Dr.ssa Anna Degiovanni
Clinica Cardiologica, Università degli studi del Piemonte Orientale "A.Avogadro"
Scuola di Specializzazione in Malattie dell'apparato cardiovascolare (Prof. Marino)
XXX Ciclo Dottorato in Scienze e Biotecnologie Mediche (Percorso d'eccellenza)

During my first year of PhD program I focused my research on the following scientific project: *" **Analysis of atrio-ventricular coupling in patients treated with a CRT device as a possible response predictor"***.

Background

Cardiac resynchronization therapy (CRT) is a standard treatment for refractory heart failure (HF) with low ejection fraction (EF) and ventricular dyssynchrony, expressed by the presence of left bundle branch block (LBBB) at the surface ecg.[1] According to current guidelines criteria, CRT is recommended in patients with LBBB with QRS duration >120 ms, chronic HF and EF ≤ 35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment (class I) and in non-LBBB patients with QRS duration > 150 ms (class IIA); non-LBBB subjects with QRS between 120-150 ms have a less stringent indication (class IIB).

As a result, only a small percentage of HF patients (probably 5-10%) should undergo CRT, but this still represents a large number of potential candidates. Based on EuroHeart Failure surveys this means about 400,000 patients per year in ESC countries. [2, 3]

There is strong evidence that CRT reduces mortality and hospitalization, improves cardiac function and structure in these patients[4,5]; however still a considerable number of implanted subjects, approximately 30%, do not exhibit a positive response. This fact is probably due not merely to the absence of correctable ventricular dyssynchrony, but also to other factors that can contribute to a good response. Cardiac dyssynchrony, in fact, besides being complex in detection and quantification, is multifactorial in origin, impacting on atrioventricular, interventricular and/or intraventricular coupling, each of these being capable of negatively affecting systolic and diastolic ventricular function.[6]

AV interval prolongation, in particular, acts on systolic contraction, encroaching on early diastolic filling, with atrial pressure falling as the atria relax. Delaying ventricular contraction, because of A-V prolongation, causes LV diastolic pressure to exceed atrial pressure, thus promoting mitral regurgitation. Furthermore, by minimizing ventricular pre-load, there will be a depression in LV contractility, due to a decline of the Frank-Starling mechanism. Both inter- and intra-ventricular conduction delays lead to asynchronous contraction of LV wall regions (ventricular dyssynchrony), impairing cardiac efficiency and reducing stroke volume and systolic blood pressure. Finally, poorly coordinated papillary muscle function may cause or aggravate functional systolic mitral regurgitation.[7]

CRT antagonizes all these phenomena, promoting reverse remodelling and leading to an improvement in NYHA class, quality of life (QoL), 6 minutes walking distance (6MWD) and a reduction in hospitalizations and all-cause mortality. [8]

Even with these potential ameliorations, however, there is still an elevated number of patients (almost 30%), who do not respond to CRT. [9] The most recent guidelines[1] try to

identify a continuum of clinical factors that could anticipate the magnitude of benefit from CRT, suggesting the presence of: female sex [10], non-ischaemic cardiomyopathy and QRS duration > 150 ms (the longer the QRS duration, the greater the benefit) as key factors in this regard. [11]

However, there are no definitive parameters capable of identifying potential responders. Even randomized controlled trials such as PROSPECT [12] or ECHO-CRT [13] were not able to identify any predictors or fostering factors in this regard, other than contributing to further generic shaping guidelines indications.

Rationale

Aim of our study is to evaluate the atrio-ventricular and intraventricular coupling depicted using an echocardiographic method that allows quantification of the atrial phasic functions (as assessed with 3D echo) besides describing the ventricular filling properties (using 2D echo) during CRT device optimization post-implant.

Methods

Study population and design protocol are described below. The clinical and instrumental data of all patients included in the study are collected in a database.

Study population

Consecutive HF patients referred for CRT implantation according to current guidelines (New York Heart Association class II- III heart failure, left ventricular ejection fraction < = 35%, QRS >= 130 ms, stable medical regimen) were enrolled during the post-implantation session of optimization. We plan to reach for the end of the project approximately 120 patients as a single center study.

Data were acquired during a basal phase (CRT-on) and a non resynchronized phase (CRT-off) at increasing heart rate steps. At the present moment we have enrolled 50 patients, acquiring all the echocardiographic data but without any further elaboration.

Echocardiographic measurements

Standard echocardiographic examinations have been performed in all patients using a 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).

During optimization of the CRT-device, we have quantified the atrial phasic functions and measured diastolic parameters such as E, A, E/A, E/e' and deceleration time, both in CRT on and off.[14]

Endpoints of the study:

• Primary endpoint: analysis of the atrial phasic functions and diastolic parameters during optimization in CRT on and off;

• Secondary endpoint: evaluation in terms of ventricular remodeling after 6 months and monitoring of absence / presence of major events (re-hospitalization for heart failure or death) during this same period.

In attachment publications, congress facts and seminars from December 2014 up to now:

Publications

Facchini E, **Degiovanni A**, Marino P. Left atrium function in patients with coronary artery disease. Curr Opin Cardiol 2014;29:423-429.

Facchini E, **Degiovanni A**, Cavallino C, Lupi A, Rognoni A, Bongo AS. Beta-Blockers and Nitrates: Pharmacotherapy and Indications. Cardiovasc Hematol Agents Med Chem. 2015;13(1):25-30.

Rognoni A, **Degiovanni A**, Cavallino C, Lupi A, Rosso R, Veia A, Rametta F, Bongo AS. Giant aneurysm of the right coronary artery: an unusual treatment. G Ital Cardiol 2015;16:250-253.

Nappo R, **Degiovanni A**, Bolzani V, Sartori C, Di Giovine G, Cerini P, Fossaceca R, Kovács SJ, Marino PN. Quantitative assessment of atrial conduit function: a new index of diastolic dysfunction. Clin Res Cardiol 2015; [Epub ahead of print]

Degiovanni A, Di Ruocco MV, Sartori C, Devecchi P, Marti G, Marino P. Preliminary study on diastolic stress echo: left atrial 3D longitudinal strain as a good descriptor of stress induced diastolic changes. European Journal of Heart Failure Abstracts Supplement 2015; 17 (Supplement 1),434.

Congress facts

75° Congresso Nazionale della Società Italiana di Cardiologia (Rome 13-15 December 2014): Poster session- **Degiovanni A**, Sartori C, Di Giovine G, Dell'Era G, Monti L, Occhetta E, Marino P. Una rara aritmia atriale concomitante ad una rara anomalia vascolare.

MEDIA (*MEtabolic* Road to DIAstolic Heart Failure) Meeting : Leiden NL 26-27 January 2015 : Partecipant

MEDIA (*MEtabolic* Road to DIAstolic Heart Failure) Meeting on diastolic stress echo protocol: Cardiff 13-14 April 2015: Partecipant

Sulle sponde del Ticino (Stresa 8 May 2015) Diagnostica e terapia cardiologica: Partecipant

Heart Failure 2015- 2nd World Congress on Acute Heart Failure 2015 (Seville- Spain 23-26 May 2015): Poster session- **Degiovanni A**, Di Ruocco MV, Sartori C, Devecchi P, Marti G, Marino P. Preliminary study on diastolic stress echo: left atrial 3D longitudinal strain as a good descriptor of stress induced diastolic changes.

Courses and seminars

- January 19, 2015 Prof Dr Yong-Sang Song “Anticancer strategy Targeting cancer cell metabolism in ovarian cancer”
- January 20, 2015 Dr Tonino Alonzi “Different molecular mechanisms regulate hepatocyte differentiation during the transitions between epithelial and mesenchymal states”
- January 21, 2015 Prof Valeria Poli “Targeting the liver to cure myocarditis: a lesson from a model of STAT3-dependent auto-immune myocarditis”
- April 9, 2015 Prof Zhong "Signal control in iNKT cell development and function"
- April 21, 2015 Prof Percipalle "Actin-based mechanisms in the control of gene expression and cell fate"
- May 7, 2015 Prof John McDonald “An Integrated Approach to the Diagnosis and Treatment of Ovarian Cancer”
- June 5, 2015 Dr Feltkamp "Recent Developments in (cutaneous) Human Polyomavirus Research"
- September 3, 2015 Prof Darko Boshnakovski “Toward animal model for Facioscapulohumeral Muscular Dystrophy (FSHD)”

References

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[2] Nieminen MS, Brutsaert D, Dickstein K et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006;2725-2736.
[3] Cleland JG, McDonagh T, Rigby AS et al. The national heart failure audit for England and Wales 2008 – 2009. Heart 2011;97:876 -886.
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[11] Barsheshet A, Goldenberg I, Moss AJ et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. Eur Heart J 2011;32:1622-1630.
[12] Chung ES, Leon AR, Tavazzi L et al. Results of the Predictors of Response to CRT(PROSPECT) trial. Circulation 2008;117:2608-2616.
[13] Ruschitzka F, Abraham WT, Singh JP et al. Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex. N Engl J Med 2013;369:1395-1405.