contracting heart. While this relationship was measured in the RV chamber, the contralateral chamber was emptied. The size of the RV chamber was indexed by the volume at which the pressure within the ventricle reached 30 mm Hg (RVV_{30}).

Ventricular chamber stiffness (α) is the slope of the Ln(EDP) vs the EDV/V_W relationship calculated from the ex vivo EDPVRs according to the equation described by Mirsky and Pasipoularides.[11] EDP is end-diastolic pressure, V is volume and V_W is myocardial wall volume (calculated from measured RV mass and assumed density of 1.05 g/ml). All calculations were performed with IGOR Pro (v 4.01) software (WaveMetrics, Inc., Lake Oswego, OR).

Myocardial Force Generation

Baseline force generation, and force generation at different rates of stimulation (force–frequency relation) and in response to β-adrenergic stimulation, were measured from RV free wall trabeculae as described previously.[2,5] Immediately after cardiectomy, trabeculae of less than 1 mm in diameter were excised and immersed in oxygenated (95% O_2, 5% CO_2) ice-cold Krebs-Ringer solution with 30 mmol/liter 2,3-butanedione monoxime.

For the functional measurements, the muscle strips were mounted in a tissue perfusion bath with one end connected to a force transducer and the other connected to a length-adjustable micrometer gauge by using fine steel hooks. During super-perfusion with 37°C oxygenated Krebs-Henseleit buffer (rate, 1 ml/liter; bath volume, 1 ml), the trabeculae were stimulated at 1 Hz and allowed to equilibrate for at least 1 hour at slack length. After the equilibration period, isometric twitches were evoked with stimulation voltage 20% above threshold (duration, 5 msec). The

Table 1. BiVAD Patient Characteristics

Pat.	Age	Disease	LVAD	RVAD	Implantation after LVAD (Day)	Support duration, (days)	Outcome
1	32	IDCM	Thoratec	Thoratec	0	62	Tx
2	63	IDCM	TCI HeartMate	Thoratec	13	26	Tx
3	64	ICM	TCI HeartMate	Thoratec	28	81	Tx

ICDM, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy; Tx, Heart Transplantation; LVAD, left ventricular assist device; RVAD, right ventricular assist device.

trabeculae were then progressively stretched to the length of maximal force generation.

To measure the force–frequency relationship, the stimulation frequency was increased every 5 minutes at 0.5-Hz increments to a maximum of 2.5 Hz (150 beats/min). After another re-equilibration period of 30 minutes at 1 Hz, the contractile response to β-adrenergic stimulation was measured by switching to a perfusate of identical composition, oxygenation, and temperature that contained isoproterenol (1 μg/ml).

Adequate muscle oxygenation was confirmed as detailed previously.[2] Myocardial force generation was calculated after normalization to cross-sectional area.

Myocyte Diameter

Freshly collected RV myocardial samples were immediately fixed in buffered formalin (10%), embedded in paraffin, and mounted on glass slides. To quantify myocyte diameter, samples were prepared with Masson trichrome stain. Images were viewed on a Optiphot-2 microscope (Nikon Corporation, Tokyo, Japan) with an MTI 3CCD digital camera (Dage-MTI Inc., Michigan City, ID). Digitally acquired images were analyzed with Image-Pro Plus (v 3.0) software (Media Cybernetics, Silver Spring, MD). At ×20 magnification, 2 orthogonal diameters were obtained per myocyte and then averaged. Only sections cut in cross-section were analyzed.

Collagen Content

Myocardial samples were collected from the RV free wall of each heart and immediately snap-frozen in liquid nitrogen and kept at −80°C for further analysis. The total myocardial collagen content was assessed by using a modified Stegemann method to measure the hydroxyproline content.[12] The tissue was lyophilized and then hydrolyzed with 6 N HCl. The hydrolysate was evaporated, the powder reconstituted with distilled H_2O, and oxidized with chloramine-T (Sigma-Aldrich Corp., St. Louis, MO). The reaction was stopped with 3.15 mol/liter perchloric acid, and p-dimethylaminobenzaldehyde solution was added. The sample was vortexed, incubated in a 60°C bath, and then cooled. The absorbency of the solutions was determined at 557 mm, and the hydroxyproline concentration was determined from the standard curve using hydroxyproline standard solutions.

Statistics

Results are presented as mean ± standard error of the mean. One-way analysis of variance was used to select differences between groups. A Student-Newman-Keuls test was used for multiple comparisons. The statistical analysis was conducted with the Statistical Package for Social Sciences (SPSS) (v 11.5) software (SPSS, Chicago, IL). A p value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics and main pulmonary hemodynamics are presented in Table 2.

Pulmonary Hemodynamics

Right atrial pressure was significantly higher in the BiVAD group than in the LVAD group before device implantation (Figure 1, $p < 0.05$). However, following BiVAD support, right atrial pressure was lowered sig-

Table 2. Patient Demographics and Pulmonary Hemodynamics

	BiVAD		LVAD		CHF
	At Insertion	At Transplant	At Insertion	At Transplant	At Transplant
Number of Patients	3		16		16
Age (yrs)	53.0 ± 18.2		46.2 ± 11.8		48.8 ± 12.1
Male/Female	2:1		15:1		8:6
ICM/DCM	1:2		9:7		8:8
RAP (mmHg)	16.0 ± 4.2*	2.3 ± 1.5†#	9.6 ± 3.4	10.4 ± 5.9	10.1 ± 5.8
PAPm (mmHg)	37.9 ± 2.6	12.5 ± 2.1‡#	34.8 ± 11.1	19.5 ± 6.9#	28.4 ± 10.3
PCWP (mmHg)	29.5 ± 4.9	9.5 ± 3.5‡#	25.7 ± 7.5	13.7 ± 7.0#	20.4 ± 6.7
Inotropic Support	3	1	14	0§	11
β-blocker therapy	0	1	1	4	12
Duration of LVAD support (days)		56.0 ± 27.8		144.8 ± 33.1	na

Values shown are Mean ± SD.

BiVAD, biventricular assist device; CHF, congestive heart failure; DCM, idiopathic dilated cardiomyopathy; ICM, ischemic cardiomyopathy; LVAD, left ventricular assist device; na, not applicable; PAPm, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

*$p < 0.05$ vs LVAD at insertion and CHF at transplant;
†$p < 0.05$ vs LVAD and CHF at transplant;
‡$p < 0.05$ vs CHF at transplant;
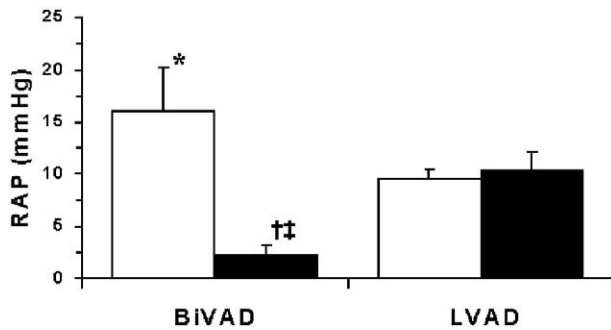#$p < 0.05$ vs BiVAD/LVAD at insertion;
§$p < 0.01$ vs LVAD at insertion.

Figure 1. Right atrial pressure (RAP) pre-left ventricular assist device (LVAD) or pre-biventricular assist device (BiVAD) implantation (open bars) and pre-cardiac transplantation (black bars), signifying a remarkable reduction in right ventricular preload after BiVAD support. All values are mean ± standard error of the mean. *$p < 0.05$ vs pre-LVAD implantation; †$p < 0.01$ vs pre-BiVAD implantation; ‡$p < 0.05$ vs LVAD pre-cardiac transplantation.

nificantly compared with still-elevated levels observed with LVAD support alone ($p < 0.05$). Mean pulmonary pressures and pulmonary capillary wedge pressures could be significantly reduced following BiVAD support compared with the CHF group ($p < 0.05$), but did not change significantly compared with only LVAD-supported hearts. The RV ex vivo EDPVR did not normalize after LVAD support alone as demonstrated in Figure 2. The RVV_{30}, a marker of end-diastolic size, was even higher compared with end-stage CHF (Figure 3).

BiVAD support did, however, significantly shift the RV EDPV relationship to the left toward normal hearts (Figure 2). RVV_{30} was significantly reduced compared with end-stage CHF and LVAD-supported hearts and reached values even lower than normal hearts (Figure 3, $p < 0.01$ vs CHF and LVAD). Consistent with the shift in the EDPVR and the reduction in RVV_{30}, RV mass was
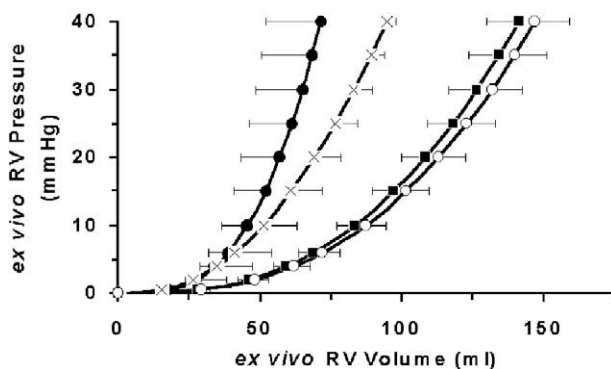

Figure 2. Right ventricular (RV) ex vivo end-diastolic pressure-volume relationships (EDPVRs) of normal hearts (crosses), heart failure without left ventricular assist device (LVAD) support (filled squares), LVAD supported (open circles) and biventricular assist device (BiVAD)-supported hearts (filled circles), presenting a tremendous leftward shift following BiVAD support, but no change in the RV-EDPVR after LVAD support. All values are mean ± standard error of the mean.
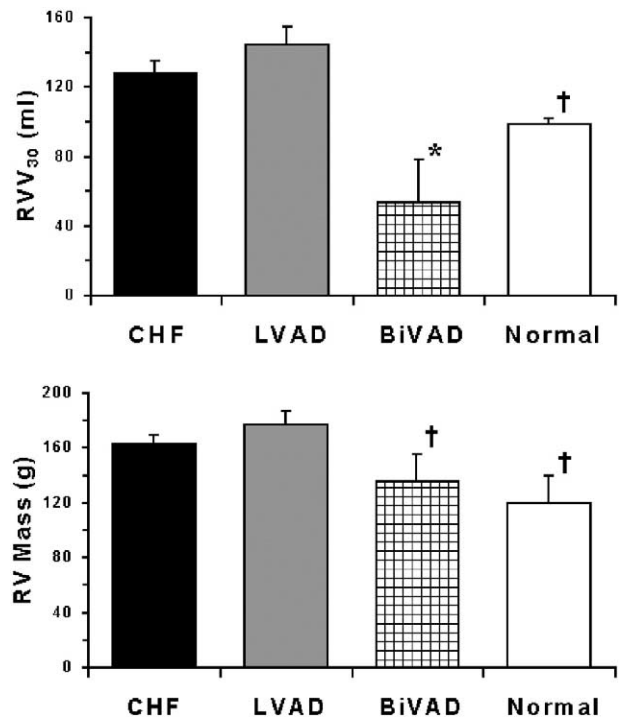

Figure 3. (Top) RVV_{30}, which is the volume at the right ventricular (RV) ex vivo end-diastolic pressure of 30 mm Hg, is an index of RV size. RVV_{30} is significantly reduced following biventricular assist device (BiVAD) support compared with hearts with congestive heart failure (CHF) and those supported with a left ventricular assist device (LVAD). (Bottom) RV mass showed a trend toward normalization following BiVAD support. All values are mean ± standard error hf the mean. *$p < 0.01$ vs CHF and LVAD; †$p < 0.05$ vs CHF and LVAD.

reduced following BiVAD support (Figure 3; $p < 0.05$ vs CHF and LVAD). The dimensionless chamber stiffness constant α was reduced in CHF hearts and after LVAD support compared with the normal hearts (Figure 4, $p < 0.05$ LVAD vs normal) and increased following BiVAD support ($p < 0.01$ vs LVAD and CHF).

Myocardial Properties

RV myocyte diameter was normalized during BiVAD support compared with other groups (BiVAD, 23.1 ± 6.1 μm; LVAD, 32.5 ± 5.6 μm; CHF, 33.5 ± 3.5 μm; normal, 23.2 ± 4.6 μm; $p < 0.01$ BiVAD and normal vs LVAD and CHF). RV total myocardial collagen content was slightly increased in the CHF and LVAD group compared with normal (Figure 4, $p < 0.05$ LVAD vs normal). However, after BiVAD support, the total collagen increased further ($p < 0.05$ vs LVAD and $p < 0.01$ vs CHF and normal).

Reverse Functional Remodeling

To test whether RV reverse functional remodeling is induced by RV mechanical unloading, we isolated muscle strips from the RV free wall and placed these in organ
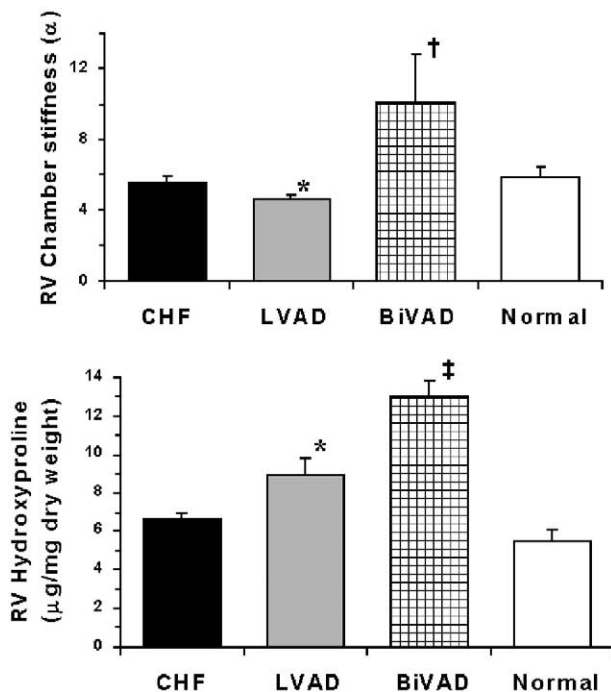
Figure 4. (Top) The dimensionless chamber stiffness constant α was decreased in congestive heart failure (CHF) and after left ventricular assist device (LVAD) support and increased in the biventricular assist device (BiVAD) group. (Bottom) Right ventricular (RV) hydroxyproline content in CHF, normal hearts, and after LVAD and BiVAD support. The increase in RV myocardial total collagen content following BiVAD support is an indirect marker for hemodynamic unloading. All values are mean $\pm$ standard error of the mean. $*p < 0.05$ vs normal; $\dagger p < 0.01$ vs CHF and LVAD; $\ddagger p < 0.05$ vs LVAD and $p < 0.01$ vs CHF and normal.

baths to determine the force–frequency relationship and the isoproterenol-induced enhancement of contractility. Compared with normal hearts, muscle strips from the CHF group exhibited a blunted response to isoproterenol (Figure 5A and B). After LVAD support, a small but significant restoration in the response to isoproterenol was evident but did not fully normalize ($p < 0.05$ vs CHF); however, the myocardial force response to isoproterenol perfusion was completely restored ($p < 0.001$ vs LVAD and CHF) after BiVAD support.

The trabecular dimensions were similar among all groups, as was developed force at 1 Hz in normal, CHF, LVAD-, and BiVAD-supported hearts. However, developed force was reduced by increasing stimulation frequency in the CHF group and showed slight improvement following LVAD support (Figure 5C). In contrast, force did not decline with increasing stimulation frequency in the BiVAD group. Patients from the LVAD group who received β-blocker therapy before cardiac transplantation ($n = 4$) showed improvement in RV myocardial force in response to isoproterenol and in the force–frequency relationship compared with LVAD patients without

β-blocker therapy ($n = 12$), but this improvement did not reach values from BiVAD-supported hearts.

DISCUSSION

We studied hearts and myocardial samples from patients after BiVAD support at the time of cardiac transplantation. This offered the opportunity to study the process of RV reverse structural remodeling (RV EDPV relationship) and reverse functional remodeling (RV cardiomyocyte function in isolated trabeculae) in these biventricular-assisted hearts.

Univentricular hemodynamic support of the LV reduces RV afterload (i.e., pulmonary arterial and wedge pressure) but does not reduce RV preload (pressure or volume) conditions. In that setting, there is no evidence of reverse structural remodeling and evidence of only limited reverse functional remodeling. In a study from Kücüker et al, LVAD support normalized RV tumor necrosis factor α but did not change myocyte size.[9] In contrast, we observed in this study that BiVAD support normalized the RV passive pressure–volume relationship, RV mass, myocyte diameter, and chamber stiffness. Furthermore, BiVAD support led to normalized cardiomyocyte function, evidenced by the response to isoproterenol stimulation and the force-frequency relationship in isolated perfused trabeculae.

Descriptions in the literature of the influence of mechanical unloading to collagen content are controversial. Some reports describe decreases in collagen content;[13,14] another group reports no change,[15] and some groups found an increase in collagen after LVAD support.[16-20] We found that RV total myocardial collagen content (assessed by hydroxyproline content) increased significantly after BiVAD support. A reason could be normalization in matrix metalloproteinases that could lead to a decreased degradation of immature collagen coupled with ongoing production of new collagen, as described by Li at al.[16,21]

BiVAD support or implantation of a RVAD, together with an LVAD, is the therapy of choice if RV heart failure is no longer manageable with medical therapy.[22] However, most RVADs are explanted before cardiac transplantation when RV function is restored. The indication for RVAD explantation is improved RV function and is usually based on echocardiographic and hemodynamic data.[23-25] Prolonged right heart support up to the time of cardiac transplantation is very rare, and as a result, the hearts of only 3 patients were studied. Nevertheless, the magnitude of the effects we observed was profound, consistent, and unambiguous. Importantly, we demonstrated that hemodynamic unloading of the RV induced reverse structural and reverse functional
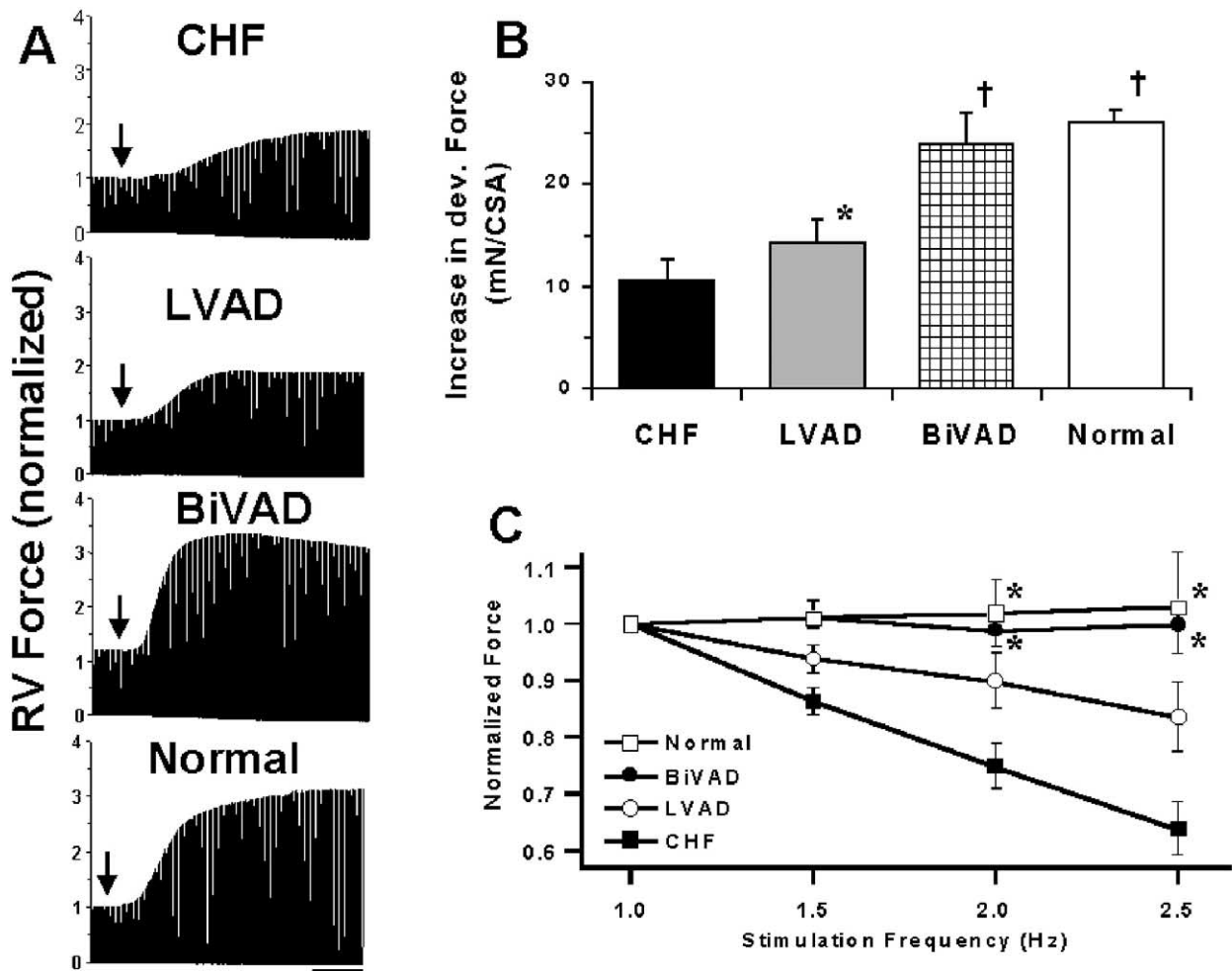
Figure 5. (A) Continuous force tracings from right ventricular (RV) trabeculae during exposure to isoproterenol (1 μg/ml). Normal heart sample showed a 3-fold increase in force after isoproterenol. Muscles from hearts with congestive heart failure (CHF) hearts showed a blunted response, similar to left ventricular assist device (LVAD) recipients. However, muscle obtained after biventricular assist device (BiVAD) support shows a 3-fold increase in response to isoproterenol similar to normal hearts. Scale bar = 1 minute. Arrows show time when perfusion was switched to a solution containing isoproterenol (B) Improvement in RV developed force generation after isoproterenol stimulation. BiVAD support normalizes the response to isoproterenol. *$p < 0.05$ vs CHF; †$p < 0.001$ vs CHF and LVAD. CSA = cross-sectional area. (C) Normalized developed force at increasing stimulation frequency (force-frequency relationship [FFR]) from isometric RV trabeculae from failing hearts, LVAD supported, BiVAD supported, and normal hearts. A negative FFR in CHF and during LVAD support became markedly normalized following BiVAD support. All values are mean ± standard error of the mean. *$p < 0.05$ vs CHF and LVAD.

remodeling, similar to what is observed in the LV following mechanical unloading by an LVAD.

In conclusion, hemodynamic unloading of the RV results in significant reverse structural and functional remodeling. Lack of RV reverse remodeling during LVAD support alone provides additional support that diastolic pressure and volume unloading is an important mechanism underlying the process of reverse remodeling.

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