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Fontan Circulation over Time

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The unique, unphysiological Fontan circulation is associated with an impaired functional status of the patients that is suggested to deteriorate over time. Unfortunately, previous studies did not integrate both pulmonary and cardiac determinants of functional status. In addition, a comparison with the natural decrease in exercise capacity in healthy subjects (in both children and adults) is lacking. This single-center study aims to investigate the functional status in a cohort of Fontan patients in relation to time since Fontan completion and to identify its determinants, including cardiac characteristics and pulmonary characteristics. Eighty-five consecutive Fontan patients ≥10 years who performed adequate cardiopulmonary exercise testing (respiratory exchange ratio >1.01) were included. Mean time since Fontan completion was 15 ± 9 years (range 2 to 37 years). New York Heart Association functional class was I in 36 patients (42%), II in 41 patients (48%), and III in 8 patients (9%). Peak oxygen uptake during exercise (VO_2 index) was 25.7 ± 7.9 ml/min/m^2 (58 ± 14% of predicted). New York Heart Association functional class and peak VO_2 index both correlated with time since the Fontan operation; however, peak VO_2 as percentage of predicted ($VO_2(pred)$) did not. In multivariate analyses, peak $VO_2(pred)$ was independently associated with maximum heart rate, oxygen pulse at peak exercise, and forced expiratory volume in 1 second ($R^2 = 0.579$) but not with cardiac output in rest. In conclusion, the present data suggest that functional status in Fontan patients is impaired already shortly after Fontan completion, whereas its subsequent deterioration seems to follow the natural decline of aging. Furthermore, functional status in Fontan patients correlates with pulmonary function and cardiac functional parameters during exercise but not with conventional cardiac measurements at rest.   © 2017 Published by Elsevier Inc. (Am J Cardiol 2017;120:461−466)

The Fontan procedure is designed for patients with a functionally univentricular heart who are not suitable for a biventricular repair. It results in the unique, unphysiological Fontan circulation, in which the systemic venous return passively flows through the pulmonary vasculature without the aid of a subpulmonary ventricle.[1,2]

With a growing cohort of Fontan survivors,[3] there has been increasing interest in the functional status of these patients. Previous studies in Fontan patients showed a decreased exercise capacity and mildly impaired New York Heart Association functional class (NYHA-FC) and suggested a progressive deterioration of functional status with age or time since the Fontan surgery.[4−6] However, the rate of functional deterioration in Fontan patients compared with healthy subjects remains unclear. Furthermore, most of the previous studies were either performed in children, hampered by relatively short follow-up durations after Fontan completion,[7] or studied heterogeneous populations comprising patients with various congenital heart diseases.[8] Finally, the functional status is believed to be related to cardiac and pulmonary function, but few studies have included both pulmonary and cardiac parameters to investigate determinants of functional status in Fontan patients.[7,9,10]

Therefore, the aim of this study was to investigate the functional status, measured by functional class and peak exercise capacity, in a cohort of children and adults with a Fontan circulation and to identify its determinants, including cardiac characteristics, pulmonary characteristics, and time since Fontan completion.

Methods

We performed a cross-sectional study among Fontan patients ≥10 years who were followed at the outpatient clinics of the Center for Congenital Heart Disease of the University Medical Center Groningen, The Netherlands. All consecutive patients who underwent cardiopulmonary exercise testing (CPET) from January 2012 to October 2013

and reached a respiratory exchange ratio (RER) ≥ 1.01 were included. This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from all study participants and/or their legally authorized representative.

Patient characteristics were collected from medical records and included gender, date of birth, cardiac anatomical diagnosis, surgical procedures performed before the Fontan operation, type and date of the Fontan procedure, and current medication use. The standard follow-up protocol for Fontan patients at our clinic currently includes 2-yearly cardiac magnetic resonance (CMR) imaging, pulmonary function test (PFT), and CPET. During these routine visits, information on height, weight, heart rate, blood pressure, and transcutaneous oxygen saturation at rest (tcO_2) was obtained. Body surface area was calculated using Haycock's formula.[11] Body mass index (BMI) was incorporated as continuous variable and classified as underweight, normal weight, or overweight according to the World Health Organization guidelines.[12] NYHA-FC was assessed according to the general definition by 2 experienced physicians. The degree of atrioventricular valve regurgitation was assessed using echocardiography. Venous blood samples were drawn from all patients during routine follow-up, and hemoglobin (Hb) was measured using mass spectrometry.

All CMR studies were performed on a 1.5 T system (Magnetom Avanto; Siemens, Erlangen, Germany). Sedation was not applied. The CMR protocol included a stack of short-axis slices from the base to the apex of the heart using cine-steady-state free precession with end-expiratory breath holding. The following scan parameters were used: slice thickness 6 mm, slice gap 4 mm, time repetition 2.7 to 3.4 ms, time echo 1.1 to 1.7 ms, flip angle 80 to 90, matrix 171 to 192, and voxel size $1.25 \times 1.25 \times 8.0$ mm, and $1.7 \times 1.7 \times 6.0$ mm. Imaging analysis was performed using commercially available software (Qmass, version 7.6.14.0; Medis Medical Imaging, Leiden, The Netherlands). End-systolic and end-diastolic phases were visually selected. The contours of the systemic and hypoplastic ventricle were manually drawn on epi- and endocardial borders from the most apical to the most basal short-axis slice. Both the volumes of the systemic and hypoplastic ventricle were included in blood volume calculations, except for patients with pulmonary atresia and intact ventricular septum. Furthermore, trabecular and papillary tissue mass was calculated using MassK semi-automatic threshold-based segmentation software and calculated as ventricular mass.[13,14] The ejection fraction and cardiac index were calculated from end-diastolic and end-systolic blood volumes, heart rate, and body surface area.

Cardiopulmonary exercise test (CPET) was performed on a stationary cycle ergometer in children and on a treadmill in adults. For children, we used a ramp protocol with an increase of 15 or 20 W per minute depending on the height.[15] For adults, a Bruce protocol or modified Bruce protocol was used. Arterial oxygen saturation was continuously monitored by transcutaneous pulse oxymetry. Oxygen uptake was measured using breath-by-breath gas analysis. The RER was calculated as the ratio between VO_2 uptake and VCO_2 production at peak exercise. Adequate performance of the

Table 1
Patient characteristics (n = 85)

Male	43 (51%)
Diagnosis	
Tricuspid atresia	33 (39%)
Double inlet left ventricle	21 (25%)
Atrioventricular septal defect / unbalanced ventricular septal defect	11 (13%)
Pulmonary atresia with intact ventricular septum	10 (12%)
Heterogeneous anomalies	6 (7%)
Hypoplastic left heart syndrome	4 (5%)
Heterotaxy	13 (15%)
Ventricular morphology	
Left dominant	68 (80%)
Right dominant	17 (20%)
Previous procedures	
Banding pulmonary artery	24 (28%)
Rashkind/atrioseptectomy	13 (15%)
Systemic-to-pulmonary shunt	37 (44%)
Partial cavopulmonary shunt	50 (59%)
Type of Fontan procedure	
Total cavopulmonary connection with lateral tunnel	44 (52%)
Total cavopulmonary connection with extracardiac conduit	22 (26%)
Atriopulmonary connection	15 (17%)
Kawashima procedure	4 (5%)
Age at Fontan procedure (years)	4.5 (3.5-6.9)
Characteristics at current evaluation	
Age (years)	19.8 (14.3-26.8)
Body mass index (kg/m^2)	21.2±4.2
Negative chronotropic arrhythmic drugs	21 (25%)
Implanted pacemaker	14 (17%)
Hemoglobin (mmol/L)	9.5±1.0
Oxygen saturation in rest (%)	94 (91-96)
Moderate/severe atrioventricular valve regurgitation	11(13%)

| Functional variables	N	Mean±SD	% of predicted, mean ± SD
Peak oxygen uptake (ml/min)	85	1468±473	
Peak oxygen uptake index (ml/min/kg)	85	25.7±7.9	58±14
Ventilation / carbon dioxide elution slope	83	29.6±6.3	114±24
Maximum heart rate (beats/min)	84	157±24	87±12
Heart rate reserve (beats/min)	84	82±31	
Oxygen pulse at peak exercise (ml/beat)	84	9.8±3.1	69±15
Workload (Watt)	84	172±78	91±32
Delta oxygen saturation (%)	64	4(2-7)	
Forced vital capacity (L)	83	3.5±1.0	88±14
Forced expiratory volume in 1 second (L)	83	2.9±0.8	88±17
Residual volume as % of total lung capacity	80	24±5	
Pulmonary diffusion coefficient for carbon monoxide, corrected for hemoglobin and alveolar volume	74	1.5±0.3	84±18
End-diastolic volume index (ml/m^2)	59	76±20	
Ejection fraction (%)	59	56±7	
Cardiac index (l/min/kg)	59	3.1±0.9	
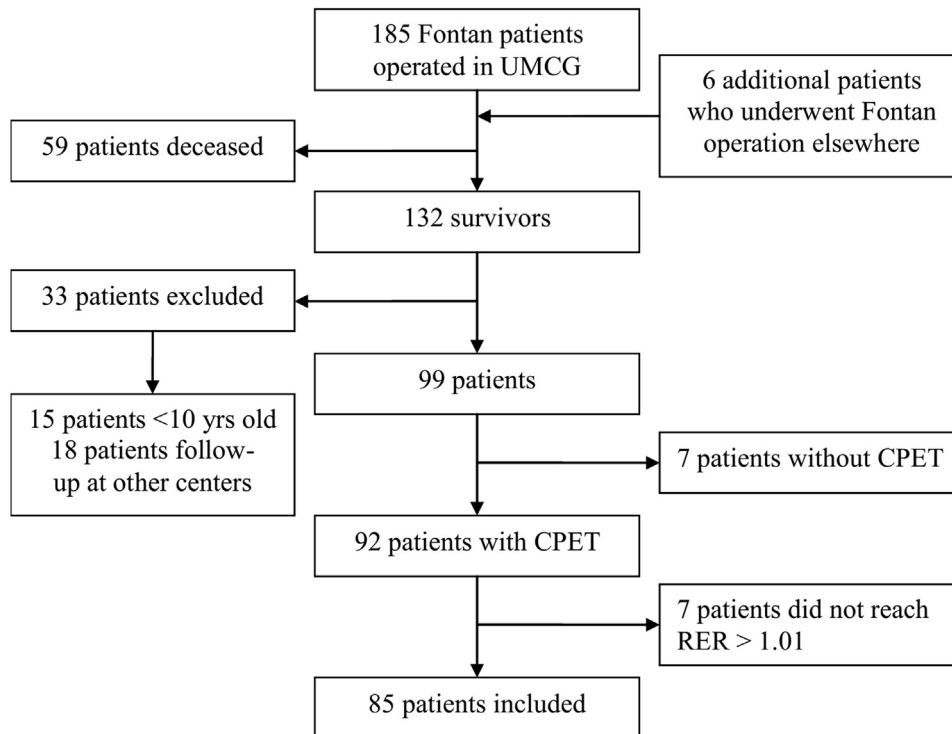
Figure 1. Flow diagram for patients included in the present study (n = 85). UMCG = University Medical Center Groningen.

CPET was defined as an RER >1.01.[16] Peak oxygen uptake was calculated as the mean of the 2 highest VO_2 measurements during exercise and indexed by body weight (peak VO_2 index). Maximal workload was reported. The peak $VO_2(pred)$ was calculated using Takken's formula for the patients <18 years and Wasserman's formula for patients ≥18 years.[17,18]

Spirometry was performed with the patient in sitting position, wearing a nose clip and using a pneumotachograph. In patients <18 years, a whole-body plethysmography was used to calculate total lung capacity and residual volume. In adults, the Helium dilution test was used. The percentage of predicted was calculated from reference data.[19−21]

Data were analyzed using SPSS for Windows (version 18; SPSS Inc., Chicago, Illinois). Continuous data were reported as mean $\pm$ SD or median (interquartile range [IQR]) and categorical data as number of patients (% of total). Concerning patient characteristics, patients who underwent a Björk modification (right atrial-to right ventricle connection) were assigned to the category "atriopulmonary connection."

Linear and logistic regression analyses were performed to identify predictors of the functional end points peak $VO_2(pred)$ and NYHA-FC (NYHA-FC I/II vs NYHA-FC III/IV). Covariates included patient characteristics and the CMR-, PFT-, and CPET-derived variables summed up in Table 1. Interaction between significant covariates and time since the Fontan completion was tested. Multivariable regression analyses were performed using a backward approach, including all independent covariates with p <0.05 in univariable regression analyses. Additional analyses included (1) regression analyses for $VO_2(pred)$ excluding

patients with pacemakers or on anti-arrhythmic drugs, (2) regression analyses for maximum workload as percentage of predicted, (3) regression analyses using O_2 pulse as percentage of predicted as covariate instead of the absolute value, (4) regression analyses for peak VO_2 index in relation to the time since Fontan surgery, and (5) regression analyses for $VO_2(pred)$ including only patients with RER >1.05. A probability value of p <0.05 was considered significant.

Results

Ninety-two patients underwent CPET in the study period, of whom 85 patients (92%) who reached an RER >1.01 were included in the present study (Figure 1). The study population comprised 36 children (42%) and 49 adults (58%). Eighty-two patients (97%) had a PFT and 59 patients (69%) had a CMR examination, within a median time window around the CPET of 5 days (IQR 0 to 31 days) and 0 days (IQR 0 to 21 days), respectively. Patients were excluded from CMR assessment because of an implanted pacemaker system (n = 14) or pacemaker leads (n = 4), severe claustrophobia (n = 2), or patient refusal (n = 6).

Patient characteristics and CPET, PFT, and CMR results are displayed in Table 1. Mean time between Fontan completion and current evaluation was 15.3 ± 8.5 years, with a minimum of 2.3 years and maximum of 37.3 years. Thirty-six patients (42%) were in NYHA-FC I, 41 patients (48%) were in NYHA-FC II, and 8 patients (9%) were in NYHA-FC III. Peak VO_2 index was 25.7 ± 7.9 ml/min/kg and peak$VO_2(pred)$ was $58 \pm 14\%$, with a minimum of 15% and a maximum of 90% of predicted.

The significant results of the univariable analyses are presented in Supplementary Table 1. The time since the
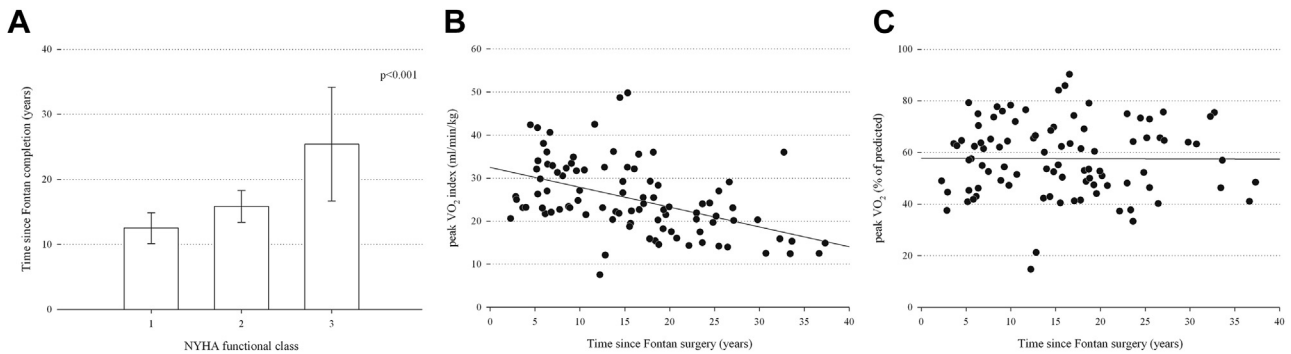
Figure 2. (A) The relation between NYHA functional class and time since Fontan completion. Error bars display the 95% confidence interval. (B) The relation between peak exercise capacity (peak VO_2 index) and time since Fontan completion. (C) The relation between peak exercise capacity (peak VO_2 as percentage of predicted) and time since Fontan completion. VO_2 = oxygen uptake.

Table 2
Multivariable regression analyses for peak oxygen uptake as % of predicted (N = 81)

	Regression coefficient (92%CI)	Standardized regression coefficient	p-value
Oxygen pulse at peak exercise	2.7(2.0-3.5)	0.588	<0.001
Maximum heart rate	0.2(0.1-0.3)	0.376	<0.001
Forced expiratory volume in 1 second % of predicted	0.3(0.2-0.5)	0.361	<0.001
	Adjusted R^2=0.579		

Fontan procedure was longer in patients in NYHA-FC III (25 ± 10 years) compared with those in NYHA-FC I (13 ± 7 years, p <0.001) and in NYHA-FC II (15 ± 8 years, p = 0.006, Figure 2). Peak VO_2 index correlated negatively with the time since Fontan completion (Figure 2 r = −0.462, p <0.001), whereas peak VO_2(pred) did not (Figure 2). The peak VO_2(pred) was 56 ± 14% in underweight patients, 59 ± 14% in patients with healthy weight, and 58 ± 13% in overweight patients (p = ns). Furthermore, neither the cardiac functional variables end-diastolic volume index, ejection fraction, and cardiac index nor the pulmonary functional variables ventilation/carbon dioxide elutionslope, delta O_2 saturation, and diffusion capacity for carbon monoxide corrected for hemoglobin and alveolar volume correlated with NYHA-FC or peak VO_2(pred).

Multivariable regression analysis to identify independent predictors for NYHA-FC was not performed because of the limited number of patients in NYHA-FC III. Multivariable analyses for peak VO_2(pred) revealed that O_2 pulse at peak exercise, maximum heart rate, and FEV1 were independent predictors for peak VO_2(pred) (Table 2, adjusted R^2 = 0.579). No interaction was found between significant covariates and time since Fontan completion.

Subsequent analyses, where we excluded patients with an implanted pacemaker or those using anti-arrhythmic drugs, did not change the contribution of heart rate in the multivariable model. Furthermore, analyses using O_2 pulse as percentage of predicted as covariate or using maximum workload as percentage of predicted as outcome variable did not change the contribution of O_2 pulse. Finally, changing the inclusion criteria to RER >1.05 excluded 14 patients but did not change the statistical results (data not shown).

Discussion

The present study described the functional status in both children and adults with a Fontan circulation and is one of the few to investigate both cardiac and pulmonary characteristics as determinants of functional status in Fontan patients. Most Fontan patients included were diagnosed with a tricuspid atresia and a minority with hypoplastic left heart syndrome, representing a West European Fontan cohort. We demonstrated that NYHA-FC and peak VO_2 index are impaired in Fontan patients and are negatively affected by the time since Fontan completion, consistent with previous findings.[4,5,22,23] Interestingly, we identified that the peak VO_2 as percentage of predicted compared with reference values did not correlate with time since Fontan completion, challenging the widely accepted idea that declining peak VO_2 index is a sign of progressive attrition of the Fontan circulation. Previous, longitudinal studies showed a progressive decrease in exercise tolerance in Fontan patients of 1.25% to 2.6% per year. However, these studies might have been biased by including only patients with ≥2 subsequent exercise tests in a nonstandardized follow-up protocol, potentially driving the decision to perform a second exercise test by a clinical suspicion of functional deterioration.[5,6] Another source of bias may be introduced by the differences in reached RER across the different studies. For example, Andersons et al[4] found a decreasing peak VO_2(pred) in a fairly younger cohort (mean age 12 years), in which it was unknown whether adequate CPET was performed (RER was not reported). In the present study, we applied an inclusion criterion of RER >1.01, which is rather low for adults but conventional in pediatric populations.[15]

Changing the inclusion to RER >1.05 did not change the statistical results.

Based on these data, one could speculate that Fontan patients have an impaired exercise capacity directly after the circulations' installment but subsequently show a rate of decrease in exercise capacity similar to healthy subjects. Conceptually thinking, restrictions in daily activities (NYHA-FC III) occur in general when the absolute peak VO_2 index falls below a certain threshold. Because patients with a Fontan circulation start off with a lower absolute peak VO_2 index directly after Fontan completion, such threshold will, thus, be reached earlier in the life of a Fontan patient than of a healthy subject (Supplementary Figure 2). Patients in NYHA-FC III had the Fontan completion for the longest time and had significantly lower peak VO_2 index compared with those in NYHA-FC I/II (Supplementary Figure 1). It is important, however, to realize that the present study is a cross-sectional study, and it obviously requires longitudinal assessments of functional status in Fontan patients to confirm this concept.

Under normal physiological circumstances, 70% to 85% of the variation in aerobic exercise capacity is explained by an increase in cardiac output as a result of increased ventricular preload, reduced afterload, increased heart rate, and increased myocardial contractility.[24] The rest of the variation is potentially related to pulmonary function and skeletal muscle and cellular characteristics.[5,10,25] In this study, we could not demonstrate an effect on BMI, either as continuous or categorical variable, on peak VO_2(pred), suggesting that BMI is not a major determinant of functional status in Fontan patients. Moreover, no correlations between cardiac index and ventricular ejection fraction at rest and functional status were found. These conventional cardiac CMR-derived measurements are known to be load dependent. In Fontan patients, the serial coupling of systemic and pulmonary circulation results in a chronically restricted ventricular preload, systemic venous congestion, and increased ventricular afterload. Apparently, the abnormal loading conditions in the Fontan circulation cause the conventional cardiac measurements to be less informative in Fontan patients than in patients with biventricular hearts. Yet, we did find O_2 pulse and maximum heart rate to be related to functional status, independent of time since the Fontan operation. Interestingly, both O_2 pulse and chronotropic impairment have previously been identified as predictors for death or transplantation in Fontan patients.[22,26] O_2 pulse (VO_2/HR) is, in the assumption that the arteriovenous oxygen difference remains relatively constant during exercise, considered a surrogate parameter for stroke volume.[18] The restricted ability to increase preload because of the absence of a subpulmonary ventricle, the degree of increased pulmonary vascular resistance, and the degree of energy loss in the Fontan circuit might affect the ability of a Fontan patient to increase stroke volume during exercise. Additional statistical analyses avoiding the mathematical relation between O_2 pulse and peak VO_2 did not change the significant contribution of O_2 pulse to the multivariable model, confirming the relation between stroke volume and exercise performance in Fontan patients. Regarding heart rate in Fontan patients, it has been suggested that increased heart rate could be harmful in Fontan patients because of decreased ventricular filling time and increased central venous pressure.[27] However, we found that higher maximal heart rate was associated with an improved exercise capacity (independent of the presence of an implanted pacemaker or the use of anti-arrhythmic drugs). Together, these data show that the ability to increase cardiac output (heart rate × stroke volume) despite the adverse, unphysiological conditions is an important determinant of functional status in Fontan patients, in contrast to the patients' cardiac output at rest.

In addition to a limited cardiac performance, exercise capacity in Fontan patients might also be affected by their impaired pulmonary function.[7,10] In the present study, impaired exercise capacity was independently associated with decreased FEV1. In Fontan patients, adverse changes in lung parenchyma because of the low, nonpulsatile pulmonary flow, respiratory muscle weakness, and restrictive thoracic cage caused by multiple thoracic operations are likely to contribute to the development of lung disease.[28,29]

The results of the present study need to be interpreted with respect to the intrinsic limitations of a cross-sectional study. The requirements for inclusion in our study, including survival up to >10 years of age and physical capability to perform a CPET, inevitably resulted in a selection bias. Furthermore, 30% of the patients did not undergo CMR analyses, which decreased the power to identify correlation between CMR parameters and functional end points. Finally, different techniques were used for CPET and PFT in children and adults. In the CPET analyses, peak VO_2 in bicycle tests might be about 10% lower than in treadmill tests.[30] However, we compared peak VO_2 results with reference values of the same tests. Thereby, we consider the overall comparison justifiable. In the PFTs, the residual volume and total lung capacity might be underestimated in the adults compared with the children, but this effect was refuted using the percentage of residual volume relative to the total lung capacity. For clinical practice, the results of the present study suggest that in Fontan patients a deterioration of the peak VO_2(pred) instead of a decrease in peak VO_2 index could timely alert the clinician for potential complications of the Fontan circulation. Diagnostics should be directed not only toward factors affecting the patients' ability to increase heart rate and stroke volume during exercise, such as rhythm and conductance disturbances, Fontan conduit obstruction, or increasing pulmonary vascular resistance, but also toward potential impairment of pulmonary function. Importantly, conventional cardiac assessment at rest does not seem to sufficiently detect cardiac causes for deterioration of functional status in a Fontan patient. Therefore, clinical evaluation of Fontan patients should include cardiac response to exercise.

Disclosures

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2017.05.005.

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