International Journal of Cardiology 167 (2013) 2167–2171

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Improved coronary artery blood flow following the correction of systolic dyssynchrony with cardiac resynchronization therapy

Fang Fang, Joseph Yat-Sun Chan, Alex Pui-Wai Lee, Shih-Hsien Sung, Xiu-Xia Luo, Xin Jiang, Joey S.W. Kwong, John E. Sanderson, Cheuk-Man Yu *

Institute of Vascular Medicine, Li Ka Shing Institute of Health Sciences, S.H. Ho Cardiovascular Disease and Stroke Centre, Heart Education And Research Training (HEART) Centre and Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong

ARTICLE INFO

Article history:
Received 23 March 2012
Received in revised form 15 May 2012
Accepted 27 May 2012
Available online 15 June 2012

Keywords:
Cardiac resynchronization therapy
Coronary blood flow
Systolic dyssynchrony
Myocardial velocity

ABSTRACT

Background: Coronary blood flow (CBF) is improved by cardiac resynchronization therapy (CRT) and impaired by right ventricular apical (RVA) pacing in patients with heart failure. However, the underlying mechanism remains unclear.

Methods: Twenty-nine non-ischemic heart failure patients who responded to CRT underwent transthoracic echocardiography examination including both left anterior descending (LAD) CBF and tissue Doppler imaging in 3 pacing modes: intrinsic conduction, RVA pacing and biventricular (BiV) pacing. LAD velocity-temporal integral (LAD-VTI) and duration were measured. Systolic dyssynchrony was assessed with the standard deviation of a 12-left ventricular segmental model (Ts-SD).

Results: BiV pacing improved while RVA pacing reduced CBF compared to intrinsic conduction (all $p<0.05$). Both Ts-SD and ventricular septal velocity deteriorated during RVA pacing but improved during BiV pacing (all $p<0.05$). When systolic dyssynchrony was induced, lower LAD-VTI (9.5 ± 3.4 versus 12.7 ± 5.1 cm, $p=0.001$) and shorter LAD diastolic duration (483 ± 92 versus 542 ± 106 ms, $p=0.010$) were detected than synchronous status. Systolic dyssynchrony was inversely related to septal velocity ($r=-0.41$), $p<0.001$ and LAD-VTI ($r=-0.30$, $p=0.007$), with the latter found to be moderately correlated to septal velocity ($r=0.30$, $p=0.007$).

Conclusion: Regional LAD flow was improved in patients subjected to BiV but worsened in those treated with RVA pacing in non-ischemic heart failure CRT responders. Systolic dyssynchrony was more commonly observed in patients subjected to RVA pacing. Reduction of septal velocity with dyssynchrony may directly lead to reduced LAD flow. Improvement of septal velocity by CRT and hence LAD flow may be an important mechanism in determining the response to CRT.

1. Introduction

It is well accepted that patients with advanced heart failure (HF) benefit from cardiac resynchronization therapy (CRT) since it improves survival, symptom status, cardiac function and systolic dyssynchrony while conventional right ventricular apical (RVA) pacing has a detrimental impact in HF patients [1,2]. Increase of peripheral blood flow was also observed in a cohort of CRT patients [3]. Moreover, recent published data further demonstrated the favorable effect of CRT on coronary blood flow (CBF) and myocardial perfusion [4–8]. In contrast, CBF was shown to be impaired by RVA pacing even in those without pre-existing coronary artery disease using different non-invasive technologies including nuclear imaging, single-photon emission computed tomography and echocardiography [9–11]. However, the underlying mechanism of the superiority of CRT to RVA pacing on CBF and myocardial perfusion remains unclear. It has been postulated that ventricular re-coordination after CRT improves the microcirculation of the myocardium [12]. However, available published data are inconclusive about the effect of dyssynchrony on CBF and myocardial perfusion [10,13–15]. Furthermore, an animal study showed that induction of left bundle branch block resulted in septal hypoperfusion [16]. The relationship between CBF changes in different pacing modalities and the adaptation to the workload reduction in myocardium due to pacing-related systolic dyssynchrony remains unknown.

We hypothesized that pacing-related changes in ventricular systolic dyssynchrony affects regional CBF with resultant alteration of myocardial function. To test this hypothesis, comprehensive transthoracic echocardiography with tissue Doppler imaging (TDI) was used to assess ventricular systolic dyssynchrony while Doppler echocardiography was

Abbreviations: BiV, biventricular; CBF, coronary blood flow; CRT, cardiac resynchronization therapy; HF, heart failure; LAD, left anterior descending coronary artery; RVA, right ventricular apical; TDI, tissue Doppler imaging; VTI, velocity–time integral.

* Corresponding author at: Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital, & Heart Education and Research Training (HEART) Centre, & Institute of Vascular Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong. Tel.: +852 2632 3127; fax: +852 2645 1699.
E-mail address: cmyu@cuhk.edu.hk (C-M. Yu).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2012.05.094

employed to assess left anterior descending coronary artery (LAD) flow in patients with idiopathic dilated cardiomyopathy who responded to CRT; and they were assessed during intrinsic conduction, RVA pacing and biventricular (BiV) pacing [17,18].

2. Methods

2.1. Study population

Twenty-nine HF patients with idiopathic dilated cardiomyopathy who responded to CRT were recruited into the study. They had refractory symptomatic HF despite optimal medical therapy and underwent CRT at our center. All patients had left ventricular ejection fraction <35%, QRS duration >120 ms, and absence of significant coronary artery disease (defined as >50% stenosis on invasive coronary angiogram). Response to CRT was defined as ≥15% reduction of left ventricular end-systolic volume at 3 months after CRT implantation. Exclusion criteria were atrial fibrillation, frequent premature beats, poor acoustic window or undetectable distal portion of LAD. The study was approved and conducted in compliance with the regulation of the institutional Ethics Committee, and informed consent was obtained from all patients.

2.2. Device programming

CRT devices were implanted in all 29 patients. The right ventricular lead was placed in RVA position. The left ventricular lead was placed through the coronary sinus with primary target of lead placement in either the lateral or posterior–lateral cardiac vein. Atrioventricular delay optimization was performed 1 day after implantation and repeated at 3 months if the patient was in sinus rhythm, using the methods described by Ritter et al. [19] However, optimization of the interventricular delay was not performed and thus all devices were programmed for simultaneous BiV pacing.

2.3. Echocardiography

Echocardiography (Vivid 7, GE Vingmed Ultrasound, Norway) was performed at rest during (1) intrinsic conduction without pacing; (2) atrioventricular sequential RVA pacing; (3) atrioventricular BiV pacing with atrioventricular interval set at the optimized interval and V–V offset set at 0 ms. A lag time of 15 min between each pacing mode was scheduled to take into account any carry-over effect.

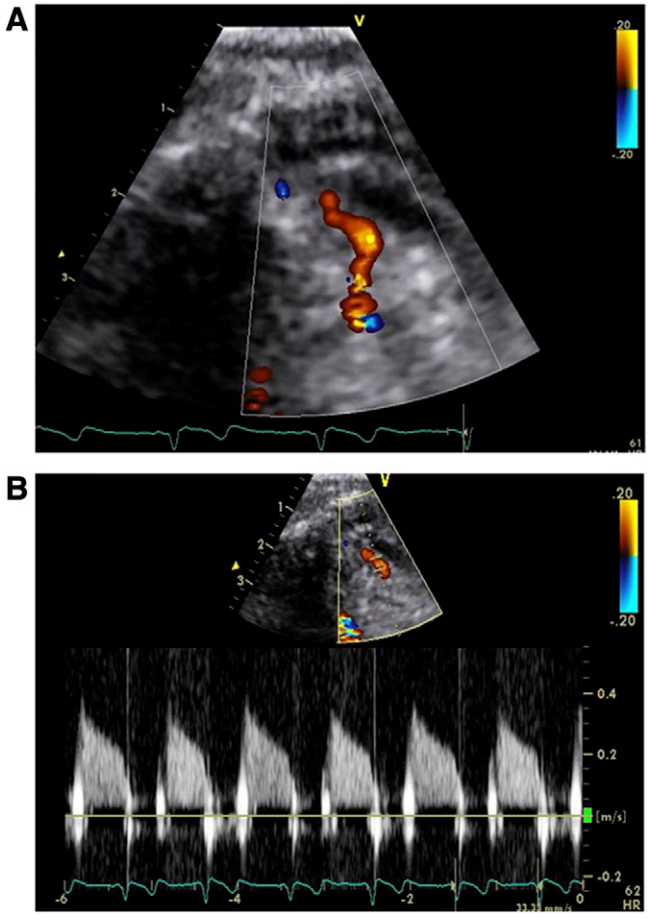

Fig. 1. Transthoracic echocardiographic detection and estimation of color Doppler (A) and pulse-wave Doppler (B) of distal left anterior descending coronary artery flow.

Two-dimensional echocardiography with TDI color imaging views (apical 4-chamber, 2-chamber, and long-axis views) was performed with optimized pulse repetition frequency, color saturation, sector size, and depth allowing the highest possible frame rate. At least 5 consecutive beats were stored, and the images were analyzed offline with the aid of a customized software package (EchoPac 6.3.6, Vingmed-General Electric). Myocardial velocity curves were reconstituted offline. The left ventricular septal longitudinal velocity was calculated by averaging the values from the basal- and mid-septal segments. Using the QRS complex as the reference point, systolic dyssynchrony was assessed by calculating the standard deviation of the time to peak myocardial systolic velocity in the ejection phase among the 12 left ventricular segments (Ts-SD) [20]. The standard deviation of time to peak myocardial early diastolic velocity of 12 left ventricular segments (Te-SD) was derived for evaluation of diastolic dyssynchrony [21].

2.4. Doppler study of the LAD

Doppler study of the LAD was performed by placing the transducer along the midclavicular line in the fourth to fifth intercostal spaces with the modified apical 2-chamber view. The coronary flow signals in the left anterior descending artery was searched under the guidance of color Doppler flow mapping. The transducer was rotated counterclockwise to obtain the best long-axis color view. When a diastolic flow was recognized in the anterior groove area, it was brought into the center of the ultrasound field by angling laterally and slightly above the central ray of the scan plane. A sample volume (5×2.5 mm) on the color signal in the distal portion of the coronary artery was used to record coronary flow velocity using the pulsed Doppler. An angle correction <30° was made when necessary. During the examination, once LAD flow was identified and optimized in the first pacing mode, recordings of LAD flow parameters were made in identical body position, vessel location and sample volume as well as the similar angle to minimize the impact of sample volume location (Fig. 1).

Antegrade systolic peak velocity (cm/s), diastolic deceleration time (ms) and velocity–time integral were calculated as the mean of ≥3 cardiac cycles [17,18]. The percentage of diastolic flow duration was expressed as the percentage of diastolic duration of coronary artery flow divided by the RR interval [22].

2.5. Reproducibility

Inter- and intra-observer variability was assessed in 20 randomly chosen patients. Variability was calculated as the percent error, derived as the absolute difference between 2 sets of measurements, divided by the mean of the observations.

2.6. Statistical analysis

All variables were expressed as mean ± SD or number (percent) as appropriate. Kolmogorov–Smirnov test was applied to test the normality of continuous variables. Group comparisons were performed using one-way ANOVA analysis with post-hoc comparison. Independent *t*-test or Chi-square test were used where appropriate. Pearson's correlation was performed to test the correlations between variables. A two-tailed $p<0.05$ was considered statistically significant. Analysis was conducted using the statistical software of SPSS version 17 (SPSS Inc, Chicago, Illinois, USA).

3. Results

Clinical characteristics of the 29 patients are listed in Table 1. Two patients were excluded from the study during on-line scanning due to suboptimal LAD Doppler recording. The mean age of the patients was 70 ± 11 years and there were 16 (55.2%) males. Eleven patients had hypertension and 2 had diabetes mellitus. Most of them were in NYHA class II to III at the enrollment.

3.1. LAD flow and ventricular dyssynchrony between different pacing mode

LAD flow parameters showed significant differences among different pacing modalities, although left ventricular volumes and ejection fraction remained unchanged (Table 2). The LAD duration was the longest with BiV pacing and the shortest with RVA pacing. A similar tendency was observed after correcting for RR interval (LAD diastolic flow duration). Similarly, LAD-VTI was the highest during BiV pacing and lowest in the RVA pacing (Fig. 2).

TDI during the 3 pacing modalities showed that the peak ventricular septal longitudinal velocity was the highest during BiV pacing and lowest during RVA pacing. Ts-SD was significantly reduced