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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Gender-related differences in coronary venous anatomy: a potential basis for various response to cardiac resynchronisation therapy

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Abstract

Background and aim: We hypothesised that small differences in the anatomy of the coronary venous tree might be one of the factors responsible for the differences in the response for cardiac resynchronisation depending on a patient's gender.

Methods: Cardiac computed tomography scans with retrospective gating were performed on 315 subjects (aged 58.3 ± 11.6 years; 117 women) according to the clinical criteria. The standard protocol for coronary arteries was used during scanning. Additional reconstructions that were focused on the coronary veins during post processing were used to analyse the data. Gender-related anatomical variants were identified.

Results: The average of 3.6 ± 1.4 veins per case were visualised. The posterolateral vein was visualised more frequently in men than in women ($p < 0.05$). Eight variants were identified as being more frequent — they were found in 237 out of 315 cases (75.24%). Those variants occurred in 95 (81.19%) of the women and in 142 (71.72%) of the men, $p = 0.080$. Six variants occurred more frequently in women; however, the differences were not significant.

Conclusions: In women a more frequent presence of favourable coronary vein variants in the target area for cardiac resynchronisation can be seen. Anatomical findings may help to explain why women more frequently respond to cardiac resynchronisation therapy compared to men.

Key words: computed tomography, coronary veins, cardiac resynchronisation therapy, female gender

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INTRODUCTION

Cardiac resynchronisation therapy (CRT) is a technique for the treatment of advanced heart failure (HF) in which the implantation of a left ventricle (LV) lead along with right ventricle and atrial leads (where applicable) is needed [1]. The anatomy of the coronary venous system can be crucial for the optimal implantation of an LV lead [2–5]. This anatomy has been described many times for different techniques in living patients and in post-mortem studies [6–8]. A great deal of anatomical variability has also been well documented. Anatomical variability starts during embryonic development. The coronary sinus is created from the sinus venous segment of the embryonic heart. After about the fourth week of creation, two sinus horns can be visible. During the subsequent few weeks the left sinus horn transforms into the coronary sinus and the vein of Marshall; the right sinus horn will be part of the atrium [9]. It is important to mention that the Thebesian valve is an embryological remnant of the right sinoatrial valve, guarding the coronary sinus (CS) ostium, and sometimes it can create problems during CS cannulation [10].

About 30% of patients do not respond properly despite seemingly proper CRT implantation — those patients are called non-responders, in contrast to responders or super-responders [11]. The results of some studies on CRT have confirmed that women can obtain greater benefit from resynchronisation as compared to men, but other studies have reached opposite

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Table 1. Characteristics of subjects included in the study divided into groups according to gender

	Women (n = 117)	Men (n = 198)	p
Age [years]	60.16 ± 1.20	57.17 ± 11.78	0.0283
Weight [kg]	72.94 ± 12.37	88.31 ± 16.78	0.0000
Heart rhythm [bpm]	59.82 ± 7.39	62.76 ± 11.58	0.0316
Systolic pressure [mm Hg]	127.83 ± 11.62	127.59 ± 12.07	0.8667
Diabetes	15.38%	16.16%	0.8558
Arterial hypertension	44.45%	45.95%	0.4347
Haemodynamic parameters			
LVEF [%]	62.6 ± 11.8	59.6 ± 11.2	0.032
LVEDV [mL]	143.1 ± 53.8	150.4 ± 44.1	0.216
LVESD [mL]	56.1 ± 46.3	60.6 ± 30.6	0.338
Stroke volume [mL]	84.7 ± 22.2	88.1 ± 19.1	0.194
Cardiac output [L/min]	5.1 ± 1.6	5.4 ± 1.5	0.070
Myocardial mass [g]	134.4 ± 48.8	138.4 ± 37.9	0.547

Student t-test used; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end diastolic volume; LVESD — left ventricular end systolic volume

conclusions. This information was also highlighted in the latest 2013 European Society of Cardiology guidelines on cardiac pacing and CRT [12]. In most research this information is taken from a uni-/multivariate analysis; however, there is no explanation as to why women are responders for CRT more often than men [13]. Some researchers believe that female patients in the population of MADIT-CRT benefit more from CRT compared to male patients but not because of a higher likelihood of being able to find lateral or posterior veins [14].

We hypothesised that differences in the anatomy of the coronary venous tree may be one of the element responsible for the differences in the response to therapy. It is possible that, due to anatomical features, placing the LV lead in the venous tree could be performed more effectively in women. There are some imaging techniques that can visualise the anatomy of the coronary venous system in live subjects [15]. Multi-slice computed tomography (MSCT) appears to be the most accurate and is probably the most frequently used imaging technique for venous anatomy evaluation [16–19].

The purpose of the study was to assess the anatomical variants of the coronary veins and to compare the anatomy of coronary venous system between men and women.

METHODS

Patients (n = 315) aged 58.3 ± 11.6 years with suspicion of coronary artery disease by a referring cardiologist, without qualification for CRT, were included in the study. Patients were divided into two groups according to gender: 117 women, aged 60.2 ± 11.2 years, and 198 men, aged 57.2 ± 11.8 years. Characteristics of subjects included in the study divided into groups according to gender are presented in Table 1.

Exclusion criteria were: the presence of atrial fibrillation, frequent cardiac extrasystoles, renal insufficiency (serum creatinine > 1.2 mg/dL), hyperthyreosis, any known allergy to iodine contrast agents, and a previously implanted pacemaker with unipolar leads. In each case, written informed consent was obtained according to clinical indications. The local Ethics Committee approved the study protocol.

Multi-slice computed tomography was carried out by using an Aquilion 64 scanner (Toshiba, Japan). Retrospective scanning gated by electrocardiogram (ECG) was performed with 64 slices, each 0.5 mm thick. The patient must hold in their breath for about 8 s during the examination, and it was checked before to adjust the CT scanner parameters. The helical pitch of the scanner was 12.8 and the rotation time was 0.4 s (typical values). The tube voltage was adjusted to the patient's body mass index. A region of interest marker in the descending aorta was placed and the triggering started at 180 HU. About 80–110 mL of non-ionic iodine contrast agent was given during the scan with an average rate of 5 mL/s. In selected patients, where heart rate was too high, metoprolol IV was given if not contraindicated. Final reconstructions of digital data on Vitrea 2 workstations (Vital Images, USA) were executed. Ten image series were created and connected to create three-dimensional volume rendering images. All data were evaluated by experienced MSCT researchers. The best RR phase was always confirmed on Multi-Planar Reformatting images.

All data were evaluated by experienced MSCT researchers with more than 300 venograms evaluated each and more than eight years' experience in cardiac MSCT.

We introduced systematic nomenclature of the coronary venous system variants to support the relations and contacts

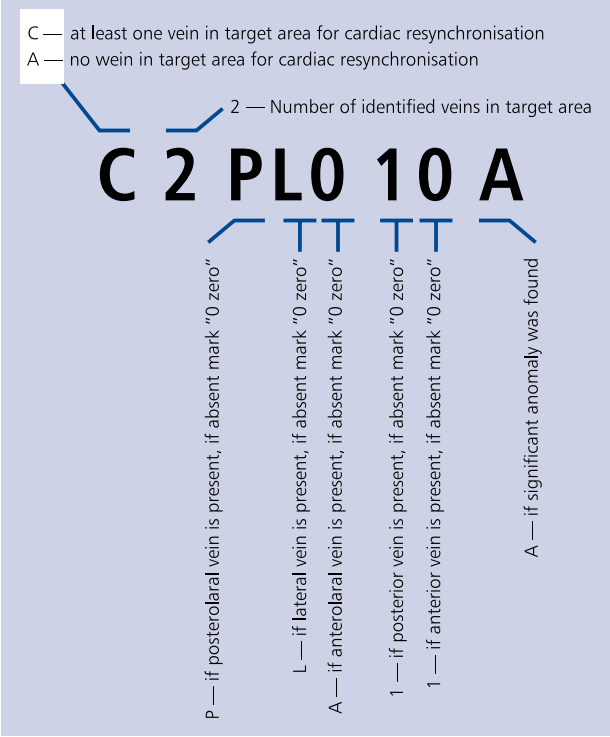

Figure 1. Nomenclature used for naming the coronary venous system variants

between radiologists, cardiologists, and surgeons. It consists of seven signs (digits or letters) that can facilitate working with many variants. The nomenclature was created based on the anatomy that is used for cardiac resynchronisation and is presented in Figure 1. As a cutoff for the "most frequent variants" a 7.5% frequency of occurrence was recognised.

Statistical analysis

Continuous data are presented as mean values and corresponding standard deviations. For the statistical comparison of the number of veins and their measurements the Student t-test was used. For the statistical comparison of coronary vein variants the χ^2 test was used; the Yates correction for χ^2 was used in selected cases, where the expected cell frequency was below or equal to five. As statistically significant $p < 0.05$ was recognised. All calculations were performed using the Polish version of Statistica (StatSoft part of Dell Software).

RESULTS

Measurements

Average coronary size ostium for the examined population was 12.9 ± 5.7 mm; for the female population it was 13.8 ± 5.9 mm, and for males it was 12.2 ± 5.4 mm. The difference was not statistically significant ($p = 0.147$). We also examined the angle of entrance of CS to the right atrium. For the general population it was 98.9 ± 11.7°. This angle for women was 100.6 ± 11.8° and for men was 97.7 ± 11.6° ($p = 0.147$; not statistically significant).

Occurrence of veins

An examples of the typical venous anatomy and coronary venous system in cardiac CT along with the scheme is presented in Figures 2 and 3. CS was visualised in all participants. The same situation took place in the middle cardiac vein, which was visualised in all included subjects. The average 3.6 ± 1.4 of the remaining veins per case were visualised — it was 3.6 ± 1.3 veins in women and 3.7 ± 1.5 in men ($p = 0.595$). A comparison of the occurrence of the five main coronary veins between women and men is presented in Table 2. The only significant difference was found in the posterolateral vein, which occurred more frequently in men ($p < 0.05$). The anterolateral and lateral veins were visualised more frequently in women; however, the differences were not statistically significant.

Frequent variants

The most frequent variant overall (C3PLA11), as presented in Figure 4, was found in 14.6% of all subjects (in 17.1% women and in 13.1% men, $p = 0.336$). The most frequent variant in women was C3PLA11 and in men was C3PLA10 — both suitable for LV lead implantation.

Eight variants identified as "more frequent" in the examined population are presented in Table 3. They were found in 237 out of 315 cases (75.2%). A trend for more frequent occurrence of those variants in women (81.2%) was observed, as compared to men (71.7%, $p = 0.08$). Among the participants, at least one vein was present in the target area for cardiac resynchronisation (variants C10L011, C10L001, and C11P0001). Two variants with at least three visualised veins were almost equally observed in men and women (C3PLA11, C3PLA00). Six variants tend to be more frequent in women. Variant C10L011 was statistically more frequent in women and variant C20LA11 in men. In Figure 5 the prevalence of anatomical variants according to the gender is presented.

Rare variants

We also analysed cases in which no vein(s) were visualised in the target area for cardiac resynchronisation (variant A000011). We found three (0.9%) cases in which optimal implantation of an LV lead appeared almost impossible.

DISCUSSION

Non-responders, responders, or super responders for CRT occurred both in men and women. Some cardiac imaging modalities can improve patients' outcome and predict their response to therapy. Echocardiography can measure mechanical dyssynchrony; however, its utilisation is still limited [20]. In most of the cases non-optimal qualification for CRT may cause the lack of positive CRT response (non-responders group).

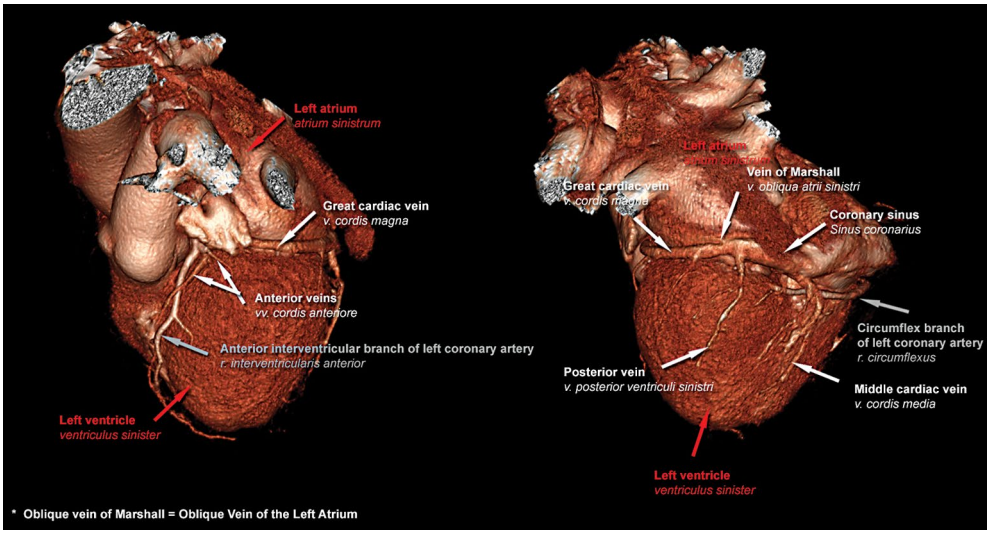

Figure 2. Typical anatomy of coronary venous system variants. English and Latin names are attached

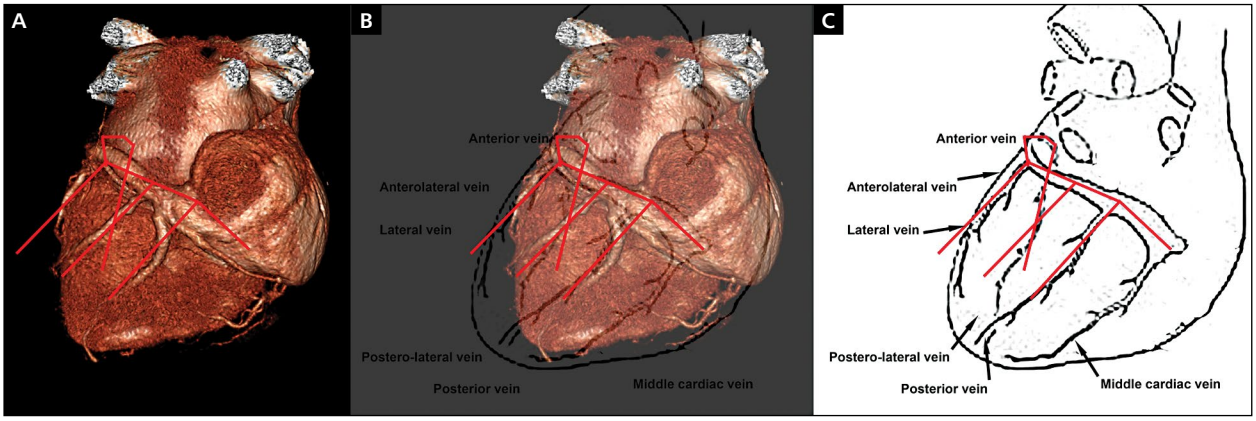

Figure 3. Example of the coronary venous system (variant C3PLA11) — multi-slice computed tomography three-dimensional volume rendering image (**A**), the scheme and superimposition of both images (**B**); **C.** Scheme of coronary venous system

Table 2. Occurrence of main coronary veins in men and women

	Women (n = 117)		Men (n = 198)		P (χ^2)
	Cases	Percentage	Cases	Percentage	
Anterior vein	65	55.5	98	49.5	0.2982
Anterolateral vein	85	72.6	125	63.1	0.0833
Lateral vein	100	85.5	167	84.3	0.7884
Posterolateral vein	38	32.4	102	51.5	0.0010
Posterior vein	103	88.0	167	84.3	0.3657

Test χ^2 used

Factors such as narrow QRS (below 120 ms) and QRS without left bundle branch block (LBBB) morphology are the most easily recognisable in CRT failure [12]. In 2012 Park et al. [21] tried to identify responders for CRT. In a univariate analysis, women with a non-ischaemic aetiology, baseline QRS duration, LBBB, and LV end diastolic volume predicted the

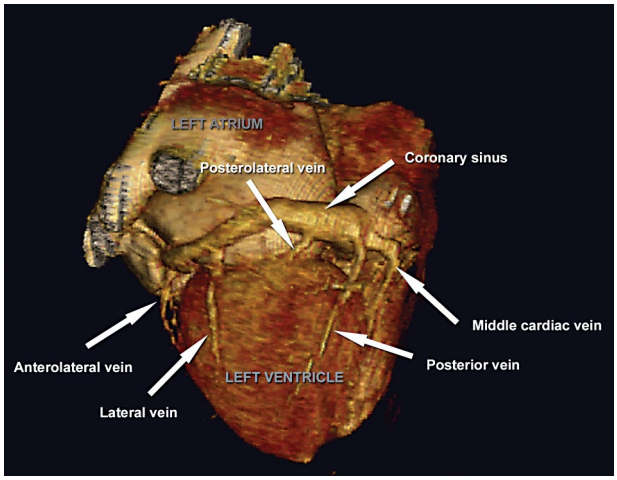

Figure 4. The most frequent variant overall (C3PLA11)

response for CRT. Meanwhile, the authors found that sex was rejected from independent predictors after correction for the LV volume.

Other studies documented that gender matters — women seemed to contribute to a positive response to CRT [22–24]. Actually, we did not find an explanation for this phenomenon in the literature on the subject.

In 2011 we described the anatomical variants of the coronary venous system [19]. In this research we confirmed a high degree of anatomical variability in the cardiac vein — this was also corroborated by Malagò et al. [17] and Chan et al. [15]. The coronary venous anatomy is also changing during different clinical situations. It was documented in two earlier publications of our team [25, 26]. In advanced coronary artery disease when coronary artery bypass graft implantation is needed, the number of coronary veins is significantly ($p < 0.001$) higher — 5.3, as compared to the situation without changes in coronaries — 3.1. We found a similar situation if we create ejection fraction-dependent analysis. The average number of visible coronary veins was 3.44 in the patients with HF and 2.72 in patients with a normal ejection fraction ($p = 0.0246$). A statistically higher number of veins in patients with HF and advanced coronary artery disease may suggest an association between a failing heart and cardiac venous anatomy retention.

Based on our previous research and literature of the subject, we hypothesised that gender might influence the coronary venous system, and in an indirect way we tried to explain why women are more likely to be responders for CRT. The results that we obtained in this paper after performing an analysis of 315 CT images may explain that the complex anatomy that is evaluated as variants can be slightly more favourable in the occurrence of coronary target veins (lateral, posterolateral, and anterolateral) for women. However, we have to remember that the population included in the pre-

Table 3. Anatomical variants of the coronary veins compared according to gender. Nomenclature of variants based on Figure 1.

Variant*	Posterior vein	Posterolateral vein	Lateral vein	Anterolateral vein	Anterior vein	Women		Men		p
						Cases	Percentage	Cases	Percentage	
C3PLA11	P	P	P	P	P	20	17.1	26	13.1	0.3359
C2PL001	N/P	P	P	N/P	P	16	13.6	23	11.6	0.5921
C1OL011	P	N/P	P	N/P	P	14	11.9	5	2.5	0.0010
C3PLA00	N/P	P	P	P	P	9	7.7	28	14.4	0.0858
C2PL010	P	P	P	N/P	P	18	15.4	19	9.6	0.1231
C1OL001	N/P	N/P	P	N/P	P	9	7.7	13	6.6	0.7043
C1P0001	N/P	P	N/P	N/P	P	7	5.9	7	3.5	0.3085
C20LA11	P	N/P	P	P	P	2	1.7	21	10.6	0.0065

Test χ^2 used; P — vein is present; N/P — vein is not present

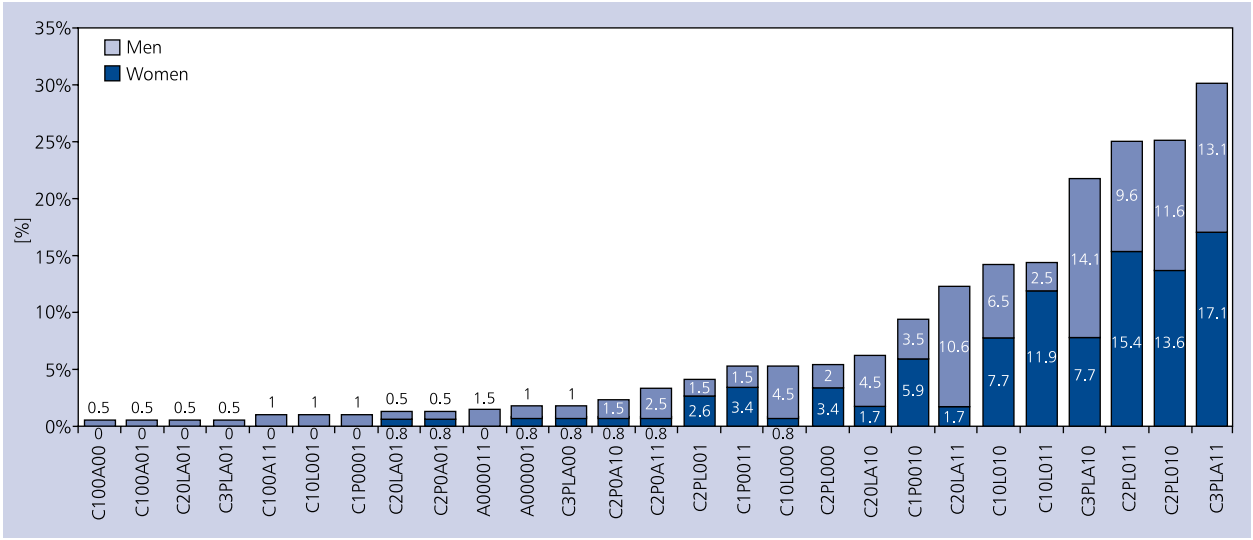

Figure 5. Prevalence of anatomical variants according to gender

sented work is not a target population for CRT, so the results should not be directly converted as explanation non-response for CRT. Most of the differences in anatomy are not statistically significant; however, eight variants that may be favourable for CRT (where veins in the target area occurred) were observed more frequently in women (81.2%) than in men (72.72%); $p = 0.080$ (a statistical trend was observed).

Our paper appears to be the first in which an analysis of the coronary veins and their variants in cardiac CT was performed taking into account the gender of the patients.

A different technique and data were used by Kawata et al. [27]. The authors analysed 223 patients who were undergoing CRT and analysed the LV lead positioning and LV lead position threshold. Intra-operational venography showed a lack of or a small size of the veins in the vicinity of the lateral and posterolateral veins in 10.8% of men and in 26.3% of women. Despite using different visualisation methods, the results in the vicinity of the posterolateral vein are not fully consistent — we observed that the posterolateral vein occurred more often in men. This is particular result is in the opposite to our main thesis. We did not observe such results in the vicinity of the lateral vein; however, we have to remember that venography and chest X-ray generate different images than the CT used in this study.

On the other hand, Kawata et al. [27] analysed the differences in patients with HF who were undergoing CRT. Our population of patients did not have CRT indications at the time that MSCT was performed, and therefore it is difficult to compare the results. Kawata et al. [27] concluded that women had anatomical disadvantages for LV lead placement and also a higher LV threshold; however, this is in contrast to the fact that women had better outcomes during follow-up after CRT.

The possibility of visualisation of coronary venous system in cardiac CT was documented; the quality of visualisation is usually optimal for clinical evaluation. However, there are some issues that should influence incorporation of this technique into clinical practice. First, the dose of X-ray radiation during coronary artery CT is significant. During this examination, iodinated contrast agent volume is also necessary. If we look at patients qualified for CRT — those patients had HF recognised, which is often connected with renal problems (higher level of creatinine). With the exception of some of the latest generation CT scanners, in previous generation scanners the heart rhythm of the examined patients should be stable below 65/min — sometimes it needed intra venous beta-blocker administration, which is contraindicated in patients with HF. We believe that this method of visualisation, despite many advantages, will never be routinely used in cardiac resynchronisation of patients. However, in selected cases, e.g. where CT was performed before CRT, it is worth trying to create some additional reconstruction to visualise coronary veins. In our opinion, CT can be recommend also if the first attempt at CS cannulation was a failure.

Limitations of the study

The aim of the study was to evaluate differences in the anatomy of the coronary venous system of men and women in a population of patients scheduled for coronary CT examination because of suspicion of coronary heart disease and not HF, which is the main indication for CRT. We did not evaluate lead location and clinical outcomes between men and women.

CONCLUSIONS

In women a more frequent presence of favourable coronary vein variants in the target area for cardiac resynchronisation

can be seen. Anatomical findings may help to explain why women more frequently respond to CRT compared to men; however, more research is necessary.

Conflict of interest: *none declared*

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Różnice zależne od płci w układzie żylnym serca — potencjalne wytłumaczenie dla różnic w odpowiedzi na terapię resynchronizującą

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Streszczenie

Wstęp i cel: Na podstawie piśmiennictwa stwierdzono, że małe różnice w anatomii układu żylnego serca mogą być jednym z czynników odpowiedzialnych za odpowiedź na terapię resynchronizującą w zależności od płci.

Metody: U 315 pacjentów (wiek 58,3 ± 11,6 roku; 117 kobiet) wykonano tomografię komputerową serca przy użyciu retrospektywnego bramkowania elektrokardiograficznego. Użyto standardowego protokołu do obrazowania tętnic wieńcowych. Ponadto wykonano dodatkowe rekonstrukcje układu żylnego. Zidentyfikowano różne warianty układu żylnego serca zależne od płci.

Wyniki: Zobrazowano średnio 3,6 ± 1,4 żyły serca na pacjenta. Żyła tylno-boczna była widoczna częściej u mężczyzn niż u kobiet ($p < 0,05$). Osiem wariantów systemu żylnego serca zostało uznanych za najczęstsze — zidentyfikowano je u 237 z 315 włączonych do badania osób (75,24%). Warianty te znaleziono u 95 (81,19%) kobiet i 142 (71,72%) mężczyzn ($p = 0,080$). Sześć wariantów pojawiło się częściej u kobiet, jednak różnice nie były istotne statystyczne.

Wnioski: W badaniu potwierdzono obecność bardziej sprzyjającej anatomii układu żylnego serca w rejonie docelowym dla resynchronizacji serca. Te anatomiczne znaleziska mogą pomóc wyjaśnić częstszą odpowiedź na terapię resynchronizującą u kobiet.

Słowa kluczowe: tomografia komputerowa, żyły wieńcowe, terapia resynchronizująca serca, płeć żeńska

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