

Functional Optimization of Cardiac Resynchronization Therapy in Heart Failure

B. D. Johnson^a, D. MacCarter^b, and C. Johnson^b

^aMayo Clinic; ^bShape Medical Systems, Inc.

Abstract

Cardiac resynchronization therapy (CRT) by bi-ventricular pacing has been an important treatment advance for patients with advanced heart failure (HF). It is estimated that there were >150,000 CRT devices implanted in North America in 2007 at an initial cost of ~\$1-3 billion dollars, with much higher post implantation costs.^{1,2} In randomized, controlled clinical trials, however, nearly 30% of subjects have been considered non-responders.^{3,4} While this may have been due to problems with patient selection, it may also suggest problems of optimization of atrioventricular (AV) and interventricular (V-V) intervals of the CRT devices. Current selection criteria for CRT are limited to LVEF <35%, QRS duration >120-130 ms (depending on trial), and refractory NYHA class III-IV symptoms despite optimized pharmacotherapy.⁵ It is clear that more individualized and physiologically based approaches are needed to improve response rates. In HF patients, low level physical activity challenges (stresses) the heart through increased metabolic demand, altered systemic venous return, influences on cardiac preload and afterload, possibly, enhanced ventricular interdependence. The lungs lie in series with the heart, share a common surface area and are intimately linked hemodynamically as well as neuro-mechanically and thus measures of breathing pattern and gas exchange during a mild cardiac load provide a dynamic window of integrated cardiac function.⁶ Low level, non-invasive cardiopulmonary exercise testing provides a novel approach for 1) determining which HF patients may be most likely to benefit from CRT; 2) defining response vs. non-response to CRT; and 3) individualizing and optimizing CRT settings.

Introduction

The United States demand for cardiac implants is expected to increase 8.8 percent annually to \$16.4 billion by 2012, with a growing demographic, epidemiological patterns, and the introduction of new and improved products promoting growth.^{7,8} Given the expected increases in healthcare cost and heart disease demographic there is a need to develop new approaches for selecting patients that will benefit from CRT and optimizing therapy outcome.⁹ Cardiopulmonary exercise testing with non-invasive measures of gas exchange has emerged as the gold standard for quantifying functional status in the HF population. Historically, this testing has required sophisticated and integrated equipment, complicated data analysis requiring special training, and difficult high-intensity exercise. Evolving science has shown that exercise testing at very low intensity provides a measure of cardiac stress that is more applicable to activities of daily living and that such measures may be more prognostic.¹⁰⁻¹⁴ Shape Medical Systems, Inc. (St. Paul, MN) offers technology that is simplified, miniaturized, portable and more automated, making it clinically feasible to employ non-invasive measures of breathing efficiency in the physician office. Such testing makes it possible to improve patient selection for CRT device therapy; optimize CRT function and thereby improving health status in patients receiving CRT devices; and reduce medical costs.

Current Issues in CRT Optimization

Widespread acceptance of CRT in clinical practice is relatively recent, although studies demonstrating its benefit in patients with HF date back more than a decade.¹⁵ Randomized controlled trials of optimal medical therapy alone vs. optimal medical therapy plus CRT have demonstrated that responsive CRT results in significant improvements in quality of life, functional

status, exercise capacity, ejection fraction (EF), and mortality.^{2,5,16,17} Despite the overall success of CRT device therapy, 25 to 30 percent of CRT implants do not yield a favorable CRT response.

Most attempts to clinically optimize the atrioventricular (AV) and interventricular (V-V) intervals of CRT devices for the treatment of class III and IV HF patients with QRS>120 msec and an EF<35% have used resting echo-based techniques.¹⁸ These techniques have been performed to avoid truncation of the mitral inflow "A" wave to prevent premature ventricular stimulation prior to completed ventricular filling by atrial contraction. Another goal of resting echo-based methods is to maximize aortic flow velocity, a surrogate measure of cardiac stroke volume. Several techniques using resting echo have been cited in the literature with a common technique referred to as the Ritter method or reiterative echo method.¹⁹ A recent industry-developed echo technique is based upon selection of the best AV delay, as judged by the max dp/dt value being achieved while invasively monitoring LV pressure. An echo-based assessment of the delay time from contraction of the septum to the lateral ventricular wall has been used to determine the optimal V-V interval or what has been termed the LV offset. A recent report by Chung et al. from a recent multicenter trial demonstrated, however, that no echo based technique resulted in improved outcomes with CRT.^{20,21}

Aside from echocardiographic techniques for optimization, heart sound/EKG monitoring with an external pre-cordial sensor has been reported to determine the optimal AV or V-V interval.²² The technique requires a resting state and assesses a systolic time interval/potential 3rd heart sound presence/absence combined index for CRT interval optimization. Yet another optimization procedure measures small changes in finger pulse pressure, as determined by finger blood pressure plethysmography.²³ In attempts to hasten the interval optimization process, several pacemaker manufacturers have developed electrical conduction based methods requiring RA to LV/RV conduction time, both paced and sensed. Others simply use pre-selected, standard or nominal settings.

While all of the optimization methods have merit, none of them are performed under conditions of exercise producing a mild cardiac load, and few give a complete integrative assessment of cardiac performance. Most patients complain of symptoms during activities of daily living, not at rest. Under these conditions, cardiac performance needs to be optimum to meet the required physiological demands, such as blood pressure regulation and blood flow requirements. It is under these conditions

where venous return increases, cardiac filling, emptying and interdependence are typically enhanced, and timing is more critical. Thus, basing CRT optimization on resting measures does not take into account these important integrated events. Similarly, using nominal settings (standard intervals) does not take into account differences among individual patients (i.e., individualized medicine). To date, therefore, no non-invasive strategy has been effective in optimizing therapy or improving patient selection for CRT and there is clearly a need for a new approach.²⁰

The Link Between Breathing Pattern, Gas Exchange and Dynamic Cardiac Function

The lungs lie hemodynamically in series with the heart, share a common surface area and are influenced by acute changes in left heart pressure and intrathoracic pressure.⁶ Cardiac stretch, intracardiac pressures (e.g., left atrial) as well as dynamic changes in fluid balance within the lungs alter ventilatory control and influence ventilatory drive, ventilatory efficiency, ventilation-perfusion matching, and dead space ventilation.²⁴ As 98% to 99% of the cardiac output passes through the lungs, gas exchange reflects variability in cardiac status. In addition, breathing pattern is influenced by changes in ventilatory control and compliance characteristics of the lungs.¹² With light exercise the augmented venous return and increases in intrathoracic pressure in the setting of a large dilated heart further influence cardiac pre- and afterload and may enhance ventricular interdependence.²⁵ Previous work shows that breathing strategy is clearly linked to disease severity and, moreover, changes in ventilation and gas exchange dynamically reflect changes in cardiac function.^{10,13,26} These important links between respiratory function and cardiac disease severity are becoming more recognized and, combined with measures of heart rate, form the bases for defining response to CRT and for functional optimization of CRT devices.

Utilizing an optimization method which tests integrated cardiopulmonary function and enhances the cardio respiratory interactions allows the ideal setting for CRT optimization. Mild exercise, such as slow walking, increases left ventricular stroke volume (SV) by 40-100% and increases heart rate (HR) by as much as 15-20 beats/min, increasing cardiac output and systemic blood flow. The increase in venous return from skeletal muscle contraction creates a higher flow state during ventricular filling, despite a slight decrease in the RR interval cycle length. The time required for RV/LV filling is increased to provide an optimal SV which does not adversely affect left atrial pressures and pulmonary blood flow.

Key measurements obtained during exercise include the ventilatory equivalents for a given metabolic demand (the V_E/V_{CO_2} ratio), end-tidal CO_2 ($P_{et}CO_2$), oxygen pulse (O_2 pulse), breathing pattern (respiratory rate-fb and tidal volume- V_T), and inspiratory time (T_i).²⁷ The V_E/V_{CO_2} ratio is influenced by ventilatory drive, breathing pattern and the dead space ventilation, V_D/V_T . While typically with exercise V_E/V_{CO_2} is calculated as a slope of change in V_E relative to V_{CO_2} , as exercise transitions from rest to moderate exercise it can also be examined as a dynamic ratio. In fact, the ratio has been shown to be quite close to the slope during low level exercise.^{28,29} Both the slope and the ratio have been shown to be highly prognostic in the HF population and reflect changes in ventilation-perfusion matching in the lungs, influencing dead space ventilation and increasing ventilatory drive and a tendency for rapid-shallow breathing.^{10,12,13,30}

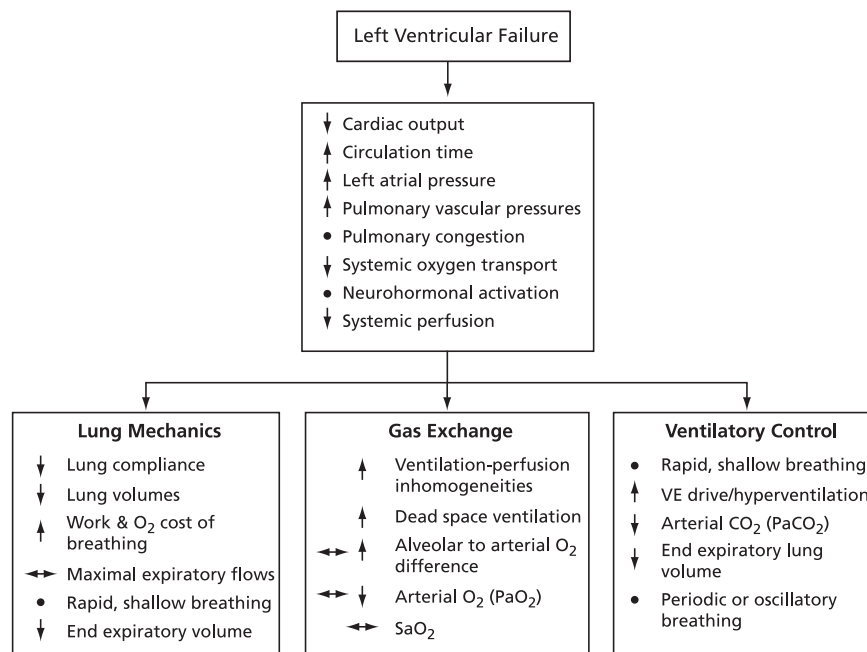
Another hallmark of HF disease severity is a reduced arterial partial pressure of CO_2 ($PaCO_2$). This is reflected non-invasively by the partial pressure of end-tidal CO_2 ($P_{et}CO_2$). Although there is an arterial to alveolar CO_2 difference in the HF population, this difference increases with increased disease severity, lowering $P_{et}CO_2$ and establishing this value as an important marker to track.²⁴ Intracardiac receptors in the heart, congestion and sympathetic drive may all promote hyperventilation resulting in the low $PaCO_2$ and $P_{et}CO_2$ levels. Finally, O_2 pulse reflects cardiac stroke volume (SV) multiplied by oxygen extraction ($a-vO_2$ difference). Oxygen extraction often tends to be enhanced in HF and

may plateau with low-intensity activity, thus the O_2 pulse is a good index of SV, particularly examining acute changes in a given subject.³¹ Measuring these non-invasive cardiopulmonary variables dynamically during light activity along with heart rate reveals which HF patients may be most likely to benefit from CRT therapy and assists optimization of device time intervals for improved performance.

Ventilation Parameters to Define and Optimize Response to Cardiac Resynchronization Therapy in Heart Failure

Figure 1 summarizes the pulmonary manifestations of HF.⁶ Hemodynamically, the lungs accept nearly all of the cardiac output and have afferent pathways that may modulate heart rate. Conversely, there are cardiac and vascular receptors that modulate ventilation and there are common receptors to both systems that are influenced by the activation of the renin-angiotensin-adrenergic system (RAAS). Thus, it is apparent that as the disease process of HF progresses, the pulmonary system is appreciably altered. As a result, there are marked adaptations in the way HF patients breathe, particularly during periods of modestly increased physiological stress and cardiac load (i.e., exercise). The signals provided by the pulmonary system can be used to gain an understanding of integrated cardiac function, to define the systemic response to patient therapy, and, therefore, to improve and simplify methods for optimizing CRT device settings.

Figure 1: Pulmonary Manifestations of Heart Failure



From: Olson TP, EM Snyder, BD Johnson. Exercise-disordered breathing in chronic heart failure. *Exerc Sport Sci Rev* 2006;34(4):194-201.

Abnormal ventilatory control is common in HF and often manifests as periodic breathing (PB), including Cheyne-Stokes respiration and central sleep apnea (CSA).³² Periodic breathing at rest, during exercise or with sleep is associated with decreased functional capacity and adverse prognosis. Retrospective analysis of pooled cohorts enrolled in MIRACLE, InSync and MIRACLE-ICD trials from the Mayo Clinic were studied to determine if exercise-induced PB was decreased with in patients with CRT. Subjects underwent cardiopulmonary exercise testing (CPET) pre- and 6 months post-CRT with CPET results compared for PB and functional response. PB was defined by regular oscillations of minute ventilation (V_E) amplitude greater than 25% of mean amplitude V_E . V_E amplitude and cycle length of oscillations were measured at 50% peak exercise and compared pre- and post-CRT. Eighteen (18)

of 28 subjects (64%) had exercise PB prior to CRT; 10 of these subjects had CPET data available pre-CRT and 6 months post-CRT. Subjects with PB pre-CRT had mean age 73 ± 9 years, BMI 26 ± 5 , LVEF $16 \pm 6\%$, NYHA Class 3.3 ± 0.5 . PB resolved ($n = 4$) or improved ($n=6$) post-CRT in all subjects associated with improved peak VO_2 (11%). Those subjects with no PB ($n=10$) prior to CRT (age 66 ± 11 years, BMI 29 ± 6 , NYHA 3.0 ± 0) had higher baseline LVEF (21.7% vs 15.8%, $p = 0.02$) and tendency for higher peak VO_2 and lower V_E/VCO_2 ($p > 0.05$) pre-CRT with minimal change in peak VO_2 (2%) or V_E/VCO_2 post-CRT (5%). Exercise PB is common in advanced HF and may be a therapeutic target for CRT. Prospective studies are necessary to confirm this observation and elucidate mechanisms and potential clinical relevance of this apparent treatment effect.

Table 1: CRT Influences on Pulmonary Gas Exchange and Periodic Breathing During Exercise

Exercise Values	PreCRT (n=10)	PostCRT (n=10)	p-value
% exercise time PB observed	$98 \pm 8\%$	$41 \pm 40\%$	<0.01
Peak perceived exertion (Borg)	17.1 ± 1.1	16.8 ± 2.4	0.77
Exercise time (sec)	342 ± 106	413 ± 156	0.08
Peak VO_2 (ml/min)	1023 ± 348	1136 ± 427	0.03
Peak VT (L)	1.58 ± 0.42	1.70 ± 0.37	0.05
Peak V_E/VCO_2	47 ± 12	42 ± 10	0.08
V_E amplitude (peak-nadir; L/min)	17 ± 10	8 ± 8	0.04
Cycle length	74 ± 22	45 ± 5	0.04

Wasserman, et al.³³ used CPET to analyze exercise data for patients participating in the Resynchronization for Hemodynamic Treatment for Heart failure Management, or RHYTHM, trial. Patients had pacemaker electrodes implanted in both ventricles in the standard manner and were randomized before exercise testing. Exercise measurements included peak VO_2 , peak O_2 pulse, anaerobic threshold, and V_E/VCO_2 , reflecting changes in peak exercise cardiac output, stroke volume, maximum sustainable exercise capacity, and ventilation-perfusion mismatching, respectively. CPET testing was completed at baseline and at a 6-month follow-up. There were 239 paired 6-month studies with 47 serving as the control with the pacemaker off (i.e., the BVP-OFF group), and 192 patients receiving pacing (i.e., the BVP-ON group).

Table 2 summarizes the results of the study. The BVP-ON group significantly improved in all exercise

parameters in contrast to the control group ($p < 0.0001$). A significant change in NYHA class was found in both the BVP-ON and BVP-OFF groups, even though patients in the BVP-OFF group should no improvement in functional capacity as measured by exercise testing. When baseline measurements for the BVP-ON group were ranked in quintiles, only patients in the three functionally worst quintiles improved significantly at 6-months. These investigators conclude that four exercise testing parameters accurately grade the severity of physiological impairment and response to CRT, including ventilation-perfusion matching (V_E/VCO_2), exercise cardiac output (end-tidal CO_2), sustainable exercise capacity (VO_2 and AT), and stroke volume (O_2 pulse). It was further determined that the patients with the most abnormal exercise testing values at baseline benefit most from BVP.

Table 2: Chronic Impact of CRT on Functional Capacity

Parameter	BVP-OFF (n=47)		BVP-ON (n=192)	
	Baseline	6 Months	Baseline	6 Months
NYHA Class	2.9 ± 0.3	2.6 ± 0.6 [‡]	2.9 ± 0.4	2.5 ± 0.6 [‡]
Peak VO ₂ % Predicted	59 ± 16	58 ± 19	52 ± 14 [#]	56 ± 14 [†]
V _E /VCO ₂ Slope	39.6 ± 12.3	41.9 ± 13.2	40.5 ± 11.0	38.2 ± 13.4 [*]
O ₂ Pulse	11.1 ± 4.4	10.7 ± 4.7	9.6 ± 3.6 [#]	10.4 ± 3.8 [†]

^{*}p<0.05 6-mo vs. baseline ; [#]p<0.05 BVP ON vs. OFF; ^{*}p<0.01 6-mo vs. baseline; [†]p<0.0001 6-mo vs. baseline. Adapted from Wasserman, et al.³³

Attempts to optimize CRT AV and/or V-V intervals are routinely performed at rest with little focus on assessment during physical exertion. MacCarter and coworkers³⁴ studied whether AV/V-V interval optimization with an exercise-induced volume load on the heart might be more appropriate to improve the functional status in this patient population. Testing was performed on 75 HF patients with implanted CRT/ICD devices (67M/8 F; age=70±9 yr). A steady-rate submaximal treadmill session (1 mph/2% grade) was performed during each test, with the first test sequence for AV interval optimization and the second for the V-V interval. Continuous, real time ventilatory expired gas was monitored during preselected AV and V-V intervals to determine the most appropriate AV and V-V interval for optimal breathing efficiency. Forty-nine acute

comparisons (same day following the AV optimization test) and 46 chronic comparisons (mean=6.2 months) were performed to determine changes in submaximal exercise performance. Table 3 shows significant improvement was observed acutely in the O₂ uptake efficiency slope and VT/TI ratio. Chronically, significant improvement was observed with the V_E/VCO₂ slope and the change in V_E/VCO₂ from rest to steady-rate exercise. This study showed that CRT device optimization based upon mild, upright exercise was clinical feasible and led to significantly improved ventilation efficiency indices both acutely and chronically. Further study is needed to test the benefits of early and sustained functional optimization on disease status compared to a control population of HF patients receiving CRT devices with standard (ie, nominal) interval settings.

Table 3: Baseline vs. Acute and Chronic Changes in Functional Capacity

	O ₂ Pulse (ml O ₂ /beat)	V _E /VCO ₂ slope	O ₂ uptake efficiency slope	V _T /T _i (ml/sec)	V _E /VCO ₂ ratio
Pre-Opt Baseline	3.34 ± 1.2	40.4 ± 10.0		342 ± 143	-3.3 ± 3.6
Acute	3.21 ± 1.2	38.1 ± 9.7	1.43 ± 0.43 [*]	253 ± 107 ^{**}	-4.3 ± 3.6
Chronic	2.97 ± 0.89	36.8 ± 8.7 ^{**}	1.35 ± 0.43	242 ± 101 [†]	-4.5 ± 4.4 [*]

^{*}p<0.05; ^{**}p<0.005; [†]p<0.0001

Conclusion

The link between cardiac and pulmonary function both acutely and chronically in the HF population has been clearly established and the benefits of CRT on pulmonary control mechanisms and gas exchange measures have been demonstrated in both acute and chronic settings. Recent studies have proven the feasibility of using pulmonary gas exchange measures, breathing patterns and HR during acute transitions in CRT AV and V-V settings during slow treadmill

walking. These studies have suggested that measures of breathing efficiency and ventilatory drive may be more important in optimization algorithms than O₂ pulse (i.e., stroke volume), particularly in determining the AV interval. In addition, they suggest that optimizing the V-V interval, usually LV stimulation first, also caused favorable changes in breathing efficiency. Whether functional optimization of CRT intervals can cause some non-responders to become responders remains unknown and deserves further study.

References

- ¹ Hlatky MA. Cost effectiveness of cardiac resynchronization therapy. *J Am Coll Cardiol*, 2005;46(12):2322-2324.
- ² Epstein AE, et al. ACC/AHA/HRS 2008 guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: executive summary. *Heart Rhythm*, 2008;5(6):934-955.
- ³ Bradley DJ, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA*, 2003;289(6):730-740.
- ⁴ Fox DJ, AP Fitzpatrick, NC Davidson. Optimization of cardiac resynchronization therapy: addressing the problem of non-responders. *Heart*, 2005;91(8):1000-1002.
- ⁵ Buxton AE, et al. ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). *J Am Coll Cardiol*, 2006;48(11):2360-2396.
- ⁶ Olson TP, EM Snyder, BD Johnson. Exercise-disordered breathing in chronic heart failure. *Exerc Sport Sci Rev*, 2006;34(4):194-201.
- ⁷ Stambler B. Success with failure: a state-of-the-art perspective on cardiac resynchronization therapy. *Heart Rhythm*, 2006.
- ⁸ Thom T, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, 2006;113(6):e85-e151.
- ⁹ Galbreath AD, et al. Long-term healthcare and cost outcomes of disease management in a large, randomized, community-based population with heart failure. *Circulation*, 2004;110(23):3518-3526.
- ¹⁰ Arena R, et al. Ventilatory expired gas at constant-rate low-intensity predicts adverse events and is related to neurohormonal markers in patients with heart failure. *J Card Fail*, In Press.
- ¹¹ Robbins M, et al. Ventilatory and heart rate responses to exercise : better predictors of heart failure mortality than peak oxygen consumption. *Circulation*, 1999;100(24):2411-2417.
- ¹² Agostoni P, et al. Exercise hyperpnea in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. *J Appl Physiol*, 2002;92(4):1409-1416.
- ¹³ Johnson BD, et al. Ventilatory constraints during exercise in patients with chronic heart failure. *Chest*, 2000;117(2):321-332.
- ¹⁴ Belardinelli R, et al. A four-minute submaximal constant work rate exercise test to assess cardiovascular functional class in chronic heart failure. *Am J Cardiol*, 1998;81(10):1210-1214.
- ¹⁵ Cazeau S, et al. Four chamber pacing in dilated cardiomyopathy. *Pacing Clin Electrophysiol*, 1994;17(11 Pt 2):1974-1979.
- ¹⁶ Cleland JG, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*, 2005;352(15):1539-1549.
- ¹⁷ Hunt SA, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*, 2005;112(12):e154-e235.
- ¹⁸ Strickberger SA, et al. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation*, 2005;111(16):2146-2150.
- ¹⁹ Siu CW, et al. Cardiac resynchronization therapy optimization by ultrasonic cardiac output monitoring (USCOM) device. *Pacing Clin Electrophysiol*, 2007;30(1):50-55.
- ²⁰ Chung ES, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*, 2008;117(20):2608-2616.
- ²¹ Cha YM, et al. Response to cardiac resynchronization therapy predicts survival in heart failure: a single-center experience. *J Cardiovasc Electrophysiol*, 2007;18(10):1015-1019.
- ²² Siejko KZ, et al. S3 Amplitude Measured at CRT Device Implant Sites Is Correlated to Echocardiographic Left Ventricular Filling Parameters. *Journal of Cardiac Failure*, 2008;14(6, Supplement 1):S111-S112.
- ²³ Butter C, et al. Cardiac resynchronization therapy optimization by finger plethysmography. *Heart Rhythm*, 2004;1(5):568-575.
- ²⁴ Olson TP, et al. Effects of acute changes in pulmonary wedge pressure on periodic breathing at rest in heart failure patients. *Am Heart J*, 2007;153(1):104 e1-7.
- ²⁵ Olson TP, et al. Competition for intrathoracic space reduces lung capacity in patients with chronic heart failure: a radiographic study. *Chest*, 2006;130(1):164-171.
- ²⁶ Olson TP, KC Beck, BD Johnson. Pulmonary function changes associated with cardiomegaly in chronic heart failure. *J Card Fail*, 2007;13(2):100-107.
- ²⁷ Johnson B, et al. Conceptual and physiological basis of cardiopulmonary exercise testing measurement. In the ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*, 2003;167:211-277.
- ²⁸ Sun XG, et al. Ventilatory efficiency during exercise in healthy subjects. *Am J Respir Crit Care Med*, 2002;166(11):1443-1448.
- ²⁹ Hansen JE, et al. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. *Chest*, 2004;126(3):816-824.

- ³⁰ Guazzi M, et al. Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO₂ partial pressure. *Eur Heart J*, 2005;26(5):472-480.
- ³¹ Spahn DR, et al. Noninvasive versus invasive assessment of cardiac output after cardiac surgery: clinical validation. *J Cardiothorac Anesth*, 1990;4(1):46-59.
- ³² Chon T, et al. Cardiac resynchronization therapy attenuates exercise periodic breathing in patients with advanced heart failure. *J Card Fail*, 2004;10(4 Suppl):S65.
- ³³ Wasserman K, X-G Sun, JE Hanson. Effect of biventricular pacing on the exercise physiology of heart failure. *Chest*, 2007;132:250-261.
- ³⁴ MacCarter D, et al. Acute and chronic improvement in breathing efficiency with exercise based AV/V-V CRT optimization. *J Card Fail*, 2008;14(6):S63.
- .

