IJC Heart & Vasculature 11 (2016) 66–73

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Acute contractile recovery extent during biventricular pacing is not associated with follow-up in patients undergoing resynchronization☆

Federica DeVecchi, Emanuela Facchini, Anna Degiovanni, Chiara Sartori, Chiara Cavallino, Matteo Santagostino, Virginia Di Ruocco, Andrea Magnani, Eraldo Occhetta, Paolo Nicola Marino *

Clinical Cardiology, Università del Piemonte Orientale, Department of Translational Medicine, Azienda Ospedaliero Universitaria "Maggiore della Carità", Corso Mazzini 28, 28100 Novara, Italy

ARTICLE INFO

Article history:
Received 31 December 2015
Received in revised form 16 March 2016
Accepted 19 March 2016
Available online 1 April 2016

Keywords:
Dyssynchrony
Resynchronization
Force–frequency relation
Speckle-tracking echocardiography
Congestive heart failure

ABSTRACT

Background: It has been reported that contractility, as assessed using dobutamine infusion, is independently associated with reverse remodeling after CRT. Controversy, however, exists about the capacity of this approach to predict a long-term clinical response. This study's purpose was to assess whether long-term CRT clinical effects can be predicted according to acute inotropic response induced by biventricular stimulation (CRT on), as compared with AAI–VVI right stimulation pacing mode (CRT off), quantified at the time of implantation.
Methods: In 98 patients (ejection fraction 29 ± 10%), acute changes in left ventricular (LV) elastance (*Ees*), arterial elastance (*Ea*), and *Ees*/*Ea*, as assessed from slope changes of the force–frequency relation obtained when the heart rate increased, and also assessed while measuring triplane LV volumes and continuous noninvasive blood pressure, were related to death or rehospitalization during a 3-year follow-up. Other covariances tested were age, gender, disease etiology, QRS duration, amount of mitral regurgitation, LV diastolic volume, ejection fraction, and the degree of asynchrony and longitudinal strain at baseline.
Results: There was a marked increment in the *Ees* slope with CRT (interaction $P = 0.004$), no *Ea* change, and modest *Ees*/*Ea* increase (interaction $P < 0.05$). In Cox analysis, however, neither slope changes nor baseline values of *Ees*, *Ea*, and *Ees*/*Ea* were associated with long-term follow-up. Only ventricular diastolic volume (direct relation $P = 0.002$) and QRS duration (inverse relation $P = 0.009$) predicted death/rehospitalization.
Conclusions: Acute contractile recovery in CRT patients is not associated with 3 years prognosis. Instead, death or rehospitalization can be predicted from QRS duration and LV diastolic volume at baseline.

1. Introduction

Studies have reported that contractility, as assessed using dobutamine infusion, is independently associated with reverse remodeling after biventricular stimulation (CRT) [1–2]. Controversy, however, exists about the capacity of the inotropic challenge to predict a long-term clinical response. A multicenter, prospective, observational study of left ventricular (LV) contractile reserve, as assessed using low-dose dobutamine infusion, was unable to demonstrate a significant difference in cardiac survival between patients who did or did not achieve an absolute increase in LV ejection fraction >5 points during the drug infusion [3]. Only the combination of cardiac survival and/or heart failure hospitalization as a clinical end-point demonstrated a significant association with the inotropic challenge [3].

Increasing heart rates have long been recognized as a potential modulator of systolic function [4]. In the normal heart, the force of contractions is augmented by an increase in heart rate, while in the failing heart, alterations in the force–frequency relation (FFR) have been identified which potentially contribute to an impaired capacity for exercise [5]. FFR has been shown to be capable of recruiting cardiac contractility in the failing heart in excess of the CRT effect, with this positive FFR contributing significantly to the enhanced capacity for exercise that most of the patients exhibit after the device implantation [6].

Thus, the purpose of this study was to assess whether and to what extent the acute gain in contractility induced by CRT, as assessed during increasing heart rate, is affecting long-term follow-up in terms of rehospitalization or death of patients evaluated at the time of the device activation.

Abbreviations: CRT, biventricular stimulation; DYS, dyssynchrony; *Ea*, arterial elastance; EDV, end-diastolic volume; *Ees*, ventricular elastance; EF, ejection fraction; FFR, force–frequency relation; HR, hazard ratio; LV, left ventricle; MR, mitral regurgitation; r^2, adjusted *r* squared; TUS, temporal uniformity of strain.

☆ Presented in part at the 63rd Annual Scientific Session of the American College of Cardiology, San Diego, March 2015.

* Corresponding author.
E-mail address: paolo.marino@maggioreosp.novara.it (P.N. Marino).

http://dx.doi.org/10.1016/j.ijcha.2016.03.012

2. Materials and methods

Ninety-eight nonconsecutive patients (mean age 70.6 ± 8.3 years, 73 males) with congestive cardiomyopathy of nonischemic ($n = 48$) or ischemic etiology ($n = 50$), LV ejection fraction (EF) <0.35 (0.30 ± 0.09), and QRS duration >120 ms (170 ± 28 ms), with left bundle branch block morphology, except for 4 patients who exhibited a right bundle branch block with left axis deviation, were prospectively studied (Table 1). Ischemic cardiomyopathy was considered in the presence of a documented previous myocardial infarction or a significant coronary artery disease (luminal narrowing >70%) shown through coronary angiography. Optimal revascularization had been previously performed in those patients. Nonischemic cardiomyopathy was considered only in the presence of angiographically "normal" coronary arteries. The patients, who fulfilled current criteria for CRT implantation, were selected to be in spontaneous sinus rhythm, except for 8 patients who were permanently bradyarrhythmic because of atrial fibrillation and 11 patients with pacing-induced rhythm for various degrees of atrioventricular block. In all these subjects a VVI pacemaker-induced regular rhythm could be guaranteed during the entire procedure (see below).

Four patients had been previously implanted with an aortic prosthesis (2 mechanical and 2 biological valves) while 7 had received a mechanical ($n = 3$) or a biological ($n = 4$) prosthesis in the mitral position. Three patients had received a mitral plus an aortic mechanical prosthesis, while 2 more patients had undergone mitral valve reconstructive surgery. In all subjects written informed consent was obtained in accordance with institutional human review studies committee guidelines and local institutional review board approval. The study complies with the Declaration of Helsinki.

3. Echocardiographic measurements

Standard echocardiographic examinations were performed on all patients using a Vivid 7 or Vivid E9 digital ultrasound system (GE Medical Systems, Horten, Norway). Cardiac cycles were stored in digital, cineloop format for off-line analysis performed with a dedicated software package (EchoPac PC, BT11 version; GE Healthcare). Two-dimensional strain is a novel non-Doppler-based method to evaluate strain from standard two-dimensional acquisitions [7]. By tracing the endocardial contour on an end-systolic frame, the software will automatically track the contour on subsequent frames. Optimal tracking could be verified in real-time and corrected by adjusting the region of interest or manually correcting the contour. A minimum frame rate of 30 Hz was required for reliable operation of this software, and frame rates of 30 to 80 Hz were used for routine gray-scale imaging.

Two-dimensional longitudinal strains were assessed in 2 orthogonal apical views (4- and 2-chambers, 12 segments) starting from the septal and the inferior atrioventricular wall junction, respectively, and averaging strains among various segments. The two-dimensional strain software had to adequately track >80% of the attempted segments in order to make the analysis acceptable.

Ventricular volumes were obtained using 3 real-time simultaneous longitudinal planes, as imaged from the apical approach, and then manually tracing the endocardial border with built-in software. The papillary muscles were excluded from the tracing. A triangular mesh was constructed by 3D interpolation between the traces, and end-diastolic volume and end-systolic volume were calculated by surface triangulation and summation of all triangles by the divergence theorem [8]. Bland and Altman's analysis of LV volumes and EF has previously demonstrated closer agreement between echocardiography and MRI results using triplane imaging, as compared with biplane imaging, both precontrast and with LV opacification [9].

Evaluation of mitral regurgitation (MR) was graded quantitatively according to the area of the regurgitant jet in a 4-chamber view using the color Doppler data [10] and expressed as a ratio relative to the atrial cavity area.

Table 1
Basic demographics, etiology, therapy, and heart rhythm.

N	98
Age, years	71.2 ± 8.3
Gender (M/F), *n*	73/25
BSA, m^2	1.84 ± 0.18
QRS width, ms	170 ± 30
Diabetes mellitus, %	30.4
NYHA functional class	2.7 ± 0.7
Device (ICD/PM), *n*	70/28
Etiology of heart disease, *n*	
Idiopathic	31
Ischemic	43
Valvular	9
Ischemic/valvular	7
Others (post-hypertensive, postpartum, tachicardiomyopathic, toxic)	8
Therapy, %	
ACE inhibitors/ARB blockers	72
Amiodarone	33
Antialdosterone	20
Anticoagulants	24
Antiplatelets	64
Beta-blockers	76
Ca^{++} channel blockers	6
Digitalis	16
Diuretics	82
Nitrates	25
ECG rhythm, *n*	
Spontaneous sinus rhythm	79
Permanent atrial fibrillation	8
Advanced atrioventricular block	11

4. Asynchrony quantitation

Data for longitudinal strain curves were exported as digital matrixes to a proprietary open-source analysis software (StrATo version 2.0.3.0). Dyssynchrony (DYS) was quantified by TUS (temporal uniformity of strain), where a time plot of regional strains, arranged for ventricular location, was subjected to a Fourier analysis [11]. In cases of a perfectly synchronous ventricle, the plot appeared as a straight line, with power only in the 0-order Fourier term, whereas regionally clustered DYS generated an undulating plot with higher power in the 1-order term [12]. The TUS index, which reflects the 0-order relative to 1-order plus 0-order power, synthesized DYS motion data because this temporal variance index could distinguish between geographically clustered regions of shortening, which are out of phase compared to those dispersed throughout the wall [13]. Due to the large number of computations associated with dyssynchrony calculation, one single beat was used for each view. Intraobserver reproducibility for TUS measurements, as assessed in the longitudinal plane in 15 patients at baseline heart rate (CRT off/on) and computed as absolute mean difference ± the percentage coefficient of variation (SD/mean), averaged 0.11 ± 1.0%, a value similar to what our group previously reported [14].

5. Echocardiography protocol

Within 2–3 days after CRT implantation, patients underwent echocardiographic-guided optimization ($n = 77$) or using the QuickOpt/Smart-Delay algorithm available with St. Jude/Boston Scientific devices ($n = 21$), respectively. Interventricular delay was set fixed at 0 ms. After optimization was obtained the device was programmed into one of 2 basic modes: either AAI (right atrial pacing for patients with spontaneous rhythm) or VVI (right ventricular pacing for patients with permanent atrial fibrillation or advanced atrioventricular block) pacing mode vs. DDD-CRT (biventricular) pacing mode, in a random sequence. In particular, during the AAI pacing mode, care was taken to confirm