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Insights into the Effects of Contraction Dyssynchrony on Global Left Ventricular Mechano-Energetic Function

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Abstract

Background—The effects of dyssynchrony on global left ventricular (LV) mechanics have been well documented; however, its impact on LV energetics has received less attention.

Objective—To assess the effects of LV contraction dyssynchrony on global LV mechano-energetic function in a pacing-induced acute model of dyssynchrony.

Methods—Using blood-perfused isolated rabbit heart preparations ($n = 11$), LV pressure, coronary flow, and arteriovenous oxygen content difference were recorded for isovolumic contractions under right atrial (RA) pacing (control) and simultaneous RA and right ventricular outflow tract (RVOT) pacing (dyssynchrony). LV mechanical function was quantified by the end-systolic pressure-volume relationship (ESPVR). Myocardial oxygen consumption-pressure-volume area (MVO_2 -PVA) relationship quantified LV energetic function. Internal PVA for MVO_{2RVOT} was calculated based on the MVO_2 -PVA relationship for RA pacing. Thus, lost PVA (internal PVA – PVA_{RVOT}) represents the mechanical energy not observable at the global level.

Results—Compared to RA pacing, RVOT pacing depressed LV mechanics as indicated by a rightward shift of ESPVR (i.e., increase in V_d from 0.58 ± 0.10 to 0.67 ± 0.10 mL, $P < 0.05$). Despite depressed mechanics, RVOT pacing was associated with greater MVO_2 such that the MVO_2 -PVA relationship intercept was markedly increased from 0.025 ± 0.003 to 0.029 ± 0.003 mL $\cdot$ O₂/beat/100gLV ($P < 0.05$). Excess MVO_2 (i.e., $MVO_{2RVOT} - MVO_{2RA}$) significantly correlated with lost PVA ($R^2 = 0.54$, $P < 0.001$).

Conclusion—A potential mechanism explaining the observed increase in MVO_2 with dyssynchrony may be that the measured PVA at the global level underestimates the internal PVA at the cellular level, which is likely to be the true determinant of MVO_2 .

Keywords

isolated heart preparation; right ventricular outflow tract; myocardial oxygen consumption; pressure-volume relationships; cardiac resynchronization therapy

Introduction

Left ventricular (LV) contraction dyssynchrony is common among patients with systolic heart failure and is associated with significantly greater cardiac risks.¹ Dyssynchronous contraction can be caused by abnormal electrical activation of the LV (e.g., left bundle branch block [LBBB]), structural changes to the myocardium (e.g., areas of scar caused by ischemia), or both, ultimately preventing normal LV activation and contraction.² A common abnormal activation sequence observed in patients with LV dyssynchrony occurs between the early-activated septum and late-activated posterior-lateral LV wall. This delayed LV contraction can be caused by structural abnormalities of the His-Purkinje system manifested as LBBB³ or right ventricular (RV) pacing, both of which have similar electrical activation patterns.⁴ The imbalance of activation begins with presystolic septal contraction, followed by late LV contraction with paradoxical movement of the septum toward the RV, and a final septal motion toward the LV now against a higher load.^{3,5} Instead of producing an efficient output, this dyssynchronous wall motion causes substantial volume shifts within the LV cavity, resulting in a decrease in stroke volume and ultimately an increase in end-diastolic volume.⁶

The effects of contraction dyssynchrony on global LV mechanical function have been well documented; however, its impact on LV energetic function has received less attention. Furthermore, results from the few studies examining this issue have not been consistent. The blood-perfused isolated heart preparation offers a rigorously controlled environment to evaluate intrinsic LV mechano-energetic function. Here the heart is devoid of external neurohumoral stimuli, loading conditions can be independently controlled,⁷ and global LV mechano-energetic function can be quantified in terms of the myocardial oxygen consumption (MVO₂)-pressure-volume area (PVA) relationship.^{8,9}

The primary goal of the present study was to assess the effects of contraction dyssynchrony on global LV mechano-energetic function in an isolated rabbit heart preparation. We used a right ventricular outflow tract (RVOT) pacing-induced model of LBBB-like contraction dyssynchrony. It should be noted that RVOT pacing was used to create dyssynchrony; it was not meant to correspond to a clinically used pacing site (e.g., right ventricular apex).

Materials and Methods

Preparation

This investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Eleven New Zealand rabbits weighing 2.60 ± 0.04 kg were used in an isolated blood-perfused Langendorff preparation to study LV mechano-energetic function. Animals were anesthetized with an intramuscular injection of ketamine (45 mg/kg) and xylazine (5 mg/kg) and thereafter an intravenous catheter was inserted into the ear vein to provide a continuous infusion of ketamine (1.38 mg/min/kg). The rabbits were artificially ventilated with room air via a tracheotomy. After median sternotomy, the heart was removed and a metal cannula was inserted into the aorta to begin retrograde perfusion of the coronary arteries at constant perfusion pressure (80 mmHg) and temperature (37°C). Hearts were perfused with oxygenated (95% O₂/5% CO₂ mixture) crystalloid perfusate (modified Krebs-Hanseleit [KH] solution) containing washed erythrocytes. Previous studies have shown that perfusion with washed erythrocytes is superior to crystalloid in that the performance of the heart is stable over a longer period and the metabolic measurements are more reliable.^{10,11} Oxygenation was accomplished using a hollow fiber membrane contactor (Membrana, Charlotte, NC, USA) and a 95% O₂/5% CO₂ mixture. The perfusate was not recirculated and the coronary perfusion pressure was held constant using a servo-controlled roller pump. To prevent microaggregates from entering the heart, an inline 40-μm filter was used. A thin latex balloon, secured at the

end of an automated volume-injection device, was positioned in the LV via the mitral orifice. The balloon did not generate any intrinsic pressure at its maximum volume; therefore, the measured pressure represented that of the LV only. A suture around excess left-atrial tissue secured the heart to the volume-injection device. Epicardial pacemaker leads were placed on the right atrium (RA) and RV free wall near the anterior infundibulum, also known as the RV outflow tract (RVOT). After all protocols were completed, the atria and RV were removed and the LV was weighed (3.45 ± 0.13 g).

Perfusion Medium

The isolated hearts were perfused with washed bovine erythrocytes suspended in a modified KH solution.¹² Whole bovine blood was collected from a local slaughterhouse and anticoagulation was maintained with heparin (10 U/mL). Gentomyosin [250 mg/L] was added to retard bacterial growth, and blood was filtered through a 40- μ m filter to remove gross particles. Red blood cells (RBCs) were isolated by washing the whole blood in KH solution (without calcium) using a cell-saver machine (Haemonetics Corp., Brain-tree, MA, USA). Isolated RBCs were then diluted with KH solution to obtain a hematocrit of $32 \pm 0.6\%$. Calcium chloride (1.8 mM) was added after another heparin bolus (10 U/mL). Albumin (0.3%) was used to maintain osmolality, and a pH of 7.46 ± 0.02 was obtained with the addition of sodium bicarbonate (3%) to the final suspension.

Experimental Measurements

Instantaneous LV pressure was measured by a catheter-tip pressure transducer (Millar Instruments Inc., Houston, TX, USA) positioned in the LV via a side port in the volume-injection system. LV end-diastolic volume was controlled using an infusion pump (Harvard Apparatus, Holliston, MA, USA). Instantaneous pressure was digitized online at a sampling rate of 1000 Hz. Total coronary flow (Q_{cor}) was measured by an ultrasonic, inline, transit-time flow probe (2N158, Transonic Systems Inc., Ithaca, NY, USA) in series with the aortic perfusion cannula. Arteriovenous oxygen content difference (AVO_2) was measured by a continuous oxygen difference analyzer (A-VOX Systems, San Antonio, TX, USA). The use of this device for accurate measurement of AVO_2 has been verified.^{13,14} Arterial blood was collected from a side port in the aortic perfusion cannula directly above the flow probe and venous blood was directed to the AVO_2 analyzer via a 12 Fr Foley catheter inserted into the right ventricle through the pulmonary artery. MVO_2 was calculated as the product of Q_{cor} and AVO_2 . Since the right ventricle was kept collapsed with the Foley catheter, the measured MVO_2 was taken to represent oxygen consumption of the LV only.

Pressure-Volume Area

Instantaneous LV pressure data were recorded during steady-state isovolumic contractions at four to six LV end-diastolic volumes (EDV) within the end-diastolic pressure range of 5–30 mmHg (Frank-Starling protocol, Fig. 1A). After each volume step, we waited approximately 2 minutes to allow for equilibrium of the metabolic state before collecting data. The functional state of the heart was quantified in terms of peak active and passive pressure-volume (P-V) relationships (Fig. 1B). End-systolic P-V relationship (ESPVR) and end-diastolic P-V relationship (EDPVR) were derived by fitting peak active and passive pressure points to linear elastance and monoexponential models, respectively.¹⁵ PVA was calculated as the area enclosed by ESPVR, EDPVR, and the pressure-volume trajectory for each EDV (Fig. 1B). MVO_2 was linearly correlated to PVA: $MVO_2 = a \cdot PVA + b$, where a and b are the slope and intercept of the relationship, respectively (Fig. 1C).

In the presence of contraction dyssynchrony, we hypothesized that the link between the mechanical activity occurring at the regional level and the mechanical activity that is observable at the global level is altered. We believe that the summation of all regional

mechanical activity represents an internal PVA (say PVA') that is greater than the PVA observable at the global level. Although only a portion of PVA' is observed at the global level, this internal PVA ultimately determines the measured MVO_2 during contraction dyssynchrony. Assuming that the MVO_2 -PVA' relationship with RVOT pacing is the same as the MVO_2 -PVA relationship with RA pacing ($\text{MVO}_{2\text{RA}} = a_{\text{RA}} \cdot \text{PVA}_{\text{RA}} + b_{\text{RA}}$), we calculated PVA' (i.e., internal PVA) for each MVO_2 measured under RVOT pacing by: $\text{PVA}' = (\text{MVO}_{2\text{RVOT}} - b_{\text{RA}})/a_{\text{RA}}$ (Fig. 1D). Thus, the lost PVA, which is the difference of *calculated* PVA' and *measured* PVA with RVOT pacing (i.e., $\Delta\text{PVA} = \text{PVA}' - \text{PVA}_{\text{RVOT}}$), represents the mechanical energy that is not observable at the global level. Accordingly, excess oxygen consumption that was wasted during global mechanical energy loss is defined as the difference between *measured* MVO_2 with RVOT pacing and *measured* MVO_2 with RA pacing (i.e., $\Delta\text{MVO}_2 = \text{MVO}_{2\text{RVOT}} - \text{MVO}_{2\text{RA}}$).

Pacing Protocols

Mechanical (LV pressure and volume) and energetics (Q_{cor} and AVO_2) data were first collected under RA pacing, which served as the heart rate control condition. Hearts were paced at 111 ± 7 beats/min. After mechano-energetic data were collected under RA pacing; contraction dyssynchrony was induced by simultaneous RA-RVOT pacing. Approximately 3 minutes after the induction of contraction dyssynchrony, mechano-energetic data were collected again. The total experimental duration was 73 ± 5 minutes.

Statistical Analysis

Data are presented as means $\pm$ SEM. The statistical analysis consisted of comparing relationships (e.g., ESPVR and MVO_2 -PVA) between two conditions: control (RA pacing) and dyssynchronous (RVOT pacing) contractions. Because these relationships were obtained for both conditions from each heart, a repeated measures analysis of covariance structure exists. A mixed linear model was used to account for random (i.e., between hearts within a condition) and fixed (i.e., between conditions) effects.¹⁶ Statistical analyses were performed using SAS statistical software package (SAS Institute Inc., Cary, NC, USA). Significance was determined as $P < 0.05$.

Results

Global LV Mechanical Function

RVOT pacing-induced contraction dyssynchrony resulted in a small change in global LV mechanical function compared to RA pacing. The depression in global LV function was apparent when comparing pressures at each end-diastolic volume during the Frank-Starling protocol (Table I). For example, the maximum peak active systolic pressure generated was 92 ± 5 mmHg after the induction of dyssynchrony, which was approximately a 10% decrease from the RA pacing value (101 ± 6 mmHg). Statistical analysis using a mixed model approach showed that the ESPVR during RVOT pacing was significantly different from that of RA pacing. The slope of the ESPVR (i.e., E_{es}) was not altered with RVOT pacing (Fig. 2A, RA pacing: 56.1 ± 5.1 , RVOT pacing: 58.5 ± 5.0 mmHg/mL, $P = \text{NS}$). However, the ESPVR volume intercept (V_d) increased from 0.58 ± 0.10 mL with RA pacing to 0.67 ± 0.10 mL with RVOT pacing ($P < 0.05$, Fig. 2B). Therefore, the depression in global LV mechanical function with dyssynchrony manifested as a small but statistically significant rightward shift of the ESPVR.

LV Energetic Function

Dyssynchronous contraction with RVOT pacing had an adverse effect on LV energetic function. In spite of lower PVA, dyssynchronous contraction for any given end-diastolic

volume was associated with greater AVO_2 and little change in Q_{cor} (Table I). Statistical analysis using the mixed model approach showed that a trend toward a greater MVO_2 -PVA relationship slope was observed with RVOT pacing (Fig. 3A; RA pacing: $1.49 \times 10^{-5} \pm 0.17 \times 10^{-5}$, RVOT pacing: $1.68 \times 10^{-5} \pm 0.17 \times 10^{-5}$ mL O_2 /mmHg/mL, $P = 0.055$). However, compared to RA pacing, the MVO_2 -PVA relationship intercept significantly increased with dyssynchronous contraction (Fig. 3B; RA pacing: 0.025 ± 0.003 , RVOT pacing: 0.029 ± 0.003 mL O_2 /beat/100gLV, $P < 0.05$).

The responses of mechano-energetic function between RA and RVOT pacing can be better appreciated by the presentation of the data in Figure 4. Mean ($\pm$ SEM) data points at each end-diastolic volume during isovolumic contraction are plotted for the ESPVR and MVO_2 -PVA relationships. Decreased global LV mechanical function with dyssynchrony was apparent by the marked rightward shift of ESPVR (i.e., increase in V_d) compared to RA pacing. Dyssynchronous contraction resulted in significantly greater oxygen consumption, as illustrated by the upward shift of the MVO_2 -PVA relationship. Thus, significantly greater energy (i.e., MVO_2) was required with dyssynchrony to achieve the same mechanical output (i.e., PVA).

For our dataset, a significant correlation ($R^2 = 0.54$, $P < 0.001$; Fig. 5) existed between excess MVO_2 (i.e., $MVO_{2RVOT} - MVO_{2RA}$) and lost PVA ($PVA' - PVA_{RVOT}$). Although this observation was derived from the data in Figure 4, the new presentation format more clearly supports the concept that the excess MVO_2 observed with RVOT pacing can be explained by the mechanical energy loss at the global level.

Discussion

The current study reports two primary findings. First, a small but significant depression in global LV mechanical function was observed with RVOT pacing. We suspect that dyssynchronous contraction induced by RVOT pacing is responsible for the depression in global LV mechanics. Second, despite the depression in LV mechanical function, LV contraction dyssynchrony was associated with greater oxygen consumption. Because RVOT pacing consumed more oxygen at a given PVA, dyssynchronous contraction results in decreased myocardial mechanical conversion efficiency (i.e., PVA/MVO_2). In addition, we showed that the increase in oxygen consumption with dyssynchrony significantly correlated with the mechanical energy loss at the global level (i.e., the energy that did not contribute to efficient mechanical output). Certain methodological issues are considered first, before we discuss these findings in detail.

Methodological Considerations

Dyssynchrony Model—In the current study, we used RVOT pacing to induce LV contraction dyssynchrony. Pacing at the RVOT is known to prematurely excite the septum and consequently produce delayed LV free wall contraction causing a LBBB-like contraction pattern.¹⁷ However, echocardiographic evaluation of septal to free-wall dyssynchrony with RVOT pacing has not been confirmed in the isolated rabbit heart preparation. We attempted to quantify septal-to-free wall motion in the isolated rabbit heart by echocardiography, but were unable to obtain reliable images for evaluation of contraction dyssynchrony. Therefore, RVOT pacing-induced contraction dyssynchrony in our model is essentially an assumption on our part. However, this assumption is supported by the changes in global mechanical function that are similar to those observed in a canine model wherein contraction dyssynchrony was independently measured.¹⁸ We also recognize that RV apical pacing, which has been implicated in dyssynchrony and heart failure exacerbation, is more relevant in the human setting than RVOT pacing. However, we previously have shown in canines that RVOT pacing induces marked dyssynchrony similar to a LBBB-contraction pattern and is also associated

with depression of global LV function.¹⁸ Therefore, we decided to use RVOT pacing as a reliable model of dyssynchronous contraction and depression of global LV function.

Stability of Isolated Heart Preparation—Although the isolated perfused heart preparation has been extensively used to study various aspects of mechano-energetic function,^{9,11,19–21} there is always the potentially confounding effects of time. Therefore, we conducted two experiments with RA pacing alone and collected data at the same time intervals as the original protocol. We observed that although global LV mechanical function slightly decreased with time, MVO₂-PVA relationships were shifted downward (Fig. 6, RA1 vs RA2). These changes in MVO₂-PVA relationships are in the opposite direction to those observed with RVOT pacing-induced dyssynchrony. However, they are consistent with downward shifts in MVO₂-PVA relationships observed with acute depression in LV contractile state (e.g., reduced extracellular calcium, infusion of β -receptor antagonists).^{19,22} Therefore, time-dependent preparation deterioration is not a confounder for the observed increase in MVO₂ with contraction dyssynchrony.

In addition, it should be noted that the expected physiological vasodilatory response of the coronary circulation was not observed in every experiment. Specifically, an increase in coronary flow was not consistently observed with an increase in energy demand (i.e., increase in PVA with increasing end-diastolic volume). This behavior may be specific to the isolated heart preparation wherein coronary flow and AVO₂ are typically higher and lower, respectively, than the values observed under *in vivo* conditions. It has been shown that changes in MVO₂ correlate better with changes in AVO₂ rather than coronary flow in the isolated heart preparation.²³ It is important to note, however, that there was no evidence of oxygen supply limitation under any experimental condition, as indicated by the absence of several functional markers of hypoxia (e.g., increase in end-diastolic pressure for a given end-diastolic volume or extremely low venous oxygen content).

Isovolumic Contractions—Because all data were collected with hearts contracting under isovolumic conditions (i.e., with a fixed LV volume throughout the cardiac cycle), the relevance of our observations to ejecting contractions may be questioned. However, previous studies have shown that for a fixed contractile state, MVO₂-PVA relationship is independent of loading conditions (preload and/or afterload) such that isovolumic or ejecting contractions yield the same relationship.^{9,19} Therefore, the observations reported here should be equally valid for ejecting contractions.

Interpretation of the Changes in MVO₂-PVA Relationship with LV Contraction Dyssynchrony

In the present study, LV contraction dyssynchrony resulted in increased MVO₂ for a given PVA. Specifically, MVO₂-PVA intercept significantly increased ($P = 0.03$) with RVOT pacing-induced dyssynchrony. Although MVO₂-PVA slope tended to increase, it did not reach statistical significance ($P = 0.055$). Based on the scatter in our data with control RA pacing (Fig. 3), it is likely that an increase in the number of experiments will yield a statistically significant increase in the slope value as well. Although an increase in slope would further strengthen our main observation of increased MVO₂ for a given PVA in the presence of LV contraction dyssynchrony, it is not a requirement for our observation to be valid.

A potential mechanism explaining the increase of MVO₂ with RVOT pacing is as follows. The observed PVA in the setting of contraction dyssynchrony may underestimate the mechanical activity at the cellular level (internal PVA, termed PVA') that determines the measured MVO₂. In other words, in the presence of contraction dyssynchrony, the link between mechanical activity occurring at the regional level and the mechanical activity observable at the global level is altered such that the “summation” of all regional mechanical activity (i.e.,

PVA') is greater than the experimentally measured (global) PVA. This is not a completely theoretical conjecture; there is experimental evidence for it. Early-activated regions with ventricular pacing are associated with presystolic shortening (or shortening against minimal load) and therefore, perform minimal regional work and contribute little to pressure generation.^{24,25} In contrast, the late-activated regions are typically stretched due to the shortening of the early-activated regions^{24,25} and they contract against higher load, resulting in greater regional work. The temporal discordance of contraction results in a loss of mechanical energy (i.e., energy that does not contribute to pressure generation or volume displacement at the global level). In addition to differential deformation patterns in early- and late-activated regions, it has been shown that myocardial blood flow is significantly higher in late-activated regions than at earlier activated regions.²⁴ Specifically, Prinzen et al.²⁴ have shown that compared to control RA pacing, RVOT pacing resulted in 87% lower fiber strain and 19% less blood flow in early-activated regions. In contrast, fiber strain and blood flow increased by 268% and 142% for the late-activated regions. It is interesting to note that the increments for the late-activated regions are significantly more than the decrements for the early-activated regions, which supports the notion that the mechanical activity summated over all regions could be greater under RVOT pacing.

Although we were unable to measure regional mechanical activity at various locations within the LV to obtain a direct measure of PVA,' we had the knowledge of the system's mechano-energetic behavior (i.e., MVO₂-PVA relationship) under synchronous contraction (i.e., control RA pacing). The luxury of having this extra piece of information allowed us to calculate PVA' (i.e., PVA that was consistent with measured MVO₂ under RVOT pacing). Our dataset revealed a significant correlation between excess MVO₂ (i.e., MVO_{2RVOT} - MVO_{2RA}) and the PVA that was not converted into an efficient mechanical output (i.e., the portion of PVA' not observable at the global level). This relationship suggests that the excess MVO₂ associated with RVOT pacing-induced dyssynchrony can be explained by the loss of mechanical energy observable at the global level, which is likely due to the competition of individual regions during dyssynchronous contraction.

LV Contraction Dyssynchrony and Mechano-Energetics: Comparison with Previous Studies

Similar to the current study, Burkhoff et al.²⁶ investigated the influence of ventricular pacing on mechano-energetic function using the MVO₂-PVA relationship. In an isolated canine heart preparation, they observed a concomitant decrease in global LV mechanics and energetics following RV free wall pacing such that the MVO₂-PVA relationship was not affected. This is inconsistent with our observation of an upward shift in the MVO₂-PVA relationship following dyssynchrony induced by RVOT pacing. The difference in the pacing site (RVOT in the current study vs RV free wall in the Burkhoff study) may explain this discrepancy. Contraction patterns are known to depend on ventricular pacing sites. We hypothesize that RV free wall pacing (Burkhoff study) produced larger early-activated regions as compared to RVOT pacing (current study), primarily because RVOT pacing provides a more direct route to the His-Purkinje system. This differential contraction pattern may explain the apparent discrepancy in MVO₂: the greater amount of early-activated regions in the Burkhoff study resulted in reduced total regional work and consequently, MVO₂ and the opposite was true for the current study. This conjecture is consistent with the potential mechanism proposed above to explain changes in the MVO₂-PVA relationship with contraction dyssynchrony (i.e., the observed PVA may underestimate the internal PVA at the cellular level that determines the measured MVO₂). The discrepancy between our results and those of Burkhoff et al. underscores the notion that all dyssynchronous contractions are not created equal; the mechano-energetic consequences are dependent on the specific pattern of dyssynchrony. Further studies are required to investigate the mechanism of changes in global LV mechano-energetics under different contraction patterns.

Clinical Implications

It is important to note that we observed an increase in MVO_2 with dyssynchrony (RVOT pacing), even though the mechanical function was depressed. Interestingly, data from the DAVID Trial indicated that RV stimulation was associated with deleterious effects, leading to progressive decline of global LV function and higher risk of congestive heart failure due to ventricular desynchronization.²⁷ Although there is a difference in RV pacing site (RVOT vs RV apical), the increased energetic demand associated with ventricular dyssynchrony as observed in the current study may be a contributing factor to the progressive decline in global LV function observed in the DAVID Trial. It is reasonable to speculate that worsening of myocardial mechanical conversion efficiency with dyssynchrony may contribute to the exacerbation of heart failure. In addition, Nelson et al.²⁸ reported that patients with LBBB and dilated cardiomyopathy benefited from LV pacing as indicated by improved systolic function and decreased myocardial energy demands. We can interpret these findings in the context of our results: cardiac resynchronization therapy (CRT) corrects dyssynchronous contraction, eliminating the difference between internal and external (measured) PVA and excess MVO_2 . This supports our proposed mechanism that the dyssynchronous myocardial elements are responsible for increased myocardial oxygen demands. Although CRT-induced improvement in mechanical function is well established, our results reveal how this therapy may reverse the adverse effects of dyssynchrony on global LV energetic function.

Conclusion

Following RVOT pacing-induced contraction dyssynchrony, global LV mechano-energetic function was adversely affected. Although a small but significant depression in global LV mechanical function was observed with RVOT pacing, this contraction pattern was associated with an increase in MVO_2 for a given PVA, resulting in decreased myocardial mechanical conversion efficiency (i.e., PVA/MVO_2). A possible mechanism explaining the observed increase in MVO_2 with dyssynchrony is that the observed PVA at the global level underestimates the internal PVA at the cellular level, which is likely to be the true determinant of MVO_2 . Irrespective of the mechanism of action, our data clearly demonstrate that dyssynchronous contraction not only depresses global LV mechanical function, but also places an energetic burden on the myocardium. Results of the present and previous studies underscore the notion that all dyssynchronous contractions are not created equal; mechano-energetic consequences are dependent on the specific pattern of dyssynchrony induced by different pacing sites.

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Figure 1.

PVA concept. (A) LV pressure was collected for incremental volumes during isovolumic contraction. (B) ESPVR and EDPVR were then fitted through peak end-systolic and end-diastolic points (dashed and dotted lines, respectively). PVA was calculated as the area enclosed by the ESPVR, EDPVR, and pressure-volume trajectory for that volume increment (e.g., gray area is the PVA for the first volume increment). (C) MVO₂ was linearly correlated to PVA at its corresponding volume step. (D) Demonstration of PVA' calculation and concept of lost PVA and excess MVO₂. Opened and closed circles represent measured MVO₂-PVA data points for RA and RVOT pacing, respectively, during one isovolumic contraction. Using the MVO₂ measured under RVOT pacing, PVA' (diamond) is calculated according to the MVO₂-PVA relationship under RA pacing (i.e., $PVA' = (MVO_{2RVOT} - b_{RA})/a_{RA}$). Lost PVA is calculated by the difference between PVA' and PVA_{RVOT}. Excess MVO₂ (i.e., ΔMVO_2) is calculated by the difference between MVO_{2RVOT} and MVO_{2RA}. Abbreviations: ESPVR = end-systolic pressure-volume relationship; EDPVR = end-diastolic pressure-volume relationship; LV = left ventricular; MVO₂ = myocardial oxygen consumption; PVA = pressure-volume area; PVA' = internal PVA; RA = right atrial; RVOT = right ventricular outflow tract.

Figure 2.

Global LV mechanical function quantified by the ESPVR for RA and RVOT pacing conditions.

(A) Compared to RA pacing, the slope (E_{es}) of the ESPVR was not different compared to RVOT pacing. (B) However, RVOT pacing increased the volume-axis intercept (V_d) of the ESPVR. Data: $n = 11$; $*P < 0.05$ versus RA pacing as analyzed using a mixed statistical model. ESPVR = end-systolic pressure-volume relationship; other abbreviations as in Figure 1.

Figure 3.

Mechano-energetic function quantified by the MVO₂-PVA relationship for RA and RVOT pacing conditions. (A) Compared to RA pacing, RVOT pacing did not alter the slope (i.e., a) of the MVO₂-PVA relationship. (B) However, RVOT pacing increased the intercept (i.e., b) of the MVO₂-PVA relationship. Data: n = 11; *P < 0.05 versus RA pacing as analyzed using a mixed statistical model. Abbreviations as in Figure 1.

Figure 4.

Mean ($\pm$ SEM) data points for global LV mechanical function (A: ESPVR) and energetic function (B: MVO₂-PVA relationship) under RA and RVOT pacing. The ESPVR was depressed with RVOT pacing indicated by a rightward shift of the ESPVR volume intercept. Despite the depression in mechanics, RVOT pacing adversely affected global LV energetics manifested as an increase in the MVO₂-PVA intercept. Data: $n = 11$; RA versus RVOT pacing as analyzed using a mixed statistical model. Abbreviations as in Figures 1 and 2.

Figure 5. Correlation between excess MVO₂ (= MVO_{2RVOT} – MVO_{2RA}) and lost PVA (=PVA' – PVA_{RVOT}). See text for details. Abbreviations as in Figure 1.

Figure 6.

Global LV mechanical and energetic function for two rabbits (A–B: rabbit #1; C–D: rabbit #2) under RA pacing conditions only. Although a slight decrease in ESPVR was observed in both experiments for the two pacing protocols (i.e., RA1 and RA2 in A and C), mechano-energetic coupling was not adversely affected with time, as indicated by a decrease in the MVO₂-PVA relationship (B, D). Abbreviations as in Figures 1 and 2.

Table 1
Global LV Mechanical and Energetic Variables during Isovolumic Contractions

Pacing	LV EDV	LV ESP	PVA	AVO ₂	Q _{cor}	MVO ₂	n
RA Pacing	1.4	44 ± 4	540 ± 100	1.7 ± 0.4	9.3 ± 1.4	3.08e-2 ± 0.42	9
	1.6	55 ± 4	795 ± 126	1.6 ± 0.4	10.1 ± 1.4	3.50e-2 ± 0.52	8
	1.8	67 ± 4	1123 ± 114	1.8 ± 0.3	10.2 ± 1.3	4.21e-2 ± 0.44	10
	2.0	82 ± 4	1502 ± 121	2.1 ± 0.3	10.0 ± 1.3	4.63e-2 ± 0.47	10
	2.2	91 ± 4	1896 ± 150	2.4 ± 0.4	9.5 ± 1.3	4.98e-2 ± 0.53	9
	2.4	101 ± 6	2431 ± 178	2.5 ± 0.5	10.5 ± 1.5	5.43e-2 ± 0.68	8
RVOT Pacing	1.4	38 ± 3	426 ± 76	1.9 ± 0.4	9.2 ± 1.3	3.56e-2 ± 0.45	11
	1.6	52 ± 3	662 ± 84	2.0 ± 0.4	9.4 ± 1.2	4.05e-2 ± 0.49	11
	1.8	65 ± 3	956 ± 88	2.2 ± 0.4	9.5 ± 1.2	4.62e-2 ± 0.54	11
	2.0	78 ± 3	1308 ± 98	2.2 ± 0.3	9.7 ± 1.2	4.82e-2 ± 0.54	10
	2.2	88 ± 4	1702 ± 116	2.6 ± 0.4	9.1 ± 1.2	5.31e-2 ± 0.62	9
	2.4	92 ± 5	2174 ± 162	2.9 ± 0.4	9.2 ± 1.4	6.07e-2 ± 0.80	7

Data are mean ± SEM for each isovolumic volume during the Frank-Starling protocol.

Abbreviations: AVO₂ = arterial-venous oxygen content difference (mL O₂/100 mL); EDV = end-diastolic volume (mL); ESP = end-systolic pressure (mmHg); LV = left ventricular; MVO₂ = myocardial oxygen consumption (mL O₂/beat/100gLV•10⁻²); PVA = pressure-volume area (mmHg•mL/100gLV); Q_{cor} = coronary blood flow (mL/min); RA = right atrial; RVOT = right ventricular outflow tract; n = number of experiments with data at each end-diastolic volume.