Comparison of the Correlation of Rebreathing Method and Echocardiography in Heart Failure Patients With Moderate to Severe Mitral Regurgitation

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SUMMARY

Objective: To follow-up and estimate cardiac function in 11 heart failure patients with moderate to severe mitral regurgitation who underwent cardiac resynchronization therapy (CRT) and to compare echocardiography to the rebreathing method (indirect Fick method) which were used for estimation.

Design: Prospective, observational, clinical study.

Setting: University teaching hospital.

Methods: Eleven cases (8 males and 3 females) were selected and followed-up during presurgery, postsurgery, and 1, 3, and 6 months after pacemaker implantation. Stroke volume was measured by echocardiography (Simpson's method and velocity-time integral method) and rebreathing each time.

Results: Correlations were found between stroke volume with the rebreathing method (RSV) and stroke volume with the velocity-time integral (VSV), $R = 0.89$, although ANOVA, the q test, and paired t test showed no statistical differences between them. Stroke volume with Simpson's rule (SSV) was poorly correlated with stroke volume using the Indirect Fick method (RSV) and with stroke volume using the velocity-time integral method (VSV) ($R = 0.58$ and 0.54 , respectively).

Conclusion: The rebreathing method (indirect FICK method) and velocity-time integral method are noninvasive methods with which to measure cardiac function and exhibited good correlation during the follow-up study. (Int Heart J 2007; 48: 69-78)

Key words: Rebreathing method, Indirect Fick method, Velocity-time integral method, Cardiac resynchronization therapy (CRT), Heart failure

ACCURATE evaluation of cardiac functional parameters is an important task of cardiologists because of its great importance to diagnosis and treatment. However, cardiologists are not satisfied with "typical" methods, which can be classified as invasive and noninvasive. Invasive methods include thermodilution, the

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direct Fick method, and catheterized left ventricular radiography, while noninvasive techniques include New York Heart Association (NYHA) class (1928), echocardiography (Teichholz method, Simpson's method, and the velocity-time integral method), treadmill test (metabolism degree), cloister test (6-minute-walk test), radiological examination (CTA, ECT), and magnetic resonance angiography (MRA). In general, noninvasive measurements are inaccurate, while relatively accurate invasive measurements (thermodilution, direct Fick) are clinically unacceptable due to the fact that they are invasive, complex, and expensive, especially in the case of congestive heart failure patients.

The indirect Fick method is a new method that has been recently introduced to measure cardiac output using foreign gas rebreathing. It is based on a newly developed insert rebreathing gas analyzer, which is considerably less expensive than a mass spectrometer and much less complex to apply in a clinical environment. The accuracy of rebreathing cardiac output determination (including RSV) has been demonstrated in recent studies.^{1,2)} In these studies, the rebreathing method was compared to the thermodilution method (Swan-Ganz catheter) and direct Fick method in the catheter room. It was found the rebreathing method had strong positive correlations with the Swan-Ganz thermodilution and direct Fick methods, and provided at least as good an estimate of cardiac output as did the thermodilution technique and direct Fick method.

In a previous study, we reported there was no correlation between Simpson's method and the rebreathing method with respect to the measurement of cardiac output parameters. We believe this phenomenon may be due to mitral regurgitation in heart failure patients. The present study was designed and conducted in order to confirm this hypothesis.

Table I. Baseline Characteristics

No.	Sex	Age	LVEF (%)	NYHA class	QRS (ms)	LVEDD (mm)	Drug therapy	6MHW (m)	MR	Left ventricular electrode
1	M	76	35	IV	128	60	ACEI, D, Dig	437	Severe	Lateral cardiac vein
2	M	73	20	III	167	65	ARB, BB, D, Dig	420	Severe	Lateral cardiac vein
3	F	65	15	IV	150	62	ARB, BB, D, Dig	223	Moderate to severe	Lateral cardiac vein
4	M	76	34	III	141	64	ACEI, D, Dig	228	Severe	Lateral cardiac vein
5	M	76	21	IV	165	72	ARB, D, Dig	215	Moderate to severe	Postero-lateral cardiac vein
6	M	69	18	IV	196	60	D, Dig	150	Severe	Postero-lateral cardiac vein
7	F	77	18	IV	192	66	ARB, BB, D, Dig	180	Severe	Postero-lateral cardiac vein
8	M	59	32	IV	164	64	ACEI, D, Dig	508	Severe	Lateral cardiac vein
9	F	60	13	IV	170	67	ARB, D, Dig	476	Severe	Lateral cardiac vein
10	M	68	12	IV	180	80	ARB, D, Dig	463	Severe	Postero-lateral cardiac vein
11	M	57	33	III	160	72	ARB, BB, D, Dig	432	Moderate to severe	Postero-lateral cardiac vein

ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β -receptor blocker; D, diuretic; Dig, digoxin; N, nitric ether; 6MHW, 6-minute-walk test; NYHA, New York Heart Association class; and MR, mitral regurgitation.

METHODS

Subjects: All patients provided written informed consent before enrollment. The study subjects included 8 male and 3 female heart failure patients with an average age of 68.7 ± 7.5 years who had undergone implantation of an atrioventricular pacemaker (InsyncIII 8042). The clinical characteristics of the subjects are presented in Table I.

These patients had an average heart failure history of 2.9 ± 2.5 years, ranging from 1 month to 10 years. All of the patients had severe idiopathic or ischemic left ventricular systolic dysfunction, and all had been receiving systemic anti-

Figure 1. Determination of stroke volume in velocity-time integral (VSV).³⁾

chronic heart failure (CHF) therapy, including life style guidance (low sodium diet, smoking cessation, weight reduction, and exercise), recovery therapy (guide therapy), and medical therapy. Medical therapy included diuretics (11 patients), digitalis (11 patients), ACE inhibitors (6 patients) or ARB (5 patients), β -receptor blockers (6 patients), and long-acting nitric ether (11 patients). However, based on upper maximal tolerated dose therapy, these patients still had 1) pertinacious chronic heart failure; 2) NYHA class greater than III; 3) left ventricular ejection fraction (LVEF) $\leq 35\%$; 4) left ventricular end-diastolic diameter (LVIDd) ≥ 60 mm; 5) significant mitral regurgitation (moderate to severe); and 6) a QRS interval ≥ 120 ms. These patients then underwent Medtronic InsyncIII implantation. The results of the implantations were assessed from the positions of the leads on chest x-ray films and from changes in the width of the QRS interval on 12-lead surface electrocardiograms.

All the patients were assigned to receive a 6-month follow-up, which was pre-surgery, and postsurgery, 1st, 3rd and 6th month after pacemaker implantation. The patients underwent an electrocardiogram (ECG), echocardiography, indirect Fick method, and 6 minute walk test (6MW) each time as per the recommendations of Guyatt and colleagues and Lipkin, *et al.*^{4,5)} In the 1st week and 3rd month, each patient underwent Doppler echocardiography to determine the optimal atrioventricular delay (electrical delay between atrial and ventricular excitation) during atrioventricular pacing.⁶⁾ All echocardiography, indirect Fick, and 6MW values are the mean of 3 measurements.

Echocardiography: A GE VIVID 7 echocardiograph was used for follow-up. Left ventricular end-diastolic diameter (LVEDd) was determined under M mode echocardiography, end-systolic volume and end-diastolic volume were determined under an apical 4-chamber view using biplane Simpson's rule, and left ventricular ejection fraction (LVEF) and Simpson's stroke volume (SSV) were calculated. Under an apical 5-chamber view, aortic velocity-time integral (VTI) was determined under pulsed-Doppler. Aortic cross sectional area (A) was also determined, and VTI stroke volume (VSV) was calculated according to the equation: $SV = A \times VTI$.^{3,7)} (see Figure 1).

Rebreathing method (indirect Fick method): The patient, lying in a supine position on the examination table, breathed through a hermetically closed circuit system (Innocor, INNOVISION A/S) containing a gas mixture of 0.1% (V/V) SF₆ (blood insoluble gas), 0.5% (V/V) N₂O (blood soluble gas), and 28% (V/V) O₂ in N₂ in a 4-L rubber bag. Rebreathing was performed over 30 seconds with a gas volume of 300% of the predicted tidal volume and a breathing rate of 18 min⁻¹. Gas was sampled continuously from the mouthpiece for analysis by the IR gas analyser of the Innocor closed circuit system. A constant ventilation rate was ensured by having the subject breathe in synchrony with a graphical tachometer

on the computer screen, and a constant ventilation volume was ensured by requesting the subject to empty the rebreathing bag completely with each breath. The rebreathing system software calculated CO_{RB} from the rate of uptake of N_2O into the blood (slope of the regression line through logarithmically transformed expiratory N_2O concentration plotted against time). After correction for system volume changes using the SF_6 concentration, the first 2 or 3 breaths were excluded from the analysis due to initial incomplete gas mixing.

For the majority of patients without a pulmonary arterial-venous shunt ($S_{\text{aO}_2} \geq 98\%$), the measured CO_{RB} value was considered equal to cardiac output, according to Friedman, *et al*⁸⁾ and Petrini, *et al*,⁹⁾ whereas for patients with a pulmonary shunt, the shunt was calculated and added to CO_{RB} . Shunt fraction was calculated according to the equation:

$$\text{Shunt fraction} = (C_{\text{capO}_2} - C_{\text{aO}_2}) / (C_{\text{capO}_2} - C_{\text{vO}_2})$$

where C_{aO_2} is arterial O_2 content and C_{vO_2} is venous O_2 content. C_{capO_2} (capillary O_2 content) can be calculated using the following formula:

$$C_{\text{capO}_2} = 1.34 [\text{HB}] \times S_{\text{capO}_2} + P_{\text{capO}_2} \times 0.003$$

where $[\text{HB}]$ is the concentration of haemoglobin. P_{capO_2} (saturation of capillary O_2) was set to 0.98 and P_{capO_2} (pressure of capillary O_2) was estimated as the alveolar oxygen tension (P_{AO_2}). P_{AO_2} was calculated from the formula:

$$P_{\text{AO}_2} = [F_{\text{iO}_2} \times (PB - 47)] - \{P_{\text{acO}_2} \times [F_{\text{iO}_2} + (1 - F_{\text{iO}_2}/RQ)]\}$$

where PB denotes the barometric pressure, F_{iO_2} is the O_2 fraction in inspired air, and P_{acO_2} is the measured arterial CO_2 tension. CO_2 excretion and the respiratory quotient (RQ) were determined with a special software program using standard formulae.

Rebreathing stroke volume (RSV) was calculated by dividing CO_{RB} by heart rate.

Statistics: All data were analyzed by a third researcher whose was blinded. Values are expressed as the $\bar{x} \pm \text{SD}$. SPSS10.0 for Windows was used for statistical analyses. ANOVA, paired q test (Newman-Keuls method), paired t test, and Bland-Altman plot regression were used to analyze the parameters.

Table II. Cardiac Function Parameters in Follow-up

	LVEDd (cm)	EF (%)	(mL)	6 MHW(m)	NYHA class
Presurgery	6.6 ± 0.6	22 ± 8.8	36 ± 14.9	343 ± 141	3.80 ± 0.42
Optimal	6.4 ± 0.8	30 ± 9.3	48 ± 14.7 [#]	373 ± 132	3.70 ± 0.43
1 st month after implantation	6.1 ± 0.7	38 ± 13.5	57 ± 15.7	385 ± 92	3.29 ± 0.49
3 rd month after implantation	6.1 ± 0.8	32 ± 11.0	53 ± 8.3	436 ± 44	2.80 ± 0.45
6 th month after implantation	6.0 ± 0.9 [#]	38 ± 9.9 [#]	57 ± 15.7 [#]	466 ± 32 [#]	2.40 ± 0.55 [#]

Note: $n = 10$; [#]: compared to presurgery, $P < 0.05$; Δ : compared to optimal $P < 0.05$

RESULTS

Cardiac function improved after implantation of the InsyncIII (Table II). We analyzed the cardiac output parameters (stroke volume) with ANOVA, q test (Newman-Keuls method), paired-samples t test, and Bland-Altman plot. As shown in Figure 2, there was good correlation ($r = 0.89$) between the stroke volume with the rebreathing method (RSV) and the stroke volume with velocity-time integral (VSV). ANOVA, the q test, and paired t test showed there was no

Figure 2. Regression of RSV and VSV. $R = 0.89$.

Figure 3. Regression of VSV and SSV, $R = 0.54$.

Figure 4. Regression of RSV and SSV, $R = 0.58$.

statistically significant difference ($P < 0.001$ in ANOVA and $P = 0.432$ in paired t test).

As shown in Figures 3 and 4, stroke volume determined using Simpson's method (SSV) was poorly correlated with stroke volume obtained by the indirect Fick method (RSV) or VSV. The r values were 0.58 ($P < 0.001$ in t test) and 0.54 ($P < 0.001$ in t test), respectively.

DISCUSSION

It is very difficult to determine and follow-up the cardiac function of a patient accurately and conveniently. Meanwhile, cardiac function parameters such as cardiac output per minute, stroke volume and cardiac index are very important. For example, in the intensive care unit and perioperative room, physicians have the common goal of maintaining adequate organ perfusion throughout the body during the course of a critical illness or surgery. Adequate organ perfusion implies 2 different physical properties: perfusion pressure that is sufficiently high to force blood into the capillary vessels of all organs; and sufficient blood flow that can deliver oxygen and substrates as well as remove metabolic byproducts and carbon dioxide. The heart provides all the power for these functions and cardiac output is the most important parameter of cardiac function. Clinicians often pay more attention to blood pressure than blood flow. One reason may be because it is difficult to determine blood flow. Indeed, in many centres the only way to obtain a measure of cardiac output is to use the thermodilution technique through a pulmonary artery catheter (Swan-Ganz catheter). The difficulties and risks associated with pulmonary artery catheter insertion may account, in part, for the lack of routine cardiac output monitoring in every patient.³⁾ Not every patient is suitable to receive an invasive examination (such as a Swan-Ganz catheter). An invasive exam may imply significant risk, especially in chronic heart failure (CHF) patients. In the present study, a noninvasive method was used in all patients.

In the follow-up visits, echocardiography and rebreathing demonstrated unique capabilities. First at all, they are both noninvasive methods and are suitable for CHF patients. Second, they are easy to perform. One echocardiography follow-up session can be completed in 40 minutes, and optimization may last 1 hour and 40 minutes. Only 1 minute is needed to obtain cardiac functional parameters using the rebreathing method. Echocardiography can determine chamber diameters, and examine the valves and wall motions at the same time, while the rebreathing method can also determine pulmonary flow, pulmonary capacity, arterial saturation of capillary O_2 , and arterial-venous shunt (see Methods). These parameters are also very important in CHF patients. These methods are both pre-

cise and repeatable. Echocardiography has been adopted for many years in CHF follow-up, and the velocity-time integral method has been proven to be a reliable method for cardiac function follow-up.¹¹⁾ The precision and accuracy of rebreathing have been verified in recent research.^{1,2)} LVEF and the tissue Doppler method are good indices of cardiac function. We used them to evaluate cardiac function and left ventricular synchronization. We did not, however, select these parameters for analysis because rebreathing can not measure LVEF. We had to select a parameter which was common to all 3 methods. Thus, stroke volume used for the comparisons.

Atrioventricular pacemakers are an evolution in the treatment of chronic heart failure. Cardiac resynchronization therapy (CRT) can improve the cardiac output of CHF patients by way of optimizing the atrioventricular interval and biventricular resynchronization, especially in patients with significant mitral regurgitation and a wide QRS interval.¹¹⁻¹⁴⁾ CRT can improve cardiac function both in acute^{12,15)} and long-term periods.¹⁵⁾ However, it has been difficult to obtain accurate and convenient cardiac parameters in follow-up. During follow-up, echocardiography, rebreathing, and the 6 minute walk test are often selected to determine cardiac parameters.

The reason we chose these CHF patients is that these patients can easily visit the hospital and all parameters are available. Six-month follow-ups were obtained for all patients. But most importantly, each patient had moderate to severe mitral regurgitation. It was strongly recommended that these patients receive clinical follow-up and the pacing parameters be optimized. Therefore, they were easy to track and follow-up was completed for every patient.

Actually, we measured the same parameter using 3 different methods. An ideal result would be that all data from these methods were consistent without error. However, what we found was different. In a previous study, we found that cardiac output measured by Simpson's method may overestimate cardiac output in patients with mitral regurgitation compared to the thermodilution method with a Swan-Ganz catheter and the rebreathing method.²⁾ In this study, we also found the parameters from the different methods were different, and some of the differences were significant. Stroke volume using Simpson's method (SSV) is poorly correlated with stroke volume obtained by velocity-time integral (VSV) and by the rebreathing method (RSV). We also observed that SSV is always larger than VSV and RSV (Figures 2 to 4). We believe the error was due to valvular regurgitation. Although Simpson's method is applied widely, it seems the velocity-time integral method and rebreathing method have more evidence about accuracy and precision. These 2 methods have been compared to invasive measurements and showed good correlation with these measurements.^{1,2,10,16)}

In Simpson's method, stroke volume is calculated by the formula:

$$SV = LVEDV - LVESV$$

Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) are just an image geometric estimation, and when regurgitation or aneurysm occurs, Simpson's method may overestimate cardiac output. In our study, all patients had moderate to severe mitral regurgitation (Table I) so SSV may not be reliable.

Compared to Simpson's method, also with echocardiography, the velocity-time integral method is better³⁾: VTI measures the flow integral from an aortic cross sectional area, and regurgitation (negative arithmetic valve) is calculated. The velocity-time integral method has been proven to be accurate and repeatable.¹⁷⁾ The rebreathing method (indirect Fick) is similar to the Fick method. They are based on the law of conservation of mass, which is independent of valvular regurgitation. The rebreathing method has also been shown to be accurate and repeatable, not only to Fick¹⁾ but also to thermodilution.^{2,18)}

Conclusion: It is concluded the rebreathing method and velocity-time integral method are excellent noninvasive methods with which to measure cardiac function. They exhibit good correlation, even in these CHF patients with moderate to severe mitral regurgitation. Furthermore, they are easy, safe, and well established methods for the noninvasive measurement of cardiac output with good prospects for clinical application. Simpson's method seems to be poorly correlated with these 2 methods.

Limitations: The major limitation of this study is the small number of subjects. There are not many heart failure patients after CRT implantation in our single centre. Also, there was no invasive cardiac output determination method in the study, such as Swan-Ganz and direct Fick. We may have been too strict with respect to subject selection. Many heart failure patients with moderate to severe mitral regurgitation can also be included. In future studies, we should add more precise methods and more patients from a greater number of centers.

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