Hindawi
International Journal of Vascular Medicine
Volume 2020, Article ID 7942381, 6 pages
https://doi.org/10.1155/2020/7942381

Clinical Study

Automatic Continuous CRT Optimization to Improve Hemodynamic Response: An Italian Single-Center Experience

Gregorio Covino, Mario Volpicelli, and Paolo Capogrosso

Department of Cardiology, Ospedale San Giovanni Bosco, Napoli, Italy

Correspondence should be addressed to Gregorio Covino; gregoriocovino@libero.it

Received 25 September 2019; Accepted 28 January 2020; Published 7 February 2020

Academic Editor: Antonio Bozzani

Background. Optimization of cardiac resynchronization therapy (CRT) settings after implant can improve response to therapy. In this Italian single-center experience, we investigated the rate of hemodynamic and clinical response in heart failure patients treated with continuously and automatically optimized CRT. *Methods*. Patients were selected from June 2015 to April 2017 according to the most recent CRT guidelines; all were in sinus rhythm at implant and received a CRT-defibrillator system equipped with SonR, which automatically optimizes AV and VV delays every week. SonR was activated just after implant and remained active during follow-up. The rate of hemodynamic response (R-HR) was defined as ΔLVEF > 5%, super-response (R-HSR) as Δ LVEF > 15%, and clinical response as a negative transition of NYHA class≥−1 at 6 months follow-up vs. baseline (preimplant). *Results*. Mean follow-up for the 31 patients (aged 69.9 ± 9.4 years; 61% male; NYHA class II/III 19%/81%; ischemic etiology 65%) was 6 ± 0.7 months. At baseline, LVEF was 29.1% ± 4.7% and QRS duration 146 ± 13 ms. LBBB morphology was observed in 65%. At 6 months, R-HR was 74% (23/31), R-HSR 32% (10/31), and clinical response rate 77% (24/31). Hemodynamically, patients with ischemic etiology benefited more than those without ischemic etiology, both in terms of response (80% versus 64%) and super-response (35% versus 27%). *Conclusions*. Continuous automatic weekly optimization of CRT over 6 months consistently improved R-HR, R-HSR, and clinical response in NYHA class II/III heart failure patients versus baseline. Patients with ischemic etiology in particular may benefit hemodynamically from this type of CRT optimization.

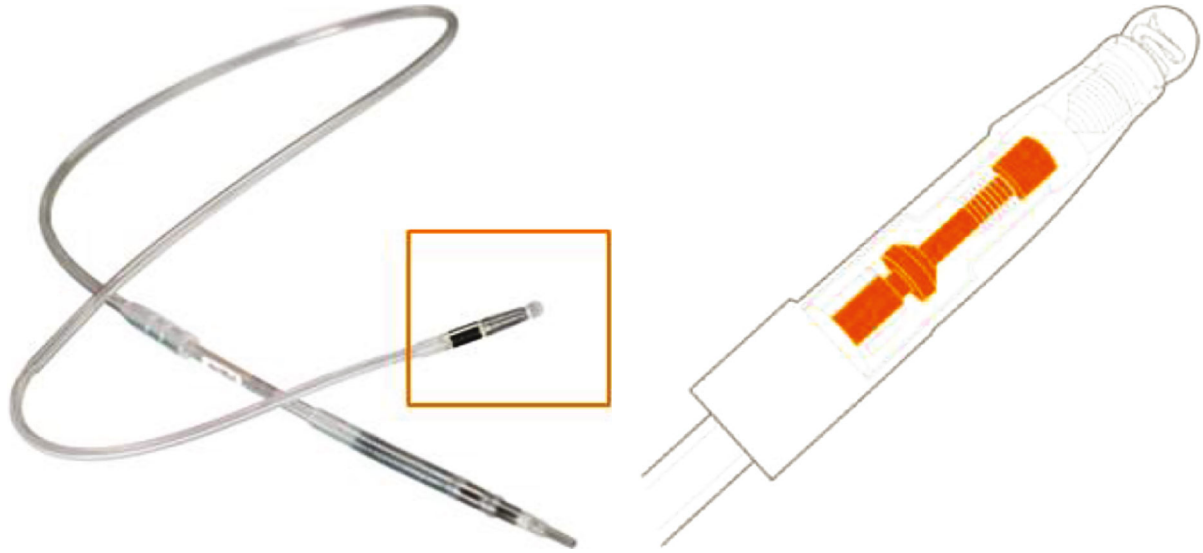
1. Introduction

Cardiac resynchronization therapy (CRT) is a well-established therapy for patients with medically refractory heart failure, left ventricular (LV) systolic dysfunction, and a wide QRS complex [1]. CRT has been shown to improve quality of life (QoL) and reduce the rates of heart failure hospitalization and overall mortality in these patients [2, 3]. However, about one-third of patients still remains nonresponsive to CRT [4]. In this context, the lack of atrioventricular (AV) and interventricular (VV) timing optimization has been indicated as one of the main causes of nonresponse to therapy, and timing customization could represent a key factor for CRT response [5]. As a matter of fact, several studies have demonstrated the acute hemodynamic benefits of AV and VV timing optimization guided by echocardiography [6].

Despite the fact that echocardiography-guided procedures are still considered "best practice" for optimizing CRT delivery during follow-up, they suffer from several limitations (time and resource consuming) ideally to be carried out systematically—i.e., at each follow-up visit—and under effort [7].

Recently introduced SonR technology uses a cardiac contractility sensor in the tip of a permanent pacing lead to endocardially measure cardiac muscle vibrations, which are directly correlated with LV dP/dt_{max} [8–10]. A dedicated algorithm in certain CRT-defibrillator (CRT-D) systems (MicroPort CRM, Saluggia, Italy) uses SonR sensor metrics to implement automatic weekly optimization of AV and VV delays [11].

In a first pilot study, CLEAR [8], there was a trend towards improvement in Packer's combined clinical outcome with the use of the SonR technology in the tip of a right



(a) (b)

Figure 1: A SonRtip atrial lead with SonR hemodynamic sensor embedded in the tip (a) and a cross-section of the lead tip showing the sensor's location inside the tip (b).

ventricular lead in a CRT pacemaker system compared with the standard of care (no or infrequent optimization). More recently, the RESPOND-CRT trial [12], a prospective, double-blind, randomized noninferiority clinical trial, confirmed in a wide range of patients ($n = 1039$) the safety and efficacy of the contractility sensor in heart failure patients treated with a CRT-D. The study's main findings were that (i) the SonRtip lead (a right atrial screw-in lead with the contractility sensor in the lead tip) is safe and (ii) the SonR automatic AV and VV optimization function is safe and as effective as echocardiography-guided AV and VV optimization in increasing response to CRT, in terms of Packer's clinical combined endpoint. Moreover, RESPOND-CRT data subanalysis demonstrated a particular benefit driven by SonR optimization in groups of patients usually less prone to respond to CRT: (a) history of paroxysmal AF, (b) LBBB and 120 ms < QRS < 150 ms, and (c) moderate renal dysfunction. No or minimal data have been made available about the rate of super-response potentially induced by the use of SonR optimization.

In this single-center experience, the authors aimed to determine the rate of hemodynamic response, super-response, and clinical response at 6-month follow-up versus baseline in a cohort of consecutive heart failure patients treated with continuous automatic optimization of CRT settings based on SonR-detected cardiac contractility.

2. Methods

Consecutive heart failure patients who were implanted at San Giovanni Bosco Hospital in Naples, Italy, between June 2015 and April 2017, with a CRT-D device capable of automatic CRT setting optimization based on SonR technology were selected as part of the OSCAR (Optimization with the SonR method in ClinicAl pRactice) trial, a prospective noninterventional study (ClinicalTrials.gov identifier: NCT02250547). Criteria for inclusion were eligibility for implantation or implantation within <6 weeks. Permanent atrial arrhythmia was an exclusion criterion. OSCAR was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients.

As per CRT guidelines and local clinical practice, heart failure patients undergoing CRT-D implantation were New York Heart Association (NYHA) class II/III, had QRS duration ≥ 120 ms and LV ejection fraction (LVEF) ≤ 35%, and were all on optimal medical therapy, including beta-blockers, angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), diuretics, and aldosterone antagonists (unless contraindicated or not tolerated by the patient) [1, 13, 14].

Baseline clinical characteristics—including NYHA functional class—were recorded prior to CRT-D implantation. Two-dimensional transthoracic echocardiography examinations were carried out before CRT implant and 6 months after implant, using a commercially available system (Toshiba Aplio, Toshiba Medical Systems Co., Ltd., Tokyo, Japan): (i) LV end-diastolic diameter was measured according to standard methods and (ii) LVEF was calculated from the apical four-chamber view, using the modified Simpson's rule. All the echocardiography examinations were carried out by a single operator to reduce potential interoperator variability.

Implantation (primo-implant, replacement or upgrade) of CRT devices was performed using a transvenous approach. All patients received a CRT-D device (Paradym RF or Platinium SonR CRT-D, MicroPort CRM, Saluggia, Italy), connected to a straight, active fixation bipolar atrial pacing lead (SonRtip, MicroPort CRM, Saluggia, Italy) (Figure 1). LV leads were preferably implanted by targeting the lateral or posterolateral branches of the coronary sinus. The right ventricular lead was mainly implanted in septal

Table 1: Baseline characteristics of heart failure patients, overall and by etiology (ischemic versus nonischemic).

Baseline characteristics Patients (*N*)	Overall 31 (100%)	Ischemic 20 (65%)	Nonischemic 11 (35%)	*p* value
Demographics				
Men	19 (61%)	14 (70%)	5 (45%)	0.18
Age (years)	69.9 ± 9.4	69.5 ± 8.1	70.6 ± 11.8	0.37
Weight (kg)	77.2 ± 18.4	77.3 ± 17.6	77.1 ± 21.1	0.49
Baseline NYHA class				
NYHA	2.8 ± 0.4	2.9 ± 0.3	2.7 ± 0.4	0.14
Class II	6 (19%)	5 (25%)	1 (9%)	<0.001
Class III	25 (81%)	15 (75%)	10 (91%)	
Comorbidities/CV risk factors				
Diabetes	9 (29%)	9 (45%)	0 (0%)	<0.01
Systemic hypertension	11 (35%)	7 (35%)	4 (36%)	0.94
Renal dysfunction	1 (3%)	1 (5%)	0 (0%)	0.45
COPD	4 (13%)	3 (15%)	1 (9%)	0.63
ECG findings				
QRS duration (ms)	146 ± 13	146 ± 20	146 ± 9	0.47
LBBB morphology	20 (65%)	12 (60%)	8 (73%)	0.012
Non-LBBB morphology	11 (35%)	8 (40%)	3 (27%)	
SBP (mmHg)	125.4 ± 16.8	127.2 ± 15	122 ± 20.3	0.23
DBP (mmHg)	71.1 ± 12.9	70.8 ± 13.2	71.7 ± 12.1	0.43
Echocardiographic findings				
LV ejection fraction (%)	29.1% ± 4.7%	28.7% ± 5.3%	29.8% ± 3.5%	0.27
≤25%	10 (32%)	8 (40%)	2 (18%)	0.21
>25%	21 (68%)	12 (60%)	9 (82%)	
Left atrial diameter (mm)	49.8 ± 6.1	49.6 ± 6.1	50.3 ± 6.1	0.39
LVEDV (mL)	61.3 ± 4.0	60.4 ± 4.1	63 ± 3.8	0.06
Medical therapy				
Beta-blockers	31 (100%)	20 (100%)	11 (100%)	—
Diuretics	31 (100%)	20 (100%)	11 (100%)	—
Aldosterone antagonist	31 (100%)	20 (100%)	11 (100%)	—
ACE inhibitor or ARNI*	31 (100%)	20 (100%)	11 (100%)	—

Data are presented as number and percentage or mean ± standard deviation. *Valsartan/sacubitril. Abbreviations: ACE: angiotensin-converting enzyme; ARNI: angiotensin receptor-neprilysin inhibitor; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; DBP: diastolic blood pressure; ECG: electrocardiogram; LBBB: left bundle-branch block; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; NYHA: New York Heart Association; SBP: systolic blood pressure.

position (28/31 patients). Just after device implantation, the SonR automatic optimization of AV and VV delays was activated in all patients.

2.1. Study Objectives. The aim of the present study was to determine clinical and hemodynamic responses to CRT at 6 months follow-up. The rate of hemodynamic response (R-HR) was computed by an increase of LVEF > 5% (6 months versus baseline). Similarly, based upon a definition used to stratify hemodynamic response in the MADIT-CRT trial, the rate of hemodynamic super-responders (R-HSR) was computed by an increase of LVEF > 15% (6 months versus baseline). Patients with a negative transition of NYHA class≥−1 were considered "clinical responders" (R-CR, rate of clinical response).

2.2. Statistical Analysis. Continuous variables are expressed as mean ± SD. Categorical data are summarized in terms of frequencies and percentages. Improvement in LVEF after device implantation, stratified by etiology of cardiomyopathy, was compared using a T-test, while the comparison between qualitative data was made using a χ^2 test. A p value < 0.05 was considered significant for interaction.

3. Results

A total of 31 patients (Table 1) were enrolled in this case series (mean age 69.9 ± 9.4 years, 61% men). At baseline, NYHA class II/III was found in 19%/81% of patients, respectively, mean LVEF was 29.1%, mean QRS duration was 146 ms, and LBBB was found in 65% of patients. Further

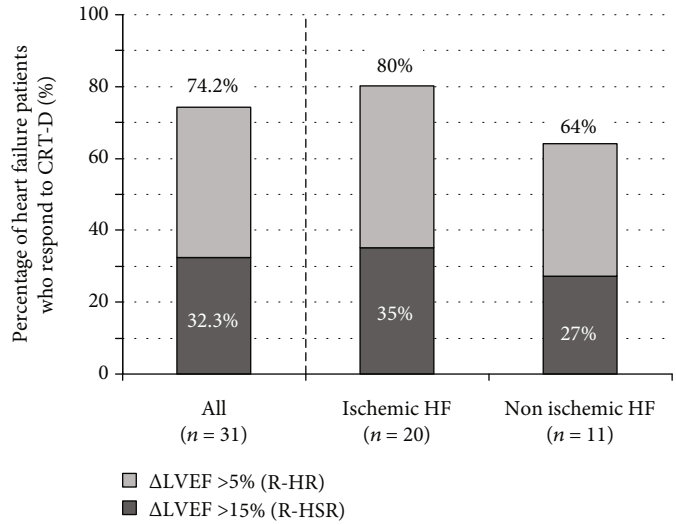


Figure 2: Rate of hemodynamic response (ΔLVEF > 5%) and super-response (ΔLVEF > 15%) in all patients (left), patients with ischemic heart failure (center), and patients with nonischemic heart failure (right) at 6 months follow-up. Abbreviations: CRT-D: cardiac resynchronization therapy-defibrillator; HF: heart failure; LVEF: left ventricular ejection fraction; R-HR: rate of hemodynamic response; R-HSR: rate of hemodynamic super-response.

information about baseline demographic, electrocardiographic, and echocardiographic characteristics as well as comorbidities and cardiovascular risk factors can be found in Table 1.

All patients came to our institution for the follow-up visit, scheduled 6 months after implant. In the overall population, LVEF increased by >5% (hemodynamic response) in 74.2% (23/31 patients) and LVEF increased by >15% (hemodynamic super-response) in 32.3% (10/31 patients) (Figure 2). When stratified according to underlying heart failure etiology, the group of patients with ischemic etiology exhibited higher nominal rates of response and super-response than the group with nonischemic etiology: 80% versus 63.6% for response ($p = 0.32$) and 35% versus 27% for super-response ($p = 0.66$). A negative transition of NYHA class≥ -1 (clinical response) was observed in 77.4% (24/31 patients).

4. Discussion

CRT delivered with continuous weekly optimization of AV and VV delays based on SonR-detected cardiac contractility was shown to be effective at improving the rates of response to therapy in NYHA class II/III heart failure patients after 6 months. In the present single-center experience, we observed a substantial hemodynamic response to CRT using the SonR automatic optimization function, which was higher than that expected in clinical practice. Moreover, a very high rate of super-response was also measured in this patient cohort as well as a high rate of clinical response.

In order to overcome the limitations of the previously mentioned echocardiography-driven CRT optimization methods, various device-based techniques have been proposed for optimizing CRT settings. These techniques—conceived to be used during in-hospital follow-up visits—were not shown to have any specific superiority in terms of clinical or hemodynamic benefit when compared with clinical practice or echocardiography-driven methods [15].

More recently, two trials have demonstrated significant clinical outcomes with CRT setting optimization. The adaptive CRT (a-CRT) and the RESPOND-CRT trials used functions able to implement continuous automatic optimization of CRT settings.

The a-CRT algorithm, an automatic system enabling RV-synchronized LV or biventricular pacing (in this case using measures of electrical activity) together with optimized AV delays [16], was demonstrated to be noninferior to echocardiography-driven optimization at 6 months follow-up in terms of Packer's clinical combined endpoint. Moreover, in a post hoc analysis of the same trial data, the authors found that the a-CRT algorithm was superior to echocardiographic optimization in the subgroup of patients with preserved AV conduction (PR < 200 ms) [17].

In the RESPOND-CRT study, a contractility sensor-guided CRT optimization approach (SonR) was shown to be safe and noninferior to echocardiography-based optimization, in terms of Packer's clinical combined endpoint at 1-year follow-up using a randomized double-blind study design [12]: the overall clinical response rate was 75% in the SonR group versus 70% in the control group ($p < 0.001$ for noninferiority). An impressive finding of the study was a 30% relative reduction in the heart failure hospitalization rate in favor of the SonR function over 2-year follow-up.

When looking at subgroups, clinical response for most of them was in favor of the SonR automatic optimization function: these data suggest that patients usually less prone to respond to CRT—for example patients with a prior history of atrial fibrillation, moderate renal dysfunction, or intermediate QRS duration (QRS < 150 ms)—seemed to benefit more from a continuous process of CRT setting

optimization, possibly because in these patients CRT delivery needs to be continuously adapted to a frequently changing substrate.

From a deeper analysis of RESPOND-CRT results, it emerges that other subgroups benefited from automatic optimization, such as patients with depressed ejection fraction or ischemic etiology. The finding in our cohort that the subgroup of patients with ischemic etiology, generally considered less likely to respond to CRT [1], exhibited even better response and super-response rates than the overall population was unexpected.

Heart failure of ischemic etiology is a cardiac condition resulting from the insufficient supply of blood to a part of the myocardium, leading to ventricular dysfunction. Myocardial ischemia may be caused by the obstruction of perfusion via plaque injury, usually in conjunction with thrombosis; endothelial dysfunction; or increased smooth muscle activity. The imbalance between myocardial oxygen supply and demand leads to a weakened myocardium and a reduced ability of the heart to pump increased quantities of blood when the body's metabolic demands increase [18]. In 2016, ischemic heart disease accounted for over half (53%) of all cardiovascular disease deaths, according to the World Health Organization [19].

The reasons that we focused on a comparison of ischemic vs. nonischemic heart failure were that (i) ischemic heart failure, which is resistant to treatment with conventional CRT-D, is a common type of heart failure and (ii) the lack of complete bundle branch block means that there are fewer electromechanical complications to address and so optimization of ventricular filling via optimization of atrioventricular timing, i.e., the SonR system, might in theory treat this group more effectively.

A potential explanation for this finding in our ischemic heart failure patients, who had all previously undergone complete revascularization via coronary artery bypass graft, is that the continuous contractility sensor-driven adaptation of AV and VV timing could compensate for the electrical and mechanical abnormalities induced by the presence of scars, particularly by maximizing ventricular filling thus optimizing cardiac performance.

4.1. Limitations. Given the small overall population size, caution should be taken in extrapolating these results to heart failure patients in general, especially so for the results pertaining to the comparison of the even smaller subpopulations of ischemic heart failure patients and nonischemic heart failure patients. The results do, nevertheless, confirm the findings of other studies showing the potential value of regular automatic optimization of AV and VV delays [8, 12]. The study was undertaken without an echocardiography core lab, but measurement variability was limited by the use of a single operator. The lack of a uniform, standardized definition of hemodynamic super-response means that the super-response results may be open to interpretation. Nevertheless, the definition for super-response that we chose was based on contemporary findings from a study that showed that the LVEF of all CRT super-responders increased by ≥14.5% [20].

5. Conclusions

The systematic use of the SonR function led to high hemodynamic response and super-response rates to CRT in NYHA class II/III heart failure patients over 6 months follow-up, with superior outcomes in patients with ischemic heart failure, who are generally considered less likely to respond to CRT. In the wake of these findings, further studies are needed to confirm our hypothesis that SonR-based continuous adaptation of AV and VV timing could compensate for the functional abnormalities induced by scars.

Abbreviations

AV: Atrioventricular
CRT: Cardiac resynchronization therapy
CRT-D: Cardiac resynchronization therapy-defibrillator
LBBB: Left bundle branch block
LV: Left ventricular
LVEF: Left ventricular ejection fraction
NYHA: New York Heart Association
QoL: Quality of life
R-HR: Rate of hemodynamic response
R-HSR: Rate of hemodynamic super-response
VV: Interventricular.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no competing interests.

Authors' Contributions

Gregorio Covino and Mario Volpicelli made substantial contributions to the acquisition, analysis, and interpretation of data. Moreover, they were involved in the drafting and revision of the manuscript. Paolo Capogrosso made substantial contributions to the critical reviewing of the intellectual content of the manuscript.

Acknowledgments

The authors wish to thank Roberta Beneduce and Giacomo Falaschi (MicroPort CRM Srl, Milan, Italy) and Ciro Provvisiero, Marianna Giardulli, and Antonio Crinisio (Department of Cardiology, Ospedale San Giovanni Bosco, Napoli, Italy) for their technical support during acquisition and interpretation of data and John Plant (MicroPort CRM, Clamart, France) for medical editing and writing assistance.

References

[1] M. Brignole, A. Auricchio, G. Baron-Esquivias et al., "2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC).

Developed in collaboration with the European Heart Rhythm Association (EHRA)," *European Heart Journal*, vol. 34, no. 29, pp. 2281–2329, 2013.

[2] W. T. Abraham, W. G. Fisher, A. L. Smith et al., "Cardiac resynchronization in chronic heart failure," *The New England Journal of Medicine*, vol. 346, no. 24, pp. 1845–1853, 2002.

[3] M. R. Bristow, L. A. Saxon, J. Boehmer et al., "Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure," *The New England Journal of Medicine*, vol. 350, no. 21, pp. 2140–2150, 2004.

[4] A. Auricchio and F. W. Prinzen, "Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues," *Circulation Journal*, vol. 75, no. 3, pp. 521–527, 2011.

[5] W. Mullens, R. A. Grimm, T. Verga et al., "Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program," *Journal of the American College of Cardiology*, vol. 53, no. 9, pp. 765–773, 2009.

[6] P. Houthuizen, F. A. Bracke, and B. M. van Gelder, "Atrioventricular and interventricular delay optimization in cardiac resynchronization therapy: physiological principles and overview of available methods," *Heart Failure Reviews*, vol. 16, no. 3, pp. 263–276, 2011.

[7] J. Gorcsan III, T. Abraham, D. A. Agler et al., "Echocardiography for Cardiac Resynchronization Therapy: Recommendations for Performance and Reporting-A Report from the American Society of Echocardiography Dyssynchrony Writing Group *Endorsed by the Heart Rhythm Society*," *Journal of the American Society of Echocardiography*, vol. 21, no. 3, pp. 191–213, 2008.

[8] P. Ritter, P. P. H. Delnoy, L. Padeletti et al., "A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs. standard methods," *Europace*, vol. 14, no. 9, pp. 1324–1333, 2012.

[9] A. F. Rickards, T. Bombardini, G. Corbucci, and G. Plicchi, "An implantable intracardiac accelerometer for monitoring myocardial contractility. The Multicenter PEA Study Group," *Pacing and Clinical Electrophysiology*, vol. 19, 12 Part 1, pp. 2066–2071, 1996.

[10] A. Tassin, A. Kobeissi, L. Vitali et al., "Relationship between amplitude and timing of heart sounds and endocardial acceleration," *Pacing and Clinical Electrophysiology*, vol. 32, Supplement 1, pp. S101–S104, 2009.

[11] S. Sacchi, D. Contardi, P. Pieragnoli, G. Ricciardi, A. Giomi, and L. Padeletti, "Hemodynamic sensor in cardiac implantable electric devices: the endocardial accelaration technology," *Journal of Healthcare Engineering*, vol. 4, no. 4, pp. 453–464, 2013.

[12] J. Brugada, P. P. Delnoy, J. Brachmann et al., "Contractility sensor-guided optimization of cardiac resynchronization therapy: results from the RESPOND-CRT trial," *European Heart Journal*, vol. 38, no. 10, pp. 730–738, 2017.

[13] P. Ponikowski, A. A. Voors, S. D. Anker et al., "2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC," *European Heart Journal*, vol. 37, no. 27, pp. 2129–2200, 2016.

[14] J. J. McMurray, S. Adamopoulos, S. D. Anker et al., "ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC," *European Heart Journal*, vol. 33, pp. 1787–1847, 2012.

[15] M. Lunati, G. Magenta, G. Cattafi et al., "Clinical relevance of systematic CRT device optimization," *Journal of Atrial Fibrillation*, vol. 7, no. 2, article 1077, 2014.

[16] D. O. Martin, B. Lemke, D. Birnie et al., "Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial," *Heart Rhythm*, vol. 9, no. 11, pp. 1807–1814, 2012.

[17] K. V. Burns, R. M. Gage, A. E. Curtin, J. Gorcsan III, and A. J. Bank, "Left ventricular-only pacing in heart failure patients with normal atrioventricular conduction improves global function and left ventricular regional mechanics compared with biventricular pacing: an adaptive cardiac resynchronization therapy sub-study," *European Journal of Heart Failure*, vol. 19, no. 10, pp. 1335–1343, 2017.

[18] A. Albakri, "Ischemic heart failure: a review of clinical status and meta-analysis of diagnosis and clinical management methods," *Clinical and Medical Investigations*, vol. 3, no. 4, 2018.

[19] World Health Organization, "Disease burden and mortality estimates - global summary estimates," 2016, January 2020, https://www.who.int/healthinfo/global_burden_disease/estimates/en/.

[20] J. C. Hsu, S. D. Solomon, M. Bourgoun et al., "Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study," *Journal of the American College of Cardiology*, vol. 59, no. 25, pp. 2366–2373, 2012.