Left Ventricular Longitudinal Function Predicts Life-Threatening Ventricular Arrhythmia and Death in Adults with Repaired Tetralogy of Fallot

Running title: Diller et al.; Long-axis function in tetralogy of Fallot

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Journal Subject Code: [41] Pediatric and congenital heart disease, including cardiovascular surgery
Abstract:

Background - Sudden cardiac death and life-threatening ventricular arrhythmias (SCD/LTA) remain a concern in adult patients with repaired tetralogy of Fallot (ToF). Longitudinal left ventricular (LV) function is sensitive in detecting early myocardial damage and may have prognostic implications in this setting.

Methods and Results – We included 413 ToF patients (age 36±13 years, QRS duration 148±27 ms, LV-EF 55±10%). A composite endpoint of SCD/LTA (sustained ventricular tachycardia, resuscitated SCD or appropriate ICD discharge) was employed. During a median follow-up of 2.9 years 5 patients died suddenly, 9 had documented sustained VT and another 5 had appropriate ICD shocks. On univariate Cox analysis QRS-duration (hazard ratio [HR] 1.02/ms, \(P=0.046\)), right atrial area (HR 1.05/cm², \(P=0.02\)), right ventricular (RV) fractional area change (HR 0.94/%, \(P=0.02\)), RV outflow tract diameter (HR 1.08/mm, \(P=0.01\)), mitral annular plane systolic excursion (MAPSE, HR 0.84/mm, \(P=0.03\)) and LV global longitudinal 2-dimensional strain (LV-LS, HR 0.87/%, \(P=0.03\)) were related to the combined endpoint. On bivariable analysis MAPSE and LV-LS were related to outcome independently of QRS-duration (\(P=0.002\) and \(P=0.01\), respectively). In addition, a combination of echocardiographic variables including right atrial area and RV fractional area change as well as LV-LS or MAPSE was also found to be significantly related to outcome (\(P<0.001\), c-statistic 0.70).

Conclusions – Left ventricular longitudinal dysfunction was associated with greater risk of SCD/LTA. In combination with echocardiographic right heart variables, also available from routine echocardiography, these measures provide important outcome information and should be considered a useful adjunct to established markers such as QRS-duration when estimating prognosis in this challenging population.

Key words: adult congenital heart disease; echocardiography; risk stratification; Tetralogy of Fallot; prognostication; sudden cardiac death
Introduction

Tetralogy of Fallot (ToF) represents the most common cyanotic heart defect at birth, accounting for approximately 10\% of all congenital cardiac defects.\(^1\) Early surgical repair has dramatically improved the outcome of ToF, but serious late complications remain of concern. Pulmonary regurgitation (PR) is common in this population and may lead to right ventricular (RV) dilatation, RV dysfunction, exercise intolerance, and eventually life-threatening arrhythmias (LTA) and sudden cardiac death (SCD).\(^2\)\(^-\)\(^7\) Timely pulmonary valve replacement may avoid irreversible RV damage with its deleterious consequences. Nonetheless, SCD is not entirely preventable by this approach.\(^8\) Accurate risk stratification and the development of appropriate algorithms for selection of patients who may benefit from an implantable cardioverter-defibrillator (ICD) would be crucial in this context. Previous studies have focused on the predictive value of surgical history, ECG variables, inducible arrhythmia, exercise intolerance and RV burden of myocardial fibrosis.\(^9\)\(^,\)\(^10\) More recently, left ventricular (LV) systolic and diastolic dysfunction have been reported to carry prognostic information in this setting.\(^10\)\(^,\)\(^11\)

Although LV impairment is not uncommon in ToF patients, few patients present with more than mildly reduced LV ejection fraction.\(^12\)\(^,\)\(^13\) Therefore, more sensitive measures of early LV dysfunction may be required. Recent studies in various cardiovascular conditions have consistently demonstrated that variables of LV longitudinal function are more sensitive in detecting early myocardial damage than ejection fraction.\(^14\)\(^-\)\(^16\) Traditionally, longitudinal LV systolic function has been assessed by measuring mitral annular plane systolic excursion (MAPSE).\(^17\)\(^,\)\(^18\) Tissue Doppler echocardiography has also been employed to assess longitudinal myocardial velocities at the mitral annular level.\(^19\) More recently, speckle tracking echocardiography has emerged as a promising tool for assessing myocardial performance. Unlike
MAPSE, speckle tracking derived strain and strain rate measurements can be performed at
different positions within the myocardium, thus allowing the measurement of local myocardial
function. Furthermore, unlike myocardial tissue Doppler velocities, 2-dimensional (2D) speckle
tracking strain measurements are not angle dependent and are not affected by tethering effects.\textsuperscript{20}
We have previously demonstrated that despite the presence of normal LV ejection fraction, 2D
peak longitudinal strain is frequently reduced in ToF patients.\textsuperscript{16} The purpose of the present study
was to assess the prognostic value of longitudinal LV function as well as its incremental value to
established predictors of outcome in a large cohort of ToF patients.

**Patients and Methods**

All patients with repaired ToF followed at the Adult Congenital Heart Disease Program, Royal
Brompton Hospital, London and at the Adult Congenital and Valvular Heart Disease Center at
the University of Muenster, Germany who had undergone transthoracic echocardiography
between 02/2004 and 10/2010 with adequate digitally stored images available were included. For
those patients who had more than one examination during this period only the first one was used.

**Echocardiography**

A comprehensive echocardiographic study including M-mode, 2-D and Doppler
echocardiography was performed. For off-line assessment of peak global longitudinal 2D LV
and RV strain (LV-LS and RV-LS) a commercially available software package (2D Cardiac
Performance Analysis Software©, TomTec, Unterschleissheim, Germany) was used. LV-LS and
RV-LS were defined as the peak negative value on the strain curve during the entire cardiac
cycle. Biventricular long axis function on M-Mode echocardiography (MAPSE and tricuspid
annular plane systolic excursion [TAPSE]) were measured as described previously.\textsuperscript{21,22} Chamber
dimensions, LV ejection fraction (EF) and RV fractional area change were measured following
current recommendations. For assessment of LV diastolic function, left atrial pressure was estimated according to the algorithm recommended by the American and European Societies of Echocardiography, based on mitral inflow E and A wave peak velocities, E wave deceleration time, early mitral annular velocities (e') and left atrial volume index. Patients were stratified into a group with normal or elevated left atrial pressure. Since the E/e’ ratio has been reported to relate to the LV end diastolic pressure, this parameter was also tested as a continuous variable in the statistical analysis.

**Clinical variables and study protocol**

New York Heart Association (NYHA) functional class and QRS duration at the time of the echocardiographic investigations as well as demographic variables were collected from medical records. Follow-up time started at the time of echocardiography. The endpoint of the study was a composite of sudden cardiac death (SCD) or life-threatening arrhythmia (LTA). Life-threatening arrhythmia was defined as documented sustained ventricular tachycardia, resuscitated nearly missed SCD or appropriate ICD discharge. Routine ICD follow-up protocols were reviewed for all ICD patients to ensure that ICD therapies were appropriate. Patients who underwent pulmonary valve replacement during the study period (n=85) were censored at the time of operation, as surgery alters ventricular volumes and function and may affect outcome. The study was approved by the local ethics committee. All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Statistics**

Values are presented as mean and standard deviation or median and interquartile range (25th and
75th percentile), depending on variable distribution. Categorical variables are presented as frequencies and percentages. Comparisons between subgroups were performed by unpaired t-test, Mann-Whitney U test or Chi-square test. The relationship between demographic, clinical or echocardiographic variables and outcome was investigated by univariable and bivariable Cox proportional-hazard analysis. In addition, the prognostic value of models incorporating different combinations of variables of LV longitudinal function and right heart variables were explored. Concordance probabilities (C- indices, indices conceptually similar to area under curve on ROC analysis) were calculated for the Cox models using a resampling validation algorithm based on the \texttt{rms R-package} \cite{26}. For all analyses, a 2-tailed $P$-value <0.05 was used as the criterion for statistical significance. R version 2.12.2 was employed for all analyses \cite{27}.

Results

Overall, 413 patients with repaired ToF and appropriate echocardiographic recordings were included. The mean age was 36±13 years and 211 patients (51%) were male. Additional demographic and clinical information is presented in Table 1.

During a median follow-up period of 2.9 years (IQR 1.4 – 4.4), 19 patients reached the predefined endpoint of SCD or LTA: 5 patients died suddenly, 9 patients had documented sustained ventricular tachycardia or required resuscitation for nearly missed SCD (and subsequently underwent ICD-implantation for secondary prevention), and 5 patients had appropriate ICD shocks delivered by an ICD implanted prior to initial echocardiography. The annual probability of SCD/LTA was 2.4%. The incidence of SCD was 0.5% per year.

Prognostic value of demographic variables, clinical markers and surgical history

Age and gender were not significantly related to the primary endpoint of SCD or LTA. In
contrast, a New York Heart Association (NYHA) functional class > 1, a longer QRS duration as well as a history of more than one previous cardiac surgery with extracorporeal circulation were significantly associated with SCD/LTA on Cox proportional-hazard analysis as shown in Table 2.

Left ventricular variables

None of the variables of LV diastolic function were significantly related to the study endpoint (Table 2). On univariable Cox proportional-hazard analysis, MAPSE and LV-LS were, however, significantly related to the risk of SCD/LTA (Table 2, Figure 1). In contrast, LV ejection fraction was not significantly associated (P=0.06) with SCD/LTA (Table 2). In addition, bivariable Cox proportional hazard analysis confirmed that both LV-LS and MAPSE were associated with SCD/LTA independently of LV ejection fraction (with LV ejection fraction not maintained in the model).

Right heart variables

Right atrial area was significantly related to the risk of SCD/LTA (Table 2). This association was independent of the presence of a restrictive RV physiology on bivariable analysis (HR 1.04 [95% CI 1.004-1.085], P=0.03 for right atrial area). In addition, RV enddiastolic area measured from an apical 4-chamber view, RV outflow tract diameter and RV fractional area change were related to SCD/LTA (Table 2), while TAPSE and RV 2D-systolic strain were not.

Incremental prognostic value of variables of longitudinal LV function

To assess the incremental prognostic value of measures of LV longitudinal function compared to known risk factors such as QRS-duration and RV function, bivariable Cox analyses with calculation of concordance indices (c-statistic) were performed. Both MAPSE and LV-LS were significantly associated with a higher risk of SCD/LTA independently of QRS-duration on
bivariable analysis ($P=0.002$ and $P=0.01$ for MAPSE and LV-LS, respectively). Furthermore, including MAPSE or LV-LS in addition to QRS duration into the model improved the c-index from 0.65 for QRS duration alone to 0.78 and 0.71 for a model including QRS duration and MAPSE or LV-LS, respectively. A similar picture emerged for RV fractional area change: MAPSE was significantly associated with a higher risk of SCD/LTA independently of RV fractional area change on bivariable analysis ($P=0.02$). Furthermore, including MAPSE or LV-LS in addition to RV fractional area change in the model improved the c-index from 0.65 for RV fractional area change alone to 0.68 and 0.76 for a model including RV fractional area change and MAPSE or LV-LS, respectively.

**Combined prognostic value of echocardiographic variables**

Echocardiographic measures significantly associated with the risk of SCD/LTA on univariable Cox analysis were assessed to estimate the combined prognostic value of echocardiographic variables. The full model included a parameter of LV systolic function (either MAPSE or LV-LS), a parameter of RV inflow and apical size (RV enddiastolic area), a measure of RV outflow tract size (RVOT diastolic diameter), a measure of RV function (RV fractional area change) and a parameter of right atrial enlargement (right atrial area). In addition, simplified models were constructed, containing only a subset of these variables. As LV ejection fraction was not significant on univariable Cox analysis this measure was not included in any of these models. Using previously published limits of normal values\textsuperscript{23,28} the following cut-off values were employed: LV-LS < 15%; MAPSE < 12 mm; RA-area>20 cm$^2$; RV-FAC<32%; RV-enddiastolic area>28 cm$^2$ and RVOT diastolic diameter>29 mm. included and the achieved c-statistic. Models incorporating LV-LS or MAPSE as well as right atrial area and RV fractional area change provided the best combination of simplicity and prognostic value (c-statistic of 0.70 for both,
compared to 0.72 for a model including all 6 variables; Cox-models: combination of MAPSE<12mm, RA-area>20cm² and RV-FAC<32% HR/unit 2.57, 95% CI 1.58 – 4.19, P=0.0001; combination of LV-LS<15%, RA-area>20cm² and RV-FAC<32% HR/unit 2.74, 95% CI 1.75 – 4.30, P<0.0001).

Discussion

The results of the current study demonstrate for the first time that LV longitudinal dysfunction is associated with SCD and LTA in patients with repaired ToF. Measures of LV longitudinal function are readily available from routine transthoracic echocardiographic assessments, using conventional echocardiography systems, and have incremental prognostic value when considering RV variables or established predictors of outcome such as QRS-duration in this challenging population. A combination of echocardiographic variables including right atrial area and RV fractional area change as well as LV-LS or MAPSE may, therefore, be useful in risk stratifying ToF patients.

The reasons for impaired LV function in ToF are poorly understood. It has been suggested that myocardial ischemia before corrective surgery may in part account for late LV dysfunction. In fact, Hausdorf et al.²⁹ have reported that severity of pre-operative hypoxemia affected late systolic function. In addition, shared myocardial fibers between LV and RV and the adverse impact of septal shift have been suggested to account for LV dysfunction in this setting.³⁰ Left ventricular dysfunction in ToF patients is rarely of the severity encountered in patients with acquired heart failure. However, previous studies have linked low LV ejection fraction in this setting fraction to poor outcome.¹¹, ³¹ We have recently demonstrated that LV ejection fraction may lack sensitivity in detecting early myocardial damage in ToF patients.¹⁶
The current study was therefore performed to test the hypothesis that variables of LV longitudinal function (especially LV-LS) are significant predictors of SCD/LTA and superior to LV ejection fraction. On univariable Cox proportional-hazard analysis LV-LS and MAPSE were significantly associated with a higher risk of SCD/LTA, while LV ejection fraction was not. Somewhat surprisingly MAPSE, a simpler measure of LV longitudinal function measured on conventional M-mode was similarly helpful as LV-LS in assessing prognosis. In contrast to a previous study employing invasive measurements of LV enddiatolic pressures (LVEDP), we could not confirm an association between LV diastolic dysfunction - as derived echocardiographically - and outcome. This could be explained with the inherent limitations of estimating LVEDP based on echocardiographic assessment. This finding, however, may have important clinical implications as cardiac catheterization merely for risk stratification is not justified in this setting and the results of our study show that extrapolating from echocardiographic measures of diastolic function on prognosis should be avoided. The current study also demonstrates the prognostic value of right atrial enlargement, impaired RV function and RV dilatation in this cohort.

Assessment of RV volumes and RV function based on conventional volumetric variables such as ejection fraction remains challenging on echocardiography due to the complicated geometry of the RV and limited acoustic windows in many patients. While LV function and dimensions can accurately be assessed on transthoracic echocardiography, these measurements therefore remain the province of cardiac MRI with its advantages of a wide field of view, lack of anatomic plane restriction, and superior reproducibility. However, there is no unrestricted access to this technique and MRI studies are currently not possible in the growing population of ToF patients with ICDs. Echocardiography will therefore remain the workhorse in the routine
assessment of ToF patients. Not surprisingly, measures of RV size and function were found to be related to outcome in this study. Interestingly, however, tricuspid annular plane systolic excursion (TAPSE) was unrelated to the endpoint of SCD/LTA. Measures of RV longitudinal function are theoretically appealing for assessing RV systolic function as anatomical studies have demonstrated that the deeper RV muscle fibers are predominantly arranged in a longitudinal fashion from the tricuspid valve annulus to the apex and RV stroke volume grossly depends on longitudinal shortening. Thus, reduced TAPSE, closely reflecting RV free wall dysfunction, should precede circumferential RV impairment. One possible interpretation for the failure of TAPSE to reflect prognosis could be its high sensitivity. In the setting of a chronically volume overloaded, enlarged and impaired RV a too sensitive parameter will provide little information on outcome. In contrast, sensitive measures of LV longitudinal function may be better suited to detect subtle changes/impairment in LV function.

Although rare overall, SCD remains a particular concern for this young patient-population and is not well predictable. Risk stratification remains challenging and has been discussed in detail elsewhere. The annual incidence of death in adult ToF patients varies with age but is generally believed to be around 0.5% per year. This concurs with the incidence of SCD in the current study. Another clinically relevant and objective outcome measure is the annual incidence of SCD or documented ventricular tachycardia. The annual incidence of SCD/LTA in the current study was 2.4%, which is similar to the rate reported by Harrild et al. (2.9%).

Khairy et al. have previously proposed a risk score based on clinical history, QRS duration, the results of electrophysiologic (EP) studies and invasive assessment of left ventricular enddiastolic pressures. However, neither invasive pressure measurements nor EP studies can
be performed routinely for risk assessment in patients after ToF repair. Thus, the results of the current study, suggesting that measures obtained from a routine transthoracic echocardiographic study can also be employed to risk stratify ToF patients may have particular clinical relevance. Due to the lack of invasive pressure and EP data in the majority of patients, the current study was unable to compare the performance of the score published by Khairy to our echocardiographic score directly. Nevertheless, the results of this study suggest that echocardiographic measures should be incorporated in future comprehensive score systems. Writing in an editorial - to the seminal paper identifying QRS prolongation as major risk factor of SCD in 1995 - Brickner estimated that approx. 1,700 ToF patients with a follow-up time of 10 years would be required to attain sufficient statistical power to construct a meaningful multivariable statistical model to predict such events. Not surprisingly, even 1½ decades later no such comprehensive model exists. Until sufficient statistical power can be achieved as part of even larger multicenter-studies, no strong recommendations will be possible and clinicians will have to rely on their training and experience, supplemented by the results of various studies rather than on an algorithmic approach. We believe that the findings of the current study should be helpful to clinicians for estimating the risk of LTA or SCD and may represent a useful adjunct or alternative to the score system provided by Khairy and colleagues.

**Limitations of the study**

This study was performed at tertiary care centers for adult congenital heart disease. Therefore, we cannot exclude the possibility that the patients in the study could be a biased sample, favoring those with more symptoms and advanced disease. Furthermore this study focused on longitudinal biventricular function using speckle tracking analysis. Analysis of radial, circumferential and torsional deformation may have provided additional prognostic information. However, global 2
Dimensional LV-LS was chosen as it can be calculated semi-automatically from speckle tracking analysis and offers good intraobserver and interobserver variability.\textsuperscript{41,42} In addition, it has been demonstrated to be useful in predicting outcome in heart failure patients.\textsuperscript{43} While virtually all patients, without a contraindication, underwent cardiac MRI scans during the follow-up period, MRI measures were available in only approximately 50\% of the patients within 6 months of the echocardiographic investigations, thus considerably reducing event rate and statistical power in this subgroup. We, therefore, did not provide estimates of the prognostic value of MRI variables. Further MRI studies are required to provide such information. Due to inadequate acoustic windows and the inability to clearly delineate the entire right heart from on an apical 4-chamber view, RV fractional area change could not be determined in 16\%, while right atrial area was unavailable in 7\% of patients. This may represent a limitation of the method described, especially if retrospective data is to be used to estimate prognosis based on the echocardiographic score provided.

Low annual event rates are a major drawback of studies attempting to improve risk stratification in ToF patients. Even in the current study including the sizable number of 413 patients with 1,144 patients-years of follow-up only 5 SCDs occurred and 19 patients had a combined endpoint of SCD/LTA. Therefore, estimates of prognosis are associated with considerable uncertainty and even very abnormal values of LV longitudinal function/high predictive scores may not – in isolation – warrant implantation of an ICD for primary prevention of SCD. This study was designed to test the hypothesis that LV-LS and MAPSE are superior to LV-EF in predicting outcome in ToF patients. Beyond the results of these hypothesis-driven analyses, we also present the results of exploratory analyses on the association between (mainly right heart) echocardiographic or clinical variables and outcome. We cannot exclude the possibility that
Type I error might be increased for these additional comparisons and clinicians should take this limitation into account when applying the results of this study in practice. Larger studies with a higher number of events are required to validate the results of the current analysis and especially to confirm the value of combinations of echocardiographic variables in predicting LTA/SCD in this setting.

Conclusions

Left ventricular longitudinal dysfunction is associated with a higher risk of SCD/LTA in contemporary ToF patients. In combination with echocardiographic measures of right atrial size, RV function and dimensions, LV-LS and MAPSE identifies a subgroup of ToF patients at increased risk of SCD/LTA. As all these variables are readily available from routine transthoracic echocardiographic assessment they should be considered as a useful adjunct to established markers such as QRS-duration when assessing prognosis in this challenging population.

Funding Sources: GD and the Adult Congenital Heart Disease Program, Royal Brompton Hospital, London, UK were supported by Actelion, UK. AK was supported by the Deutsche Herzstiftung. The Adult Congenital and Valvular Heart Disease Center, University Hospital of Muenster has received support by the EMAH Foundation Karla Voellm, Krefeld, Germany

Conflict of Interest Disclosures: None

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24. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left


Table 1. Baseline characteristics

<table>
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<tr>
<th>Demographics</th>
<th>All patients n=413</th>
<th>Patients without SCD or LTA n = 394</th>
<th>Patients with SCD or LTA n = 19</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>35.9 (13.4)</td>
<td>35.9 (13.4)</td>
<td>35.8 (14.5)</td>
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<tr>
<td>Male, n (%)</td>
<td>211 (51)</td>
<td>199 (51)</td>
<td>12 (62.5)</td>
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<tr>
<td>Weight, kg</td>
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<td>72.2 (17.6)</td>
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<tr>
<td>Height, cm</td>
<td>168.8 (11.4)</td>
<td>168.8 (11.6)</td>
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<td>BSA, m²</td>
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<td>1.83 (0.25)</td>
<td>1.80 (0.19)</td>
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<td>25.1 (5.3)</td>
<td>23.3 (2.7)</td>
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<tr>
<td>Clinical status and history</td>
<td></td>
<td></td>
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<td>NYHA FC I / II / III / IV (%)</td>
<td>52 / 38 / 9 / 1</td>
<td>54 / 38 / 8 / 0</td>
<td>17 / 65 / 18 / 0</td>
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<td>Palpitations, n (%)</td>
<td>107 (26)</td>
<td>95 (24)</td>
<td>12 (63)</td>
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<td>Angina, n (%)</td>
<td>17 (4)</td>
<td>16 (4)</td>
<td>1 (5)</td>
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<tr>
<td>Antiarrhythmics, n (%)</td>
<td>63 (15)</td>
<td>55 (14)</td>
<td>9 (47)</td>
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<tr>
<td>Number of cardiac surgeries, n</td>
<td>IQR 1.0-2.0 (1.40±0.6)</td>
<td>IQR 1.0-2.0 (1.4±0.6)</td>
<td>IQR 1.0-2.0 (1.8±0.7)</td>
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<td>Age at corrective surgery, years</td>
<td>IQR 2.0-9.4 (8.2±10.0)</td>
<td>IQR 2.0-9.4 (8.1±9.9)</td>
<td>IQR 1.8-10.3 (8.6±9.2)</td>
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<table>
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<tr>
<th>Echocardiographic and ECG variables</th>
<th>All patients n=413</th>
<th>Patients without SCD or LTA n = 394</th>
<th>Patients with SCD or LTA n = 19</th>
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<tbody>
<tr>
<td>Moderate-severe TR, n (%)</td>
<td>17 (4.1)</td>
<td>15 (3.8)</td>
<td>2 (10.5)</td>
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<td>Moderate-severe PR, n (%)</td>
<td>210 (51)</td>
<td>201 (51)</td>
<td>9 (47)</td>
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<td>Right atrial area, cm²</td>
<td>22.3 (8.2)</td>
<td>22.1 (8.2)</td>
<td>26.8 (7.8)</td>
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<td>RV enddiastolic area, cm²</td>
<td>31.4 (8.9)</td>
<td>31.0 (8.8)</td>
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<td>RVOT diastolic diameter, mm</td>
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<td>34.5 (7.5)</td>
<td>38.3 (6.3)</td>
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<td>RV fractional area change, %</td>
<td>38.3 (9.5)</td>
<td>38.9 (9)</td>
<td>33.7 (12.3)</td>
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<td>TAPSE, mm</td>
<td>15.6 (3.7)</td>
<td>15.7 (3.7)</td>
<td>14 (3.6)</td>
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<tr>
<td>LV ejection fraction, %</td>
<td>55.3 (10.3)</td>
<td>55.8 (9.9)</td>
<td>50.4 (10.3)</td>
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<td>MAPSE, mm</td>
<td>14.1 (3.3)</td>
<td>14.2 (3.3)</td>
<td>12.4 (3.8)</td>
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<td>LV longitudinal 2D strain, %</td>
<td>15.4 (4.7)</td>
<td>15.8 (4)</td>
<td>13.5 (4.8)</td>
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<td>QRS duration, ms</td>
<td>148 (27)</td>
<td>147.7 (27.2)</td>
<td>160.4 (17.7)</td>
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</table>

SCD, sudden cardiac death; LTA, life-threatening arrhythmia; BSA, body surface area; BMI, body mass index; NYHA FC, New York Heart Association Functional Class; MRI, magnetic resonance imaging; TTE, transthoracic echocardiography; TR, tricuspid regurgitation; PR, pulmonary regurgitation; RV EDV, right ventricular end diastolic volume; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricle.
Table 2. Predictors of the combined primary endpoint of SCD or LTA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>per</th>
<th>HR</th>
<th>95% CI</th>
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<td>Age at corrective surgery</td>
<td>1 year</td>
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<td>0.96-1.05</td>
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<td>Cardiac surgeries &gt; 1</td>
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<td>3.92</td>
<td>1.45-10.6</td>
<td><strong>0.007</strong></td>
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<tr>
<td>NYHA FC &gt; 1</td>
<td>-</td>
<td>5.95</td>
<td>1.71-20.7</td>
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<td>QRS duration</td>
<td>1 ms</td>
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<td>1 sq.cm</td>
<td>1.05</td>
<td>1.01-1.09</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>RVOT diastolic diameter</td>
<td>1 mm</td>
<td>1.08</td>
<td>1.02-1.15</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>RV end diastolic area</td>
<td>1 sq.cm</td>
<td>1.08</td>
<td>1.03-1.12</td>
<td><strong>0.0005</strong></td>
</tr>
<tr>
<td>RV fractional area change</td>
<td>1 % unit</td>
<td>0.94</td>
<td>0.89-0.99</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>TAPSE</td>
<td>1 mm</td>
<td>0.89</td>
<td>0.78-1.02</td>
<td>0.09</td>
</tr>
<tr>
<td>RV longitudinal strain</td>
<td>1 % unit</td>
<td>0.96</td>
<td>0.86-1.07</td>
<td>0.50</td>
</tr>
<tr>
<td>LA area</td>
<td>1 sq.cm</td>
<td>0.97</td>
<td>0.88-1.08</td>
<td>0.62</td>
</tr>
<tr>
<td>Elevated LAP *</td>
<td>-</td>
<td>0.29</td>
<td>0.04-2.19</td>
<td>0.23</td>
</tr>
<tr>
<td>E/e'</td>
<td>-</td>
<td>0.92</td>
<td>0.75-1.12</td>
<td>0.40</td>
</tr>
<tr>
<td>LV end diastolic volume</td>
<td>1 ml</td>
<td>1.01</td>
<td>0.99-1.02</td>
<td>0.06</td>
</tr>
<tr>
<td>LV EF</td>
<td>1 % unit</td>
<td>0.96</td>
<td>0.92-0.99</td>
<td>0.06</td>
</tr>
<tr>
<td>MAPSE</td>
<td>1 mm</td>
<td>0.84</td>
<td>0.71-0.98</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>LV longitudinal strain</td>
<td>1 % unit</td>
<td>0.87</td>
<td>0.77-0.99</td>
<td><strong>0.03</strong></td>
</tr>
</tbody>
</table>

SCD, sudden cardiac death; LTA, life-threatening arrhythmia; NYHA FC, New York Heart Association functional class; RA, right atrium; RVOT, right ventricular outflow tract; LA, left atrium; LV, left ventricle; LAP, left atrial pressure; TAPSE, tricuspid annular plane systolic excursion; EF, ejection fraction; MAPSE, mitral annular plane systolic excursion; sq cm, square centimeter. * LAP assessed according to the recommendations of the American and European Societies of Echocardiography (see text for details). Significant variables are in bold.

Figure Legend:

Figure 1. Survivor function for the freedom of sudden cardiac death (SCD) or life-threatening arrhythmia (LTA) computed from the Cox proportional hazards model. LV=left ventricle, LV LS=LV global longitudinal strain, MAPSE = mitral annular plane systolic excursion,
Left Ventricular Longitudinal Function Predicts Life-Threatening Ventricular Arrhythmia and Death in Adults with Repaired Tetralogy of Fallot
Gerhard-Paul Diller, Aleksander Kempny, Emmanouil Liodakis, Rafael Alonso-Gonzalez, Ryo Inuzuka, Anselm Uebing, Stefan Orwat, Konstantinos Dimopoulos, Lorna Swan, Wei Li, Michael A. Gatzoulis and Helmut Baumgartner

Circulation. published online April 11, 2012; Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2012 American Heart Association, Inc. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

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