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(RESEARCH ARTICLE)

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Relationship between CTGF levels and echocardiographic parameters in patients after permanent pacemaker implantation

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Abstract

Introduction: In recent decades, the dual-chamber pacemaker has become the gold standard for treating high-degree atrioventricular block. Despite the incredible benefits of overcoming conduction disorders, undeniable evidence has accumulated in recent years of negative effects of permanent right ventricular apical stimulation. The aim of our study was to examine the cytokines responsible for activation of the fibrotic process in patients after PPM implantation with apical right ventricular stimulation.

Material and Methods: CTGF levels were investigated by enzyme-linked immunoassays in plasma from 45 patients (25 men, 20 women, aged 72.1±9 years) and 46 controls (24 men, 22 women, aged 71.9±8.7 years) without known cardiovascular diseases (except arterial hypertension, conduction disorder, indication for the procedure) at baseline (for patients immediately before PPM implantation), at 12 and 24 weeks. At the same visits echocardiography was performed.

Results: There was no difference in baseline CTGF levels between patients and controls (312.66±15.25 vs 313.05±12.98 $p>0.05$). In patients, at week 12, CTGF levels were significantly increased compared to baseline in controls (627.74±41.81 vs 313.05±12.98 pg/ml $p<0.001$). At week 24, values continued to increase, being again significantly higher than baseline in controls (400.83±13.29 vs 313.05±12.98 pg/ml $p<0.001$).

Conclusion: Our data analysis gives us reason to conclude that there is a significant increase in the levels of the growth factor after PPM implantation and it plays a major role in fibrotic remodeling of the myocardium. We guess increase in filling pressure of the left ventricle that is followed by LA pressure load and is a prerequisite for its dilatation.

Keywords: Pacemaker; Fibrosis; CTGF; Left atrium

1. Introduction

After the invention of permanent cardiac stimulation in 1958 by Dr. Rune Elmqvist, a new era in the treatment of bradycardia patients began [1]. In recent decades, the dual-chamber pacemaker has become the gold standard for treating high-degree atrioventricular block [2]. Advances in modern medicine have led to an increase in the average lifespan of patients with heart diseases, causing a rise in the implantation of electronic devices [3]. Despite the incredible benefits of overcoming conduction disorders, undeniable evidence has accumulated in recent years of negative effects of permanent right ventricular apical stimulation [4]. Follow-up of patients with implanted pacemakers has shown that induced asynchronous ventricular contraction results in ineffective LV emptying and functional mitral regurgitation [5].

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This results in a 10% drop in left ventricular ejection fraction in most patients as early as the first year after implantation [6].

These data raise the issue of searching for alternative pacing sites in order to approach the physiological path of myocardial depolarization [7]. In recent years, the benefits of His bundle (HB) as well as left branch bundle area (LBBA) pacing have been proven. At present, however, apical right ventricular stimulation still remains the main method used [2].

Over the past decade, a number of researchers have been investigating the pathophysiological mechanisms underlying cardiac remodeling after pacemaker implantation and their results suggest a multifactorial process [8]. A common principle in the development of myocardial contractility disorder is remodeling of the extracellular matrix at the expense of enhanced replacement interstitial fibrosis [9]. There is activation of a number of signaling molecules leading to increased collagen deposition in the interstitium, the expression of which is contractile dysfunction [10].

The above data gave us the reason to conduct the present study, the aim of which was to examine the cytokines responsible for activation of the fibrotic process in patients after PPM implantation with apical right ventricular stimulation. We studied the level dynamics of CTGF (one of the main signaling molecules involved in the profibrotic cascade), and sought a relationship with the echocardiographic parameters reflecting the function of the left atrium.

2. Material and Methods

2.1. Study design

The study was conducted at the Cardiology Department of the Virgin Mary Hospital, Burgas, Bulgaria for the period March, 2019 - August, 2021. Participants were included after approval of the Research Ethics Committees at the Medical University of Varna 82/28.03.2019 and Virgin Mary Hospital, Burgas 502/21.03.2019 and in compliance with the requirements of the Helsinki Declaration (The World Medical Association Declaration of Helsinki, 2008). Participants over 18 years of age were included after prior explanation and signing an informed consent.

Two groups were formed, patients and controls. The selection of study participants was based on clearly stated Inclusion and Exclusion Criteria (see below).

The study design involved equalization of demographic and clinical characteristics of patients and controls in order to minimize selection errors and provide objective comparison [11]. This contributed to the credibility of conclusions and established cause and effect relationships. The control group was created to be similar to the patient group in terms of sex, age and comorbidities.

For the purpose of the study, CTGF levels in peripheral venous blood taken from a cubital vein were studied in each participant. Transthoracic echocardiography was performed on the day after PPM in order to avoid the effect of atrioventricular asynchrony on left ventricular pump parameters.

In the patient group, the indicator was determined thrice: immediately before PPM implantation (baseline or visit 1 - V1), at 12 (visit 2 - V2) and 24 (visit 3 - V3) weeks after implantation. In the control group, the same indicator was examined thrice: at baseline (visit 1 - V1), at 12 (visit 2 - V2) and 24 (visit 3 - V3) weeks after selection for the study. Blood was centrifuged and resulting plasma was frozen and stored according to the requirements of the applied tests. In the control group, an ECG and echocardiography clinical examination was performed during selection for inclusion in the study. At follow-up visits, blood was taken to assess fibrosis score, and participants were also questioned about new complaints and illnesses.

Indication for implantation in patients included in the study was presence of complete atrioventricular block. After signing informed consent, they were implanted with DDDR pacemakers according to the requirements described in the EHRA expert consensus for the procedure [2]. This ensured sustained apical right ventricular pacing over 80% in all participants and was verified by telemetry at each follow-up visit.

For the purposes of the study, all participants underwent transthoracic echocardiography on the day after implantation to assess LV pump parameters and determine the indexed left atrial volume, as well as to rule out structural heart diseases according to current recommendations [12]. Left atrial volume was used as an indirect marker to assess left ventricular end-diastolic pressure and impact of right ventricular apical pacing on hemodynamics [13]. The obtained values were normalized to the patients' body surface area and then subjected to statistical processing. All used methods

of echocardiographic measurements adhered to the current recommendations for evaluation of cardiac chambers described in the European Association of Cardiovascular Imaging [12].

2.2. Study population

For the purposes of the study we screened 144 patients and selected 45 (25 men, 20 women, aged 72.18 ± 1.35 years) without known cardiovascular disease (except arterial hypertension and conduction disorder, indication for the procedure). 99 patients were excluded from the study due to presence of exclusion criteria (see below).

We formed the control group after screening 102 patients and selecting 46 (24 men, 22 women, aged 71.96 ± 1.29 years) by applying inclusion and exclusion criteria. They were included in the study after signing informed consent. There had no anamnestic and ECG data of existing rhythm-conduction pathologies. 39 of them had arterial hypertension as a concomitant disease, which was optimally controlled with medications.

For the purposes of the study, it was of utmost importance to minimize the influence of fibrotic response by medications and comorbidities in selected patients and controls. For this reason, both groups were treated with pharmaceuticals with no current evidence of direct influence on the renin-angiotensin aldosterone system (RAAS). After selection, the participants were treated with one or a combination of the following medications: dihydropyridine calcium antagonist - amlodipine, thiazide diuretic - hydrochlorothiazide and, if necessary, a centrally acting medication - methyldopa was added in doses necessary to achieve blood pressure control.

2.2.1. Inclusion criteria for patients

- Presence of complete atrioventricular block as an indication for dual-chamber pacemaker implantation.
- Acceptable comorbidity: moderate arterial hypertension under good medical control.
- Absence of exclusion criteria.

2.2.2. Inclusion criteria for controls

- Absence of anamnestic or ECG data for rhythm-conduction pathology.
- Acceptable comorbidity: moderate arterial hypertension under good medical control.
- Absence of exclusion criteria.

2.2.3. Exclusion criteria

Presence of cardiovascular diseases: ischemic heart disease (acute coronary syndrome; experienced myocardial infarction, regardless of age; coronary revascularization PCI/CABG; stable angina pectoris); heart failure with depressed pump function; uncontrolled hypertension; inflammatory heart diseases (myocarditis, pericarditis, infectious endocarditis); congenital heart defects; clinically significant acquired valvular defects; cardiomyopathies; thromboembolic events.

Presence of other diseases: kidney or liver failure; diseases of the central nervous system; inflammatory and/or infectious diseases in the last three months; neoplastic or autoimmune diseases; nutritional lung diseases; diseases of the endocrine system; operative intervention in the last three months;

Pregnancy, systemic intake of NSAIDs and antithrombotic medications and mineralocorticoid antagonists.

2.3. Collection and testing of blood samples

Blood samples were collected from the cubital vein (left or right) with a vacutainer system. Collected venous blood samples were centrifuged for 15 min at 3500 rpm. The serum was frozen at

−20 C°, and after 3 to 4 weeks transferred to storage at −80 C°. Patients meeting the inclusion criteria had 3 blood samples drawn as follows: at baseline before pacemaker implantation, at 12 and 24 weeks after the implantation. Same protocol was followed for controls.

2.4. Laboratory procedures

Factors studied: CTGF levels were determined by the ELISA method [14] using MyBioSource OmniKine kits for Human CTGF Sandwich ELISA with a detection range of 63 pg/ml to 4000 pg/ml. Before analysis, serum samples were diluted according to manufacturer's instructions. The study procedure is described above.

2.5. Statistical analysis

All analyses were conducted using STATISTICA 13.3.0, StatSoft Inc, USA.

Continuous variables were expressed as mean ± standard error of the mean (SEM) and categorical variables were expressed as percentage of the total group. Two-tailed Student's t-test for independent samples was used to compare quantitative variables measured in controls and patients. Values $p<0.05$ were adopted for statistically significant.

3. Results

There was no statistical difference ($p>0.05$) between patients and controls in terms of number, average age, sex and BMI (table 1).

According to the study design, the patient and control groups showed no significant differences in terms of comorbidities ($p>0.05$) and antihypertensive therapy ($p>0.05$) (table 2).

From the conducted transthoracic echocardiography, no significant difference was found between LV end-diastolic (EDV) and the end-systolic volume (ESV), as well as in ejection fraction (EF%) in patients and controls. Also, the values measured were within the normal range accepted by the European Association of Cardiovascular Imaging [12]. Left atrial end-systolic volume was measured from the apical four-chamber position using the Simpson method and was indexed according to subject's body surface area. For definition of reduced ejection fraction, a value below 50% was taken as recommended by the ESC [15]. We adopted >34 ml/m^2 as definition value for increased left atrial volume, as recommended in the same reference.

Table 1 Demographic characteristics of patients and controls

	Patients	**Controls**	**P values**
Number of participants	45	46	>0.05
Average age (years)	72.18 ± 1.35	71.96 ± 1.29	>0.05
Men/women	25/20	24/22	>0.05
BMI (kg/m^2)	27.45 ± 0.64	26.51 ± 0.49	>0.05

Table 2 Clinical characteristics of patients and controls

	Number of patients (%)	**Number of controls (%)**	**P value**
Comorbidities			
Hypertensive disease	39 (86.66 %)	37 (80.43%)	>0.05
Antihypertensive therapy			
Dopegit	23 (51.11%)	24 (52.17%)	>0.05
Amlodipine	35 (77.78%)	33 (71.74%)	>0.05
Hydrochlorothiazide	35 (77.78%)	35 (76.09%)	>0.05

3.1.1. Abnormalities in CTGF levels

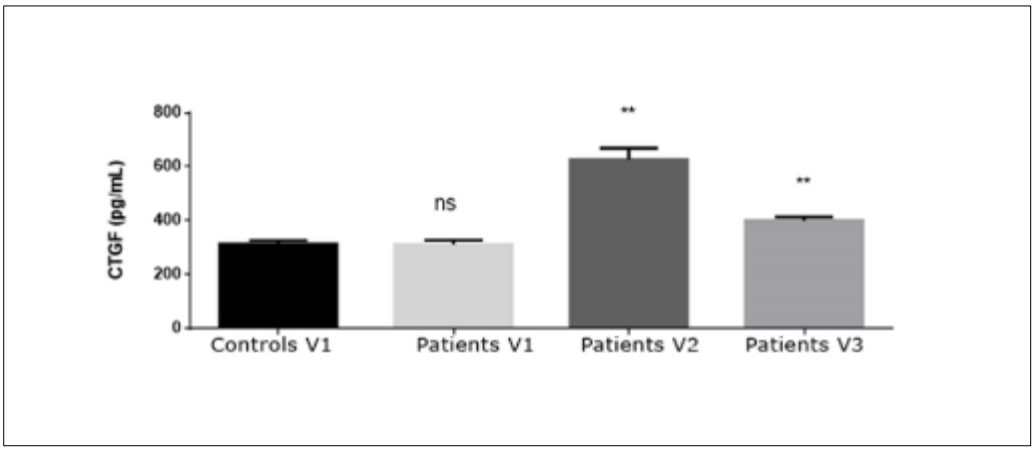

Figure 1 CTGF values at baseline (Patients V1), at 12 weeks (Patients V2) and at 24 weeks (Patients - V3) in patients compared to baseline in controls (Controls V1). (*- p<0.05; ** - p<0.001; ns- statistically insignificant difference

Figure 1 shows that there was no significant difference in baseline CTGF values between patients and controls (V1 patients vs. V1 controls; 312.66±15.25 vs 313.05±12.98 p>0.05). At 12 weeks after PPM implantation in patients (V2 patients), we observed significantly increased values compared to baseline in controls (see Figure 1) (627.74±41.81 vs 313.05±12.98 pg/ml p<0.001). At week 24 post-implantation, the increase in the monitored parameter in patients (V3 patients) was still statistically significantly higher compared to baseline in controls (V1 controls) (see Figure 1), (400.83±13.29 vs 313.05±12.98 pg/ml p<0.001).

There were no significant changes in plasma levels of the indicator during the follow-up period in controls. No significant difference was found between the values from the second and third visits compared to baseline (311.02±11.47 vs 313.05±12.98 pg/ml; 324.74±14.20 vs 313.05±12.98 pg/ml p>0.05). There was also no significant difference in the levels of the third and second follow-up visits (324.74±14.20 vs 311.02±11.47 pg/ml, p>0.05) (see Figure 2).

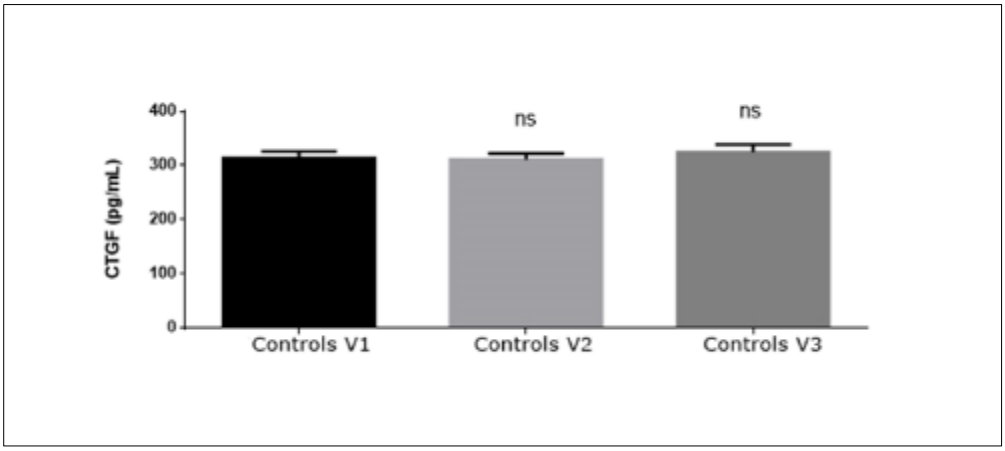

Figure 2 CTGF levels in controls: at baseline (controls V1), at 12 weeks (controls V2) and at 24 weeks (controls V3). ns- statistically insignificant difference

3.1.2. Abnormalities in echocardiographic parameters

Figure 3 shows that baseline LAVI values were significantly higher than controls (20.03±0.71 vs. 16.69±2.23 ml/m2, p<0.001). At the follow-up visits, respectively on the 6th, 12th and 24th weeks, the values were significantly increased compared to controls (Figure 3) (25.48±1.33 vs. 16.69±2.23 ml/m2, p<0.001; 27.42±1.34 vs. 16.69±2.23 ml/m2, p<0.001; 27.05±1.33 vs. 16.69±2.23 ml/m2, p<0.001).

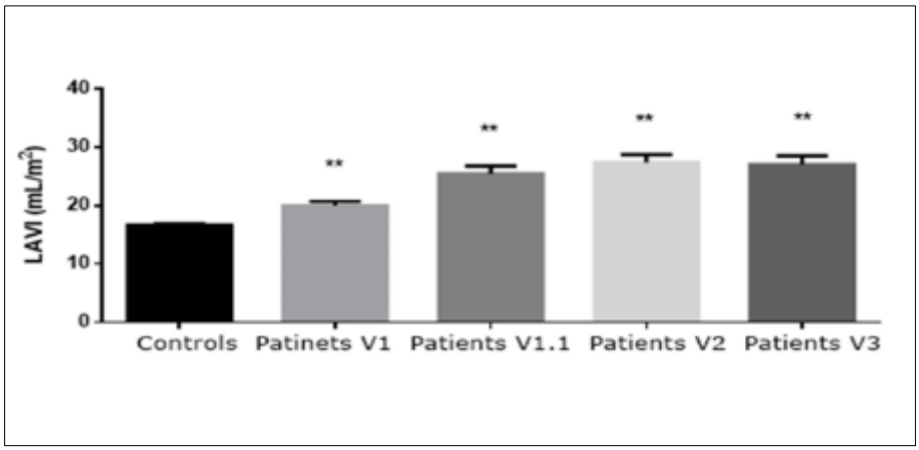

Figure 3 Comparison of LAVI values at baseline (V1 patients), at 6 weeks (V1.1 patients), at 12 weeks (V2 patients) and at 24 weeks (V3 patients) with those in controls (Controls). (*- $p<0.05$; ** - $p<0.001$; ns- statistically insignificant difference)

4. Discussion

CCN proteins are a family of extracellular matrix (ECM)-associated proteins involved in intercellular signaling. The acronym CCN is derived from the first three members of the group, namely: CYR61 - cysteine-rich angiogenic protein 61 or CCN1, CTGF - connective tissue growth factor or CCN2, and NOV - nephroblastoma overexpressed or CCN3. CTGF, also known as CCN2, is a matrix protein that is expressed in cardiac fibroblasts and cardiomyocytes. It is involved in the regulation of a number of processes such as: cell adhesion, structural remodeling and production of matrix proteins in the ECM, angiogenesis, cell proliferation and differentiation. The presence of mechanical stressors, a number of cytokines, neurohumoral factors, as well as growth factors, including TGF-β1, regulate CTGF gene expression. Experimental animal model research of myocardial infarction has shown that both TGF-β1 and CTGF are expressed in cardiac fibroblasts [16]. This leads to increased fibronectin and type I and type III collagen levels in the ECM of an ongoing myocardial infarction. The high CTGF levels are associated with marked cardiac fibrosis, both in humans and animal models [17]. CTGF activation leads to fibroblast proliferation and increased collagen deposition in the ECM and has a synergistic effect with TGF-β1. As it became clear, CTGF takes an active part in the activation of fibrotic response in myocardial pathologies [18].

The results of our study showed an extremely early increase in CTGF levels in patients, as early as 12 weeks after pacemaker implantation (Figure 1), and it was statistically significant compared to baseline values in controls. At the 24 weeks follow-up, CTGF levels in patients (Figure 1) remained significantly elevated compared to baseline in controls. These changes were possibly due to the activation of a cytokine response provoked by apical right ventricular stimulation and asynchronous ventricular contraction. To minimize the possibility that additional factors affect the fibrotic system in the heart muscle, only those without serious concomitant cardiovascular pathologies were included in our follow-up group.

In recent decades, various techniques have been developed for accurate diagnosis of myocardial dysfunction and its etiology. However, echocardiography is considered the gold standard for assessing cardiac chamber size and function due to its ease of application, sensitivity, and specificity [19].

As heart failure progresses, there is an increase in LV and LA filling pressures, which leads to their remodeling. LA size and volume can be determined echocardiographically, and indexing the measurements to body surface area is recommended [20]. This enables comparison of the results between different individuals with an accepted upper normal limit of 34 ml/m^2. LAVI (left atrial volume index) has been shown to be an independent predictor of atrial fibrillation, stroke, heart failure, and cardiovascular death [21].

The left atrium is extremely sensitive to volume and pressure loading as a result of increased left ventricular filling pressure [22]. Also, disruption of LA function leads to remodeling of pulmonary vessels, as well as to a decrease in their compliance, which leads to right ventricular pressure load and pulmonary hypertension. Therefore, early detection of LV dysfunction plays an important role in the evaluation of a number of heart diseases [23].

In our study, a significant LAVI increase was observed in patients compared to baseline as early as 6 weeks post-implantation (Figure 3). This confirms the extremely early onset of LV pressure changes as a result of provoked asynchronous cardiac contraction, which also leads to an increase in its volume. Similar results were reported when comparing a group of patients with apical right ventricular stimulation and those with HBP (His Bundle Pacing), where cardiac contraction occurred as a result of electrical activation of the native conduction system. 24 weeks post-implantation, there was a significant LAVI increase in the apical right ventricular pacing group and a decrease in the HBP group [24].

Non-physiological activation of the myocardium causes systolic asynchrony, disrupts its relaxation, reduces the degree of longitudinal shortening and circular twisting [25]. These changes affect left atrium function and structure, which can lead to development of arrhythmias and other complications [26].

Also, right ventricular apical stimulation induces left ventricular diastolic dysfunction and increases left atrial afterload [27]. This process increases atrial pressure and contributes to left atrial enlargement in the early postoperative period, as shown by the results of the study by Xie et al.

An important finding in our study is that LV volume continues to increase during the follow-up period, and we can assume that this results from the induced asynchronous cardiac contraction by apical right ventricular stimulation (Figure 3). Data from MOST (MOde Selection Trial), reported as early as 10 years ago, strongly associated right ventricular pacing with new-onset AF [28]. This confirms the statement that apical left ventricular stimulation leads to left atrium pressure loading, followed by its dilatation, as can be seen from our results.

5. Conclusion

Our data analysis gives us reason to conclude that there is a significant increase in the levels of the growth factor after PPM implantation and it plays a major role in fibrotic remodeling of the myocardium. The hemodynamic consequences of the provoked asynchronous contraction are development of left ventricular diastolic dysfunction and an increase in its filling pressure. It is followed by LA pressure load and is a prerequisite for its dilatation.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] Nicholls M. Pioneers in cardiology: Rune Elmqvist, MD. Circulation 2007;5:109e11

[2] Burri H, Starck C, Auricchio A et al. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). Europace. 2021; doi: 10.1093/europace/euaa367.

[3] Phyo AZZ, Freak-Poli R, Craig H et al. Quality of life and mortality in the general population: a systematic review and meta-analysis. BMC Public Health. 2020;20(1):1596

[4] Xu H, Li J, Bao Z, et al., Early Change in Global Longitudinal Strain is an Independent Predictor of Left Ventricular Adverse Remodelling in Patients With Ventricular Apical Pacing. Heart, Lung and Circulation. 2019; 28(12): 1780-1787. https://doi.org/10.1016/j.hlc.2018.11.004

[5] Bansal R, Parakh N, Gupta A et al. Incidence and predictors of pacemaker-induced cardiomyopathy with comparison between apical and non-apical right ventricular pacing sites. J Interv Card Electrophysiol.2019; **56,:**63–70 https://doi.org/10.1007/s10840-019-00602-2

[6] Khurshid S, Epstein AE, Verdino RJ, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. Heart Rhythm. 2014; 11:1619–1625. http://dx.doi.org/10.1016/j.hrthm.2014.05.040

[7] Zanon F, Ellenbogen K, Dandamudi G,et al. Permanent His-bundle pacing: a systematic literature review and meta-analysis. Europace. 2018; 20:1819–1826. https://doi.org/10.1093/europace/euy058.

[8] Algazzar AS, Katta AA, Ahmed KS, Elkenany NM, Ibrahim MA. Changes in Left Ventricular Global and Regional Longitudinal Strain During Right Ventricular Pacing. Cardiol Res. 2016 Feb;7(1):17-24. doi: 10.14740/cr454w. Epub 2016 Feb 20. PMID: 28197264; PMCID: PMC5295530.

[9] Tokuda K, Kai H, Kuwahara F, Yasukawa H, Tahara N, Kudo H, Takemiya K, Koga M, Yamamoto T, Imaizumi T. Pressure-independent effects of angiotensin II on hypertensive myocardial fibrosis. Hypertension. 2004 Feb;43(2):499-503. doi: 10.1161/01.HYP.0000111831.50834.93. Epub 2003 Dec 29. PMID: 14699000.

[10] Creemers EE, Pinto YM. Molecular mechanisms that control inter- stitial fibrosis in the pressure-overloaded heart. Cardiovasc Res. 2011; 89:265–272. DOI:10.1093/cvr/cvq308 .

[11] Kang M, Ragan BG, Park JH. Issues in outcomes research: an overview of randomization techniques for clinical trials. J Athl Train. 2008;43(2):215-221

[12] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for car- diac chamber quantification by echocardiography in adults: an up- date from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16(3):233–270

[13] Nagueh S, Smiseth O, Appleton C, Byrd B, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

[14] Engvall E, Perlmann P. Enzyme-linked immunosorbent assay (ELISA). Quantitative assay of immunoglobulin G. Immunochemistry. 1971;8:871-874.

[15] Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20(11):1505–1535

[16] Sklepkiewicz P, Shiomi T, Kaur R, Sun J, Kwon S, Mercer B, Bodine P, Schermuly RT, George I, Schulze PC, et al. (2018). Loss of Secreted Frizzled-Related Protein-1 Leads to Deterioration of Cardiac Function in Mice and Plays a Role in Human Cardiomyopathy. Circ Heart Fail 8: 362–372

[17] Koshman YE, Patel N, Chu M, Iyengar R, Kim T, Ersahin C, et al. Regulation of Connective Tissue Growth Factor Gene Expression and Fibrosis in Human Heart Failure. J. Card. Fail. 2013;19:283-294

[18] [PMC free article] [PubMed] Zou ML, Chen ZH, Teng YY, Liu SY, Jia Y, Zhang KW, Sun ZL, Wu JJ, Yuan ZD, Feng Y, Li X, Xu RS, Yuan FL. The Smad Dependent TGF-β and BMP Signaling Pathway in Bone Remodeling and Therapies. Front Mol Biosci. 2021 May 5;8:593310

[19] Ponikowski P, Voors AA, Anker SD, Good H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group. (2016). 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 37:2129–2200

[20] Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. EACVI Scientific Documents Committee. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18(12):1301-1310.

[21] Di Tullio MR, Qian M, Thompson JLP, Labovitz AJ, Mann DL, Sacco RL, et al. Left atrial volume and cardiovascular outcomes in systolic heart failure: effect of antithrombotic treatment. ESC Heart Fail. 2018;5(5):800-808.

[22] Dernellis JM, Stefanadis CI, Zacharoulis AA, Toutouzas PK. Left atrial mechanical adaptation to long-standing hemodynamic loads based on pressure-volume relations. Am J Cardiol. 1998;81:1138-1143

[23] Sugimoto T, Bandera F, Generati G, Alfonzetti E, Bussadori C, Guazzi M. Left Atrial function dynamics during exercise in heart failure: pathophysiological implications on the right heart and exercise ventilation inefficiency. JACC Cardiovasc Imaging 2017;10:1253–64

[24] Michalik J, Dabrowska-Kugacka A, Kosmalska K, Moroz R, Kot A, Lewicka E, et al. Hemodynamic Effects of Permanent His Bundle Pacing Compared to Right Ventricular Pacing Assessed by Two-Dimensional Speckle-

Tracking Echocardiography. International Journal of Environmental Research and Public Health. 2021;18(21):11721

[25] Tops LF, Suffoletto MS, Bleeker GB, Boersma E, van der Wall EE, Gorcsan J 3rd, Schalij MJ. (2007). Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. J Am Coll Cardiol 50: 1180–1188) (Tops LF, Schalij MJ, Bax JJ. (2009). The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol 54: 764–776.

[26] Matsuoka K, Nishino M, Kato H, Egami Y, Shutta R, Yamaguchi H, et al. Right ventricular apical pacing impairs left ventricular twist as well as synchrony: Acute effects of right ventricular apical pacing. J Am Soc Echocardiogr. 2009;22:914–919; quiz 970–971

[27] XIE J, FANG F, ZHANG Q, SANDERSON J, YAT-SUN CHAN J, LAM Y, YU C. Acute Effects of Right Ventricular Apical Pacing on Left Atrial Remodeling and Function. Pacing and Clinical Electrophysiology, 2012a; 35(7): 856–862. doi:10.1111/j.1540-8159.2012.03403.x

[28] Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA. (2003). Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107: 2932–2937