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Clinical Research

Severity Scores for Ebstein Anomaly: Credibility and Usefulness of Echocardiographic vs Magnetic Resonance Assessments of the Celermajer Index

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ABSTRACT

Background: The severity score of Ebstein anomaly (EA) that corresponds to clinical status is still under research, with the Celermajer index (Cel-ind) being one of those. The agreement between echocardiographic and cardiac magnetic resonance (CMR) assessment of Cel-ind is not known. We determined the agreement between echocardiography- and CMR-derived Cel-ind and its relationship with heart failure markers.

Methods: A total of 37 unoperated adults with EA (mean age, 43.0 ± 14.4 years) underwent echocardiography, CMR, and cardiopulmonary tests. For the Cel-ind, end-diastolic areas in echocardiography or end-diastolic volumes in CMR were used according to the following formula: Cel-ind = (right atrium + atrialized right ventricle)/(functional

RÉSUMÉ

Contexte : Les scores d'évaluation de la sévérité de la maladie d'Ebstein correspondant aux observations cliniques sont toujours à l'étude; l'indice de Celermajer fait partie de ces scores. On ne sait pas dans quelle mesure les évaluations de l'indice de Celermajer obtenues par échocardiographie et par résonance magnétique cardiaque (RMC) concordent. Nous avons donc déterminé la concordance entre l'indice de Celermajer évalué par échocardiographie et le même indice évalué par RMC, ainsi que le lien entre cet indice et les marqueurs de l'insuffisance cardiaque.

Méthodologie : Au total, 37 adultes non opérés présentant une maladie d'Ebstein (âge moyen : 43,0 ± 14,4 ans) ont été soumis à une échocardiographie, à un examen par RMC et à des épreuves car-

Ebstein anomaly (EA) is a rare, complex congenital heart defect (CHD) resulting from an impaired process of delamination of the tricuspid valve leaflets.[1,2] An apical displacement of the leaflet insertion points divides the right ventricle (RV) into 2 distorted portions: the atrialized right ventricle (aRV), which along with the anatomic right atrium (RA) constitutes the functional right atrium (fRA), and the functional right ventricle (fRV). Abnormal coaptation of the tricuspid leaflets causes a significant regurgitation with resulting enlargement of the right heart chambers. Subsequently, a leftward shift of the interventricular septum occurs, compromising the left ventricle (LV) geometry. These anatomic abnormalities impair cardiac hemodynamics and complicate quantification of the severity of the defect. A few severity classifications have been proposed over the decades based on different parameters, including the combination of right ventricular size and anatomic features of the tricuspid valve (Carpentier classification),[3] the size of the aRV,[4] the ratio of right-to-left heart volumes,[5] the ratio of right-to-left ventricular volumes, and the ratio of the apical displacement of the septal leaflet to the length of the interventricular septum.[6] However, one of the most widely known classifications is the Celermajer index (Cel-ind), which is named after its originator and in which the ratio between the fRA (consisting of anatomic RA and aRV) and the sum of the remaining chambers is calculated.[7] Although its prognostic value has been verified in pediatric cohorts, the outcomes of studies conducted on adults remain inconsistent and its usefulness questionable.

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right ventricle + left atrium + left ventricle). On the basis of this assumption, patients were classified as follows: grade 1 = Cel-ind < 0.5, grade 2 = 0.5 to 0.99, grade 3 = 1.0 to 1.49, grade 4 > 1.5. The agreement between echocardiographic and CMR was determined with the intraclass correlation coefficient or Cohen's kappa (<0.2 poor agreement; 0.2-0.4 fair agreement; 0.4-0.6 moderate agreement; 0.6-0.8 good agreement; 0.8-1.0 very good agreement).

Results: The median echoCel-ind was 0.9 (range, 0.4-2.3), and the median cmrCel-ind was 0.7 (range, 0.3-5.3). Grade 1 or 2 was found in 19 patients (51.3%) by echocardiography and in 27 patients (72.9%) by CMR. The agreement between imaging methods was only fair (kappa = 0.39, *P* = 0.002) for the 4-grade classification and moderate (intra-class correlation coefficient = 0.43; 95% confidence interval, 0.13-0.66) for Cel-ind calculation. Significant correlations between Cel-ind in CMR and cardiopulmonary parameters were found (for peak oxygen uptake: R = −0.35, *P* = 0.034; for the ventilation/carbon dioxide slope: R = 0.46, *P* = 0.005). Neither of them correlated with echocardiographic severity score.

Conclusions: The agreement between echocardiographic and CMR assessment of the Cel-ind is at most moderate; echocardiography usually overestimates, but rarely underestimates, EA severity. Cel-ind by CMR seems to be more valuable, because it is associated with heart failure markers.

diopulmonaires. Pour calculer l'indice de Celermajer, nous avons utilisé les aires en fin de diastole obtenues par échocardiographie ou les volumes en fin de diastole obtenus par RMC selon la formule suivante : indice de Celermajer = (oreillette droite + portion « auricularisée » du ventricule droit)/(ventricule droit fonctionnel + oreillette gauche + ventricule gauche). Sur la base de cette hypothèse, les patients ont été classés comme suit : grade 1 = indice de Celermajer < 0,5; grade 2 = de 0,5 à 0,99; grade 3 = de 1,0 à 1,49; grade 4 > 1,5. La concordance entre les évaluations obtenues par échocardiographie et par RMC a été déterminée au moyen d'un coefficient de corrélation intraclasse ou du kappa de Cohen (< 0,2 : faible concordance; 0,2-0,4 : concordance passable; 0,4-0,6 : concordance modérée; 0,6-0,8 : bonne concordance; 0,8-1,0 : très bonne concordance).

Résultats : L'indice de Celermajer médian obtenu par échocardiographie s'établissait à 0,9 (min.-max. : 0,4-2,3) et à 0,7 (min.-max. : 0,3-5,3) dans le cas de la RMC. Selon l'évaluation par échocardiographie et l'évaluation par RMC, 19 patients (51,3 %) et 27 patients (72,9 %), respectivement, présentaient une affection de grade 1 ou 2. La concordance entre les deux techniques d'imagerie était seulement passable (kappa = 0,39, *p* = 0,002) pour les affections de grade 4 et modérée (coefficient de corrélation intraclasse = 0,43; intervalle de confiance à 95 % : de 0,13 à 0,66) pour le calcul de l'indice de Celermajer. Des corrélations significatives entre l'indice de Celermajer obtenu par RMC et les paramètres cardiopulmonaires ont été observées (consommation maximale d'oxygène : R = -0,35, *p* = 0,034; pente ventilation/dioxyde de carbone : R = 0,46, *p* = 0,005). Aucune corrélation avec le score de sévérité obtenu par échocardiographie n'a été observée.

Conclusions : La concordance entre les indices de Celermajer obtenus par échocardiographie et par RMC est au mieux modérée; la sévérité de la maladie d'Ebstein évaluée par échocardiographie est habituellement surestimée, mais rarement sous-estimée. L'indice de Celermajer obtenu par RMC semble être plus utile, parce qu'il est associé à des marqueurs de l'insuffisance cardiaque.

The Cel-ind was originally developed in the era of echocardiography considered to be the most accurate imaging tool. However, it is clear that echocardiographic assessment of the RV remains challenging,[8] with even more controversies arising on the evaluation of distorted cardiac chambers in EA.[9] During recent decades, cardiac magnetic resonance (CMR) has emerged as a reference method for RV imaging, with the possibility of precise multidimensional analysis being particularly needed in the population with CHD population.[10-12] Currently, the evaluation of chamber size made by CMR enables a reliable volumetric calculation of the Cel-ind. However, the fact that CMR is still a technique that is both expensive and not always available leads us to conclude that the value of echocardiography should be especially appreciated in the clinical setting. In this context, we still lack knowledge on how the echocardiographic calculations are consistent with reference CMR measurements. Moreover, because the outcomes of the studies investigating the role of the Cel-ind in an adult EA population are inconsistent, we think that there is still scope for further analysis and additional data in this debate.[4-7]

Therefore, the aim of our study is 2-fold: to assess the agreement between the Cel-ind calculated by echocardiography and by CMR, and to assess the relationship between severity scores and exercise capacity among adults with EA.

Methods

A database of adult congenital heart disease obtained from the outpatient clinic of the Department of Cardiology, Poznan, Poland, identified 52 patients with EA. The diagnosis was based on echocardiographic measurement of apical displacement of the septal or posterior tricuspid leaflet exceeding 8 mm/m^2.[2] Four of these patients refused to participate in the study, 5 were excluded because of previous cardiac surgery, 5 were excluded because of implanted pacemakers, and 1 was excluded because of claustrophobia. The remaining 37 patients (23 male) formed our study group. The mean age was 43.0 ± 14.4 years (range, 18-76 years). Thirty-six patients were in sinus rhythm at the time of examination, and 1 patient presented with atrial flutter with a regular ventricular rate of 90 beats/min enabling CMR calculations. A coexisting cardiac anomaly was present in 3 patients (8.1%): 2 trivial secundum atrial septal defects, 1 mild pulmonary valvular stenosis (peak gradient of 22 mm Hg, mean gradient of 10 mm Hg). The study protocol comprised the following: physical examination, echocardiography, CMR, brain natriuretic peptide (BNP) assessment, 12-channel electrocardiogram, and cardiopulmonary exercise test.

Echocardiography was performed with a VIVID 7 GE Medical System device (Boston, MA), using a 2.5 Hz probe in 2-dimensional mode, in standard and modified views due to altered anatomy. Echocardiographic classification of EA severity, called the "Cel-ind" (echoCel-ind), was calculated as the ratio of the combined area of the RA and aRV to that of the fRV, left atrium (LA), and LV in a 4-chamber view at end diastole.[7] The values obtained were used to define 4 grades of increasing severity of EA: echo1 (echoCel-ind < 0.5); echo2 (echoCel-ind 0.5 to 0.99); echo3 (echoCel-ind 1 to 1.49); echo4 (echoCel-ind >1.5). We considered grades 1 and 2 to be a mild form of EA, whereas grades 3 and 4 were considered severe. In 2 patients (5.4%), the measurements were difficult to obtain because of extremely dilated right heart chambers, although they were eventually included in the analysis once having been accepted by 2 experienced echocardiographers who independently stated that the degree of miscalculation is presumably small and therefore could be disregarded.

CMR was performed on a 1.5 Tesla scanner (Magnetom Avanto, Siemens, Munich, Germany) with the use of a 6-element matrix coil combined with a 2-4 element spinal coil. All images were electrocardiogram gated and performed during patient breath-holds. During standard protocol for EA, among other sequences, steady-state free-precession imaging was used to assess the volume of the ventricles and atria. Standard 4-, 3-, and 2-chamber views with a stack of short-axis views and contiguous axial slices covering the heart from the RV outflow tract to the diaphragmatic surface of the RV were used. The imaging parameters were as follows: TR/TE 2 R-R intervals/27 ms, field of view 380 × 260 mm, slice thickness 8 mm without gap, and matrix size 104 × 256.

The compartments of the right heart were defined according to Yalonetsky et al.[13] A line connecting the free wall attachment of the anterior tricuspid valve leaflet and the tricuspid valve annulus (ie, the point of presumed septal leaflet attachment) was considered the border between RA and aRV. A line connecting the free wall attachment of the anterior tricuspid valve leaflet and the septal attachment of the displaced leaflet demarcated the border between aRV and fRV (Fig. 1). Apical displacement of the septal leaflet was measured in ventricular diastole in the 4-chamber view and indexed to the body surface area. The end-diastolic volume and end-systolic volume of the RA and ventricle were measured on axial planes (Fig. 1). LV and LA parameters were calculated in short-axis slices. The trabeculae and papillary muscles were included in the blood pool. All measurements were done with the use of dedicated software (QMass, Medis, Leiden, The Netherlands). The Cel-ind originally designed for echocardiographic assessment of EA severity[7] was modified in our analysis and adjusted for CMR-derived end-diastolic volumes. It was labeled cmrCel-ind and calculated as the ratio of the summed volumes of RA and aRV to that of the summed volumes of fRV, LV, and LA. The values obtained were used to define 4 grades of severity of EA: cmr1 (cmrCel-ind < 0.5); cmr2 (cmrCel-ind 0.5 to 0.99); cmr3 (cmrCel-ind 1 to 1.49); cmr4 (cmrCel-ind > 1.5). As with echocardiographic assessment, we considered grades 1 and 2 a mild form of EA, whereas grades 3 and 4 were considered severe.

The tricuspid valve regurgitant volume (mL/beat) and fraction (%) were calculated from RV stroke volume (RVSV) and phase contrast velocity mapping flow measurements of the pulmonary artery according to the following formulas:

Regurgitant volume (mL/beat) = RVSV (mL/beat) - pulmonary forward flow (mL/beat) Regurgitant fraction (%) = regurgitant volume (mL/beat) × 100/RVSV (mL/beat).

A cardiopulmonary exercise treadmill test based on the Bruce and symptom-limited protocol was performed in all patients being studied. The equipment was calibrated with a standard gas mixture before each test. Standard 12-lead electrocardiography was continuously recorded. Patients were encouraged to continue the exercise until the respiratory exchange ratio exceeded 1.0. Oxygen uptake (peak VO_2), carbon dioxide production, and minute ventilation were measured with the breath-by-breath technique using a SensorMedics, model Vmax29 (SensorMedics Corp, Yorba Linda, CA). Peak VO_2 was defined as the average oxygen uptake for the last 20 seconds of exercise and expressed as mL/kg/min, the percentage of ranges predicted for sex, age, height, and weight.[14] Impaired exercise capacity was defined as % peak VO_2 < 85% of the predicted value; values less than 60% were considered as severely impaired exercise capacity. The ventilation/carbon dioxide slope was assessed by linear regression for the whole exercise.

The serum BNP level was measured in venous blood samples taken after 15 minutes of rest, in the supine position using the Abbott AxSYM Immunoassay system (Chicago, IL). According to the current ESC guidelines, a BNP concentration exceeding 35 pg/mL was considered the threshold for probable diagnosis of chronic heart failure.[15] Functional status was assessed according to the New York Heart Association (NYHA) classification.

Statistical analysis

Data were presented as mean values with standard deviation (for a normal distribution) and median values with range (for a non-normal distribution). For variables following a Gaussian distribution, a statistical analysis was performed using the Student *t* test for unpaired samples; otherwise, the Mann−Whitney *U* test was used. Cohen's kappa was used to calculate agreement between categorical measurements of EA severity grades with the following interpretation: Kappa < 0.2 = poor agreement; Kappa > 0.2-0.4 = fair agreement; kappa 0.4-0.6 = moderate agreement; kappa 0.6-0.8 = good agreement; kappa 0.8-1.0 = very good agreement.[16] The inter-rater agreement between linear Celermajer indices calculated by echocardiography vs CMR was assessed using intra-class correlation coefficients (ICCs), and Bland−Altman plots, as well as the mean bias and the corresponding 95% limits of agreement (ie, mean bias ± 1.96 × standard deviation of the bias), were calculated. The study group was also divided into 2 subgroups: mild (grade 1+2) and severe (grade 3+4) EA. Comparison of various parameters between both subgroups was made using the chi-square test with Yates' correction or Fisher exact test. To determine the relationship between variables not following normal distribution, the Spearman rank order correlations were analyzed; otherwise, the Pearson correlation coefficients were calculated. The data were presented as a coefficient of

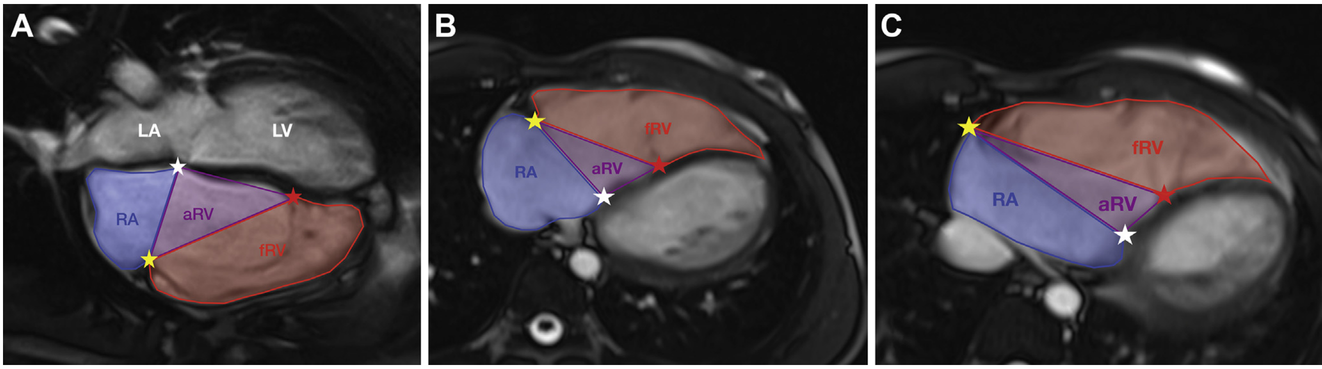

Figure 1. Contours of the compartments of the right ventricle (RV) and the right atrium (RA) on cardiac magnetic resonance (CMR) in a patient with Ebstein anomaly (EA). Celermajer index (Cel-ind) is calculated using end-diastolic volumes according to the formula (RA + aRV)/(fRV + LV + LA). (**A**) End-diastolic contours in 4-chamber view. (**B, C**) End-diastolic contours in axial views. **White asterisk**, presumed septal leaflet attachment of the tricuspid valve; **yellow asterisk**, free wall attachment of the anterior leaflet; **red asterisk**, real attachment of the displaced septal leaflet. aRV, atrialized right ventricle; fRV, functional right ventricle; LA, left atrium; LV, left ventricle.

correlation (R). To determine interobserver and intraobserver variability for each imaging method, the measurements of the Cel-ind were repeated by the same observer and remeasured by the second rater in 10 randomly chosen patients after an interval of at least 3 months. The variability was presented as ICC, 95% confidence interval, and absolute mean difference. $P < 0.05$ was considered statistically significant. Calculations were performed using STATISTICA v.10 statistical software (Dell Statistica [data analysis software system], version 10 [2016]; Dell Inc, Aliso Viejo, CA).

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the

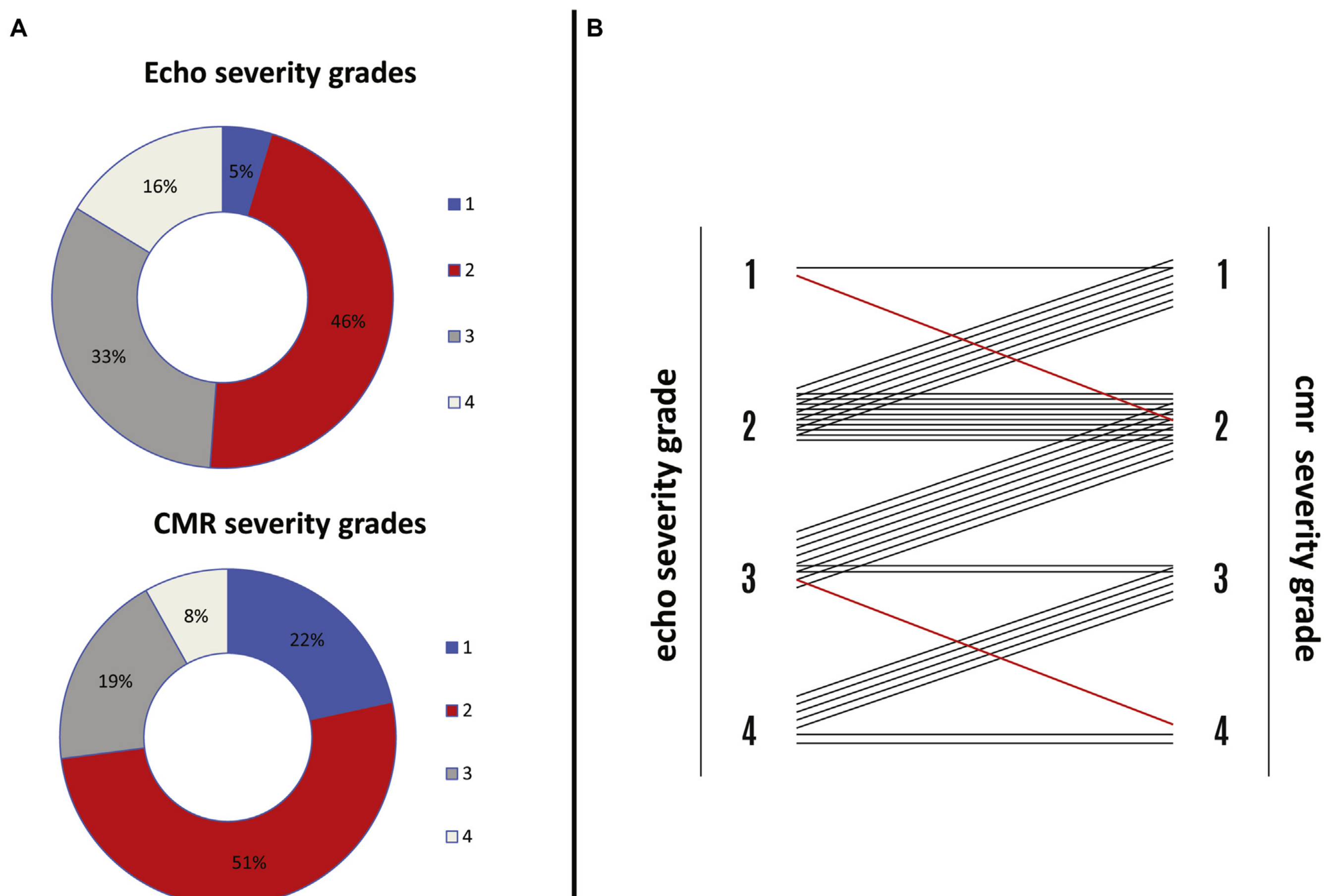

Figure 2. Distribution of 4 grades of EA severity classification. (**A**) Based on the imaging modality (**B**), an illustrative presentation of differences in grade assessment according to the method used (each line depicts 1 patient; **red lines** depict patients with echocardiography underestimating severity score).

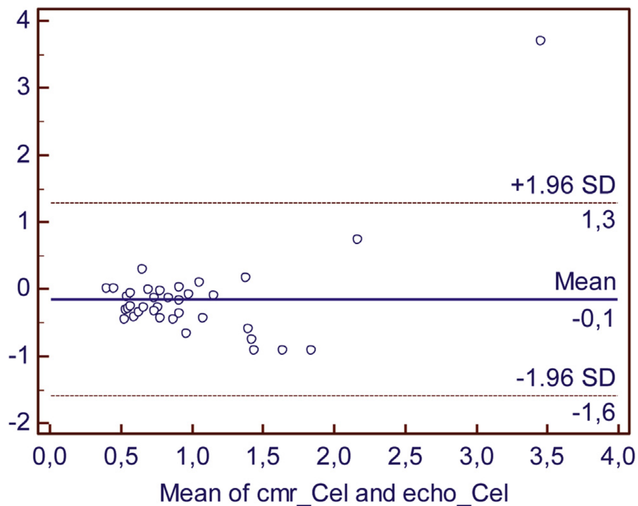

Figure 3. Cel-ind calculated by echocardiography vs CMR. Bland–Altman analysis with the difference between both measurements on the x-axis and the average of both measurements on the y-axis.

local human research committee. All of the individuals who were enrolled gave written informed consent to participate in the study.

Results

Agreement of the Cel-ind assessed by echocardiography and CMR

The median Cel-ind calculated by echocardiography was 0.9 (range, 0.4-2.3), whereas CMR-derived median was 0.7 (range, 0.3-5.3). Figure 2A shows the distribution of 4 severity grades according to the imaging method introduced. Echocardiographic evaluation revealed that 18 patients (48.7%) had a severe form of EA, whereas CMR evaluation assigned only 10 individuals (27.0%) to this subgroup. As presented in Figure 2B, in the majority of patients (n = 20, 54.1%) echocardiographic severity scores were higher than those calculated in CMR. Conversely, the severity scores reported by CMR were higher than the echocardiographic ones in only 2 cases.

The agreement of EA severity grades between these 2 imaging modalities was calculated as fair (kappa coefficient = 0.39, $P = 0.002$). The agreement of the Cel-ind, which is a linear parameter, was calculated as moderate (ICC, 0.43; 95% confidence interval [CI], 0.13-0.66) (Fig. 3).

Intraobserver and interobserver variability of the echocardiographic Cel-ind was as follows: ICC = 0.86, 95% CI, 0.74-0.93, mean difference 0.1, $P < .0001$; ICC = 0.74, 95% CI, 0.49-0.88, mean difference 0.12, $P < .0001$), respectively. Intraobserver and interobserver variability of CMR calculations was as follows: ICC = 0.91, 95% CI, 0.83-0.97, mean difference 0.1, $P < .0001$; ICC = 0.88, 95% CI, 0.80-0.93, mean difference 0.13, $P < .0001$), respectively.

Clinical value of the Cel-ind

A subjective assessment of exercise capacity was good in all patients; 32 patients (86.5%) were classified as NYHA I, and the rest were classified as NYHA II. Nevertheless, cardiopulmonary test revealed that normal exercise capacity (>85% of the predicted values) was present only in 5 (13.5%) of them and severely impaired (<60% of the predicted values) in 14 (37.8%). The mean BNP level was 51.8 (4.5-155) pg/mL, and in 27 patients (73.0%), it exceeded the threshold of 35 pg/mL suggestive of heart failure.[15]

Our analysis showed statistically significant correlations of Cel-ind with cardiopulmonary parameters, only if the former was calculated by CMR (for peak VO_2: $R = -0.35$, $P = 0.034$, ventilation/VO_2 slope: $R = 0.46$, $P = 0.005$). The level of BNP was the only parameter that correlated significantly with both echocardiographic and CMR assessment of Cel-ind (Table 1).

Table 2 depicts the values for the heart failure markers in patients with mild and severe forms of EA determined by different imaging methods. Our study showed no significant differences in the cardiopulmonary parameters among patients with mild EA compared with those with a severe form of the defect. This finding applied to both echocardiographic and CMR-based assessment of the severity grade. Nonetheless, the level of BNP was proven to be higher in patients with severe EA, regardless of the imaging method used for evaluating EA severity.

The fraction of tricuspid regurgitation was found to be significantly greater in patients with a severe form of EA compared to mild EA for both imaging modalities (for CMR: 40.0% [6.1-65.6] vs. 67.7% [12.7-87.5], $P = .005$; for echocardiography: 38.6% [6.1-65.6] vs. 42.5% [11.3-87.5], $P = .03$). We also demonstrated a positive correlation between the TR fraction and Cel-ind measured by both modalities (Table 1).

Discussion

Agreement of EA severity scores

EA severity scores assessed by echocardiography and CMR were in fair agreement. In the majority of patients, the score differed by at least 1 grade, with echocardiography overestimating this parameter in more than one-half of the study group. In only 2 patients was the severity score assessed by echocardiography lower than that calculated by CMR. Both patients had extremely enlarged hearts, and echocardiographic evaluation was hampered by inadequate acoustic windows. Analysis based on linear values of the Cel-ind showed a moderate agreement between the 2 imaging methods.

Such a discrepancy in the assessment of EA anatomic severity score may be primarily attributed to the limitations of echocardiographic visualization. A planimetric evaluation of the RV in the apical view is mostly confined to its inflow tract. Thus, for many decades a misleading assumption held true, namely, that the aRV was believed to encroach on the fRV, thus significantly reducing the size of the former.[2,7] With the CMR technique, however, researchers have recently proved that in the majority of EA population, the volume of RV exceeds normal ranges with the outflow tract significantly contributing to this enlargement.[4,5,17] This dilatation can be explained mostly by a rotational displacement of the septal and posterior tricuspid leaflets, resulting in very eccentric

Table 1. Correlation of heart failure markers with Celermajer indices measured by echocardiography and CMR in the population with EA

	cmr-Cel ind		echo-Cel ind	
peak VO_2 (mL/kg/min)	R = −0.35	***P* = 0.034**	R = −0.25	*P* = 0.107
% peak VO_2	R = −0.18	***P* = 0.299**	R = −0.08	*P* = 0.621
VE/VCO_2 slope	R = 0.46	***P* = 0.005**	R = 0.20	*P* = 0.213
BNP (pg/mL)	R = 0.51	***P* = 0.002**	R = 0.56	***P* < 0.0001**
TR fraction (%)	R = 0.55	***P* < 0.001**	R = 0.58	***P* < 0.001**
TV displ (mm/m^2)	R = 0.29	*P* = 0.114	R = 0.31	*P* = 00.091

Bold indicates *P* values of statistical significance.

BNP, brain natriuretic peptide; cmr-Cel ind, Celermajer index of EA based on end-diastolic volumes of the cardiac chambers calculated in CMR; EA, Ebstein anomaly; echo-Cel ind, Celermajer index of EA based on end-diastolic areas of the cardiac chambers calculated in echocardiography; peak VO_2, peak oxygen consumption; R, correlation coefficient; %peak VO_2, percentage of predicted peak VO_2 values; TR, tricuspid regurgitation; TV displ, displacement of insertion point of the septal tricuspid leaflet measured in CMR; VE/VCO_2, ventilation/carbon dioxide.

regurgitant jets directed toward the infundibular part of RV, which is simply not appreciated in 4-chamber echocardiographic views.[18,19] Therefore, the Cel-ind calculated in echocardiography would be higher than the CMR assessment, because the former imaging method tends to underestimate the size of fRV.

Clinical value of the EA severity score

In our study, the Cel-ind calculated in CMR showed a significant correlation with the most relevant cardiopulmonary parameters, including peak VO_2 and ventilation/carbon dioxide slope. However, in the study by Tobler et al.[4] (27 patients of a similar age range), the relationship between peak VO_2 and the severity score assessed in CMR reached only borderline statistical significance. There was no association between the Cel-ind and cardiopulmonary parameters found in a study by Hösch et al.[5] performed in 25 individuals, but this group was more heterogeneous in age, including pediatric patients. However, it should be emphasized that the way of delineating borders between the right heart chambers and calculating the volumes varied between the studies: The researchers implemented methodology in accordance with Yalonetsky et al.[13] or Fratz et al.[17] This also could contribute to the inconsistency in study outcomes and should be subject to further investigation. We chose the method introduced by Yalonetsky et al. as potentially less prone to intra-rater and interrater variability because of the simplistic way of tracing the tricuspid valve leaflets. Indeed, our calculations were shown to be in good agreement.

Our study did not reveal any relationship between the echocardiography-derived Cel-ind and cardiopulmonary parameters. Data published on echocardiographic evaluation and cardiopulmonary tests are scarce. In a prospective study of 51 patients, it was shown that individuals characterized by a higher EA severity score in echocardiographic assessment had worse peak oxygen consumption (peak $VO_2 < 60\%$) and worse outcomes.[20] However, in contrast to our study, a significant number of the patients enrolled had interatrial shunts, which might have affected the cardiac diameters and, thus, the EA severity score evaluation. On the other hand, our previous study demonstrated a tendency toward deterioration of heart failure seen in patients with a higher echocardiographic severity score. However, the difference did not reach a level of significance and the population was half the size of that in the current study.[21]

Our analysis demonstrated both echocardiographic and CMR assessment of the Cel-ind to be related with the BNP level. The prognostic value of this peptide has already been proven in a population with CHDs[22] with higher values seen in patients with left-sided (in contrast to right-sided) heart failure.[23] In patients with EA, the interpretation of the BNP level is obscured by the complex pathomechanism of heart failure mostly based on the ventricle−ventricle interaction.[2,5,24,25] The analysis by Rydman et al.[6] did not demonstrate any impact of serum BNP concentration on the composite endpoint (ventricular tachycardia/heart failure hospital admission/heart transplant/death).

A detailed analysis of the clinical usefulness of EA severity scores in adult patients reveals considerable discrepancies between the results published so far. This can be partially attributed to the inconsistency in methodology implemented for CMR calculations in the studies.[13,17] Moreover, the severity score by Celermajer et al.[7] was originally introduced and investigated in the pediatric population. Thus, its prognostic value in children might not reflect the hemodynamic conditions present in adults with EA. Indeed, a prospective analysis performed on a relatively large group of adults did not demonstrate any impact of the CMR-derived Cel-ind on the prognosis of these patients.

Table 2. Comparison of various clinical and anatomic parameters between subgroups with mild (grade 1 and 2) and severe (grade 3 and 4) form of EA assessed by different imaging modalities

		CMR			Echocardiography		
	Study group n = 37	Mild EA n = 27	Severe EA n = 10	*P*	Mild EA n = 19	Severe EA n = 18	*P*
peak VO_2 mL/kg/min	23.6 ± 4.5	24.5 ± 4.6	21.9 ± 3.6	0.12	24.1 ± 4.8	22.6 ± 4.2	0.29
% peak VO_2	65.5 (43.0-114.0)	66.0 (43-114)	65.0 (44-86)	0.72	65.5 ± 10.5	71.5 ± 20.3	0.24
VE/VCO_2 slope	32.9 (28-47.5)	31.8 (28-47.5)	34.5 (29-40)	0.12	31.9 (28.0-38.0)	32.9 (28.0-47.5)	0.32
BNP pg/mL	51.8 (4.5-155)	39.2 (4.5-155)	73.2 (21.4-116)	**0.02**	27.9 (4.5-155.0)	77.9 (14.9-134.9)	**0.004**
TR fraction (%)	41.2 (6.1-87.5)	40.0 (6.1-65.6)	67.7 (12.7-87.5)	**0.005**	38.6 (6.1-65.6)	42.5 (11.3-87.5)	**0.03**
TV displ mm/m^2	17.8 ± 6.3	16.7 ± 6.2	20.3 ± 6.1	0.16	15.9 ± 6.2	19.6 ± 6.1	0.11

Bold indicates *P* values of statistical significance.

BNP, brain natriuretic peptide; EA, Ebstein anomaly; peak VO_2, peak oxygen consumption; %peak VO_2, percentage of predicted peak VO_2 values; TR, tricuspid regurgitation; TV displ, displacement of insertion point of the septal tricuspid leaflet measured in CMR; VE/VCO2 slope, ventilation/carbon dioxide slope.

A single parameter that will account for the complex mechanokinetic interdependency, but which simultaneously remains simple and accessible in everyday practice, is yet to be established. In patients with EA, the pathomechanism of heart failure is not solely related to chamber volumes.[24,25] A leftward shift of the interventricular septum (as a consequence of the enlarged aRV) affects the geometry and function of the LV. In this context, some researchers speculate that this unfavorable ventricle-ventricle transverse interplay could be best characterized by indices that calculate right-to-left heart volumes.[5,6] Meanwhile, the Cel-ind describes the complex mechanokinetics of EA by merging left heart chambers with the functional part of the RV, thus setting them "in opposition" to the fRA. This, in fact, combines both longitudinal (LA to LV) and transversal (LV to RV) interactions, which may not be the most accurate description of hemodynamics in EA. The impact of tricuspid regurgitation on the mechanokinetics should also be appreciated, because rotationally displaced tricuspid orifice results in dilatation of the right ventricular outflow tract and RA. Not surprisingly, our study shows a significantly greater tricuspid regurgitation in patients with a more advanced form of EA. Finally, we speculate that the pathomechanism of heart failure in patients with EA is not confined to hemodynamic conditions, but is also affected by intrinsic myocardial issues at the cellular level. Some researchers advocate that EA should be considered a cardiomyopathy, because failure of delamination of the tricuspid leaflets is believed to be a defect of the embryological development of myocardium per se.[19] Myocardial fibrosis seen in EA heart specimens or detected in CMR assessment seems to support this thesis.[26-28] Perhaps it would be of great value to develop a classification that implements both myocardial and hemodynamic interplay.

Nevertheless, our study suggests that the severity score calculated by CMR might still play a potential role in the clinical assessment of EA patients. Of note, from a real-life perspective, most clinicians would still consider the size of the fRA in 4-chamber view to be somehow illustrative of the general impression of what is "mild" and what is "severe" EA. In our opinion, this fact supports further investigation on the Cel-ind, particularly in the setting of so far inconsistent study outcomes. However, as shown in our study, the agreement between echocardiographic and the reference method of CMR with regard to the Cel-ind is, at most, moderate; echocardiography tends to overestimate the severity score, but rarely underestimates it. Thus, a patient labeled in echocardiography as mild EA (grade 1 or 2) is highly unlikely to be classified as severe in CMR assessment. We suggest that echocardiography, as a "first-line" imaging method, could be used as a "screening tool" for EA severity, especially for the management of patients in whom CMR is contraindicated or not feasible. However, it is important to be aware of its limitations, because only when calculated in CMR is it associated with heart failure markers.

Limitations

This study was cross-sectional in nature with a relatively small study group; the statistical power was inherently limited. Nevertheless, in the population of adults with CHD all of the published single-center reports describe comparable samples. Because patients with an implantable device were not included in the study (because of probable artifacts disabling proper analysis in CMR), we consider this fact a potential selection bias. The methodology for the delineating and calculating the volumes of the right heart chambers in CMR varies between studies,[13,17] which may contribute to inconsistent outcomes and obscured comparison and interpretation of the results. Echocardiographic measurements of the distorted and dilated RV also may be impaired by a poor acoustic window. This issue was found in 2 patients and addressed in the methodology section. The intraobserver and interobserver variability for echocardiographic and CMR assessment should also be taken into consideration, although it remained within the acceptable ranges.

Conclusions

The agreement between echocardiographic and CMR assessment of the Cel-ind is, at most, moderate; the severity score of EA calculated by echocardiography is usually overestimated but rarely underestimated. CMR, in comparison with echocardiography, seems to be a more useful method for evaluating the severity index of EA, because the data obtained by CMR correlate better with heart failure markers.

Disclosures

The authors have no conflicts of interest to disclose.

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