Relationships between cardiac resynchronization therapy and N-terminal pro-brain natriuretic peptide in patients with heart failure and markers of cardiac dyssynchrony: an analysis from the Cardiac Resynchronization in Heart Failure (CARE-HF) study

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Aims
The Cardiac Resynchronization in Heart Failure (CARE-HF) study showed that cardiac resynchronization therapy (CRT) reduces mortality in HF patients with markers of dyssynchrony. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) might predict which patients benefit most from CRT. We evaluated whether the prognostic value of NT-proBNP was influenced by CRT and the effects of CRT stratified according to NT-proBNP.

Methods and results
A total of 813 patients were enrolled in CARE-HF. Baseline log-transformed NT-proBNP independently predicted all-cause mortality, sudden death, and death from pump failure. In a multivariable model including log-transformed NT-proBNP, assignment to CRT remained independently associated with better prognosis without evidence of interaction. Stratifying patients according to the median NT-proBNP and to CRT treatment allocation, all-cause mortality was 12% if <median + CRT, 25% if <median + control group, 35% if ≥median + CRT, and 51% if ≥median + control group. There was no evidence of a difference in the relative effect of CRT across different values of NT-proBNP.

Conclusion
NT-proBNP retains its prognostic value in HF patients with CRT. Deploying CRT before the patients have reached end-stage HF may maximize the benefit of treatment.

Keywords
Heart failure • Cardiac resynchronization therapy • Natriuretic peptides • Prognosis

Introduction
In patients with reduced LV systolic function and prolonged QRS, cardiac resynchronization therapy (CRT) improves cardiac function,1–3 heart failure (HF) symptoms2–4 and quality of life,2,3 increases exercise capacity3 and partially reverses maladaptive remodelling.2,3 Two large multicenter trials have demonstrated that CRT reduces morbidity,2,4 one of which, the Cardiac

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Resynchronization in Heart Failure (CARE-HF) study, also found a substantial reduction of total mortality. Both studies mainly included patients with moderate (New York Heart Association (NYHA) class III) symptoms at enrolment. Less than 15% of patients had severe symptoms (NYHA class IV). It is unclear if the survival benefits by CRT apply similarly to patients with different severity of disease.

Brain natriuretic peptide (BNP) and its precursor NT-proBNP are secreted from the heart in response to myocardial stretch which is related to atrial and ventricular filling pressures. Plasma concentrations are higher in patients with more severe symptoms or worse LV function and are powerful predictors of unfavourable outcomes such as all-cause mortality, sudden death, or readmission for decompensated HF. As natriuretic peptides often eliminate all other predictors of prognosis in statistical models, they are strong candidate markers for staging the severity of HF.

The CARE-HF study demonstrated a clear survival benefit from CRT in patients with chronic HF and markers of cardiac dysynchrony. Despite including mainly patients in NYHA class III, the baseline NT-proBNP levels were distributed over a wide range, indicating different severities of disease and prognosis. N- terminal pro-brain natriuretic peptide might be used to identify high-risk patients who have more to gain, prognostically, from CRT. Also, reversion in NT-proBNP by CRT might lead to a change in the relationship between BNP and prognosis. This analysis investigates these issues.

Methods

Design overview

The CARE-HF trial was a multi-centre, randomized, open-label study evaluating the effect of CRT on morbidity and mortality. Patients were recruited in 82 sites across Europe. Inclusion criteria were LV ejection fraction ≤35%, a QRS duration ≥150 ms or QRS ranging from 120 to 149 ms in addition to echocardiographic criteria for dysynchrony, and NYHA functional class III or IV despite optimized medical therapy. Patients who were not in sinus rhythm were excluded. The protocol was approved by all relevant Ethics Committees, and patients provided written informed consent. The detailed study methods have been described elsewhere.

Randomization and interventions

Using a minimization procedure (Quintiles, Dublin), patients were randomly assigned to receive medical therapy alone or with CRT (Medtronic Bakken Research Center, Maastricht, The Netherlands). Blood samples for measurement of NT-proBNP levels were drawn at baseline and at 3 months. The extracted plasma was analysed at the neurohumoral core-laboratory (Medical University Graz) using a Roche Diagnostics proBNP radioimmunoassay on an Elecsys 2010 analyser. As the analysis of NT-proBNP was performed after completion of the main study, the investigators were not aware of NT-proBNP values throughout the study.

Follow-up and outcomes

Patients were evaluated prior to discharge, at 1 month, 3 months, every 3 months for the first year, and every 6 months thereafter. Detailed assessments were performed at baseline and at 3 months. Investigators were asked to report all adverse events, which were adjudicated by an endpoints committee in a blinded fashion. The endpoints of this secondary analysis were all-cause mortality, sudden death, and death from pump failure using the extended follow-up period. The follow-up of the extension period ended on 30 September 2004.

Statistical analysis

All analyses were conducted according to the intention-to-treat principle and patients were analysed according to the group to which they were randomized, regardless of whether they received the treatment they were allocated to. All efforts were made to minimize missing data. However, some NT-proBNP values were missing because either the sample was mislaid during storage at investigator sites or inadequately labelled when received in the core laboratory. Data on certain echocardiographic variables were missing due to poor quality examination, damaged tapes, and the core laboratory not receiving certain tapes. The principal analyses were conducted on available data, and additional supportive data were conducted using multiple imputation techniques to assess the extent to which missing data may have affected the observed results. Multiple imputation was undertaken using the MI and MIANALYZE procedures in SAS V9.1 (SAS Institute, Cary, NC, USA). Tests were two-sided at P < 0.05. Cox proportional Hazards models were used to determine independent predictors of all-cause mortality, sudden death, and death from pump failure. Patients, who died from other causes than analysed, were censored at time of death. The models included patient level covariates that were pre-specified in the statistical analysis plan, namely age, sex, baseline clinical (aetiology, NYHA functional class, heart rate, supine systolic blood pressure, glomerular filtration rate), electrocardiographic (QRS duration), and echocardiographic characteristics (ejection fraction, mitral regurgitation area, end-systolic volume index, inter-ventricular mechanical delay), baseline medical therapy (use of an angiotensin converting enzyme-inhibitor or an angiotensin receptor blocker, use of a beta-blocker), NT-pro-BNP, and CRT. Variables were transformed using the logarithm and cubic spline to test for non-linear relationships with the outcome. The Akaike Information Criteria was used to determine the most appropriate transformation. The multivariable analysis was carried out using Cox proportional hazards model, with a stepwise approach. A P-value of 0.1 was set as the criterion for entry of each variable into the model, and a P-value of 0.05 was set as the criterion to stay in the model. The proportional hazards assumption was tested using Kolmogorov-type supremum tests computed on 1000 simulated patterns and was satisfied for all variables. Simple models including CRT treatment, BNP and an interaction term (log BNP x CRT treatment) were used to test whether BNP retains its prognostic power for these outcomes, irrespective of CRT treatment. Time-dependent covariate models were used to account for short-term changes in NT-proBNP. In these models, baseline values of NT-proBNP were updated with 3 months values for those individuals who had still not reached the endpoint under consideration, i.e. were still at risk of an event after this time. In the next step, patients were stratified according to the median NT-proBNP and treatment allocation, to illustrate the effects of CRT on patients with
different stages of disease. Analyses were performed using SAS V9.1 (SAS Institute). The multivariable models were validated using the design library in the statistical package R (R Foundation for Statistical Computing, 2008) using the approach suggested by Harrell et al.10 Two hundred bootstrap samples were drawn from the original dataset. For each sample, a model was fitted using backward stepwise selection. This model was then frozen and applied to the original dataset. The differences between Somers’s D for the model calculated on the bootstrap sample and the original dataset were averaged and this was subtracted from the value of D for the original model. This provides an estimate of the model optimism.

Results

Patients

Of 813 patients enrolled, 409 were randomly assigned to CRT and medical therapy and 404 to medical therapy alone. The patient characteristics have been published.2,5 In brief, patients were characterized by a median LV ejection fraction of 25% (IQR 22–29), a median NT-proBNP level of 1814 pg/mL (IQR 744–4199), and median QRS duration of 160 ms (IQR 152–180). Ischaemic heart disease was present in 42% of patients, 94% of patients were in NYHA class III and 6% in class IV. Almost all patients (95%) were treated with an ACE-inhibitor or ARB, 72% of patients had a beta-blocker, and more than half of the patients were treated with spironolactone. (Table 1).

Table 1: Characteristics of patients assigned to CRT and medical therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRT Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>Median 744</td>
<td>Median 1814</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>Median 152</td>
<td>Median 160</td>
</tr>
<tr>
<td>NYHA class</td>
<td>95%</td>
<td>6%</td>
</tr>
<tr>
<td>ACE-inhibitors or ARB use</td>
<td>72%</td>
<td>95%</td>
</tr>
<tr>
<td>Beta-blocker use</td>
<td>51%</td>
<td>33%</td>
</tr>
<tr>
<td>Spironolactone use</td>
<td>25%</td>
<td>20%</td>
</tr>
</tbody>
</table>

There was no missing data for treatment allocation, age, sex, use of ACE-inhibitors or ARB, and beta-blocker use. There was <5% missing data for heart rate, QRS, systolic blood pressure, and ischaemic cause for HF. There was <10% missing data for end-systolic volume index, NT-proBNP, intraventricular mechanical delay, glomerular filtration rate, and ejection fraction. Mitral regurgitation index was not available in 25.6% of subjects.

Outcome

Details of the main result and extension phase have been published showing that CRT reduces both morbidity and mortality in this patient population.2,5 The present analysis uses the extended follow-up period. The median follow-up was 37.6 months (IQR 31.5–42.5 months). One hundred and fifty four of 404 patients died in the control group compared with 101 of 409 patients in the CRT group (Kaplan–Meier analysis—P < 0.0001). Cardiac resynchronization therapy reduced both the risk of sudden death (55 vs. 32 patients; Kaplan–Meier analysis—P = 0.0040) and death due to pump failure (64 vs. 38 patients; Kaplan–Meier analysis—P = 0.0028).

Univariate and multivariable predictors

All variables except sex, heart rate, and QRS duration were univariate predictors of all-cause mortality as well as death from pump failure. Univariate predictors of sudden death were CRT, ischaemic heart disease, log-transformed NT-proBNP, log-transformed end-systolic volume index, and inter-ventricular mechanical delay. All independent predictors of the multivariable analyses are given in Table 2. In multivariable analyses, CRT and log-transformed NT-proBNP emerged as independent predictors of all-cause mortality, death from pump failure, and sudden death. Model optimism for all-cause mortality was 1.0%, for sudden death was 2.4%, and for HF death was 2.2%.

The application of multiple imputation techniques to assess the potential influence of missing data on the statistical models performed led to no material differences in models for sudden death and death from HF. The analysis of all-cause mortality was also substantially unchanged; however, although the prognostic effects of mitral regurgitation index remained statistically significant, the strength of the association was reduced. In addition, NYHA class was included in the final model with a modest effect, which was just statistically significant.

Influence of cardiac resynchronization therapy on the prognostic performance of N-terminal pro-brain natriuretic peptide

Simple multivariable models tested the effects of CRT treatment, log NT-proBNP and an interaction term (log NT-proBNP×CRT treatment) on outcomes including all-cause mortality, sudden death, and death from pump failure. The addition of this interaction term did not improve the fit of the models: NT-proBNP retained its prognostic power and the interaction term was not significant. These results indicate that a higher baseline plasma concentration of NT-proBNP predicts a higher risk of all-cause mortality, sudden death, and death from pump failure, irrespective of treatment group. We stratified patients according to the median NT-proBNP and to CRT treatment-allocation, to illustrate the effects of CRT on two patient groups with different stages of disease. Patient characteristics of these four subgroups are given in Table 1. In patients with <median NT-proBNP, there were 48 deaths (25%/ annual mortality rate 7.4%) in 189 patients assigned to the control group and 22 deaths (12%/3.4%) in 177 patients assigned to CRT. In patients with ≥median NT-proBNP, there were 93 deaths (51%/17.7%) in 181 patients assigned to the control group and 65 deaths (35/14.1%) in 185 patients assigned to CRT. Patients with below median NT-proBNP had similar absolute and somewhat greater relative reduction (52% vs. 31%) in mortality compared with those with levels above the median. The Kaplan–Meier estimates of the time to all-cause mortality in these four subgroups are given in Figure 1. Data on the mode of death according to subgroups are presented in Table 3 and Figure 2.

Time-dependent covariate models

In a time-dependent covariate model, log-transformed NT-proBNP, updated from baseline to 3 months values for 669 subjects still at risk of an event after this time, was the strongest independent predictor of all-cause mortality (P < 0.0001). Intraventricular mechanical delay (P = 0.0024), log-transformed mitral regurgitation area (P = 0.0034), CRT (P = 0.0040), and presence of ischaemic heart disease (P = 0.0118) provided additional prognostic information. Note that patients with greater intraventricular mechanical delay had a better outcome.
<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt;Median CRT</th>
<th>Controls</th>
<th>&gt;Median CRT</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>177</td>
<td>189</td>
<td>185</td>
<td>181</td>
</tr>
<tr>
<td>Age (years)—median (IQR)</td>
<td>64 (57–69)</td>
<td>64 (55–70)</td>
<td>69 (63–75)</td>
<td>68 (62–74)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>135 (76)</td>
<td>144 (76)</td>
<td>141 (76)</td>
<td>127 (70)</td>
</tr>
<tr>
<td>NYHA class IV (%)</td>
<td>5 (3)</td>
<td>6 (3)</td>
<td>15 (8)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>80 (45)</td>
<td>62 (33)</td>
<td>90 (49)</td>
<td>79 (44)</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)—median (IQR)</td>
<td>68 (59–76)</td>
<td>67 (59–75)</td>
<td>72 (62–82)</td>
<td>70 (62–80)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)—median (IQR)</td>
<td>120 (110–130)</td>
<td>120 (110–130)</td>
<td>110 (100–125)</td>
<td>110 (100–123)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)—median (IQR)</td>
<td>70 (64–76)</td>
<td>70 (64–80)</td>
<td>70 (60–80)</td>
<td>70 (60–80)</td>
</tr>
<tr>
<td>LVEF (%)—median (IQR)</td>
<td>26 (24–31)</td>
<td>27 (24–31)</td>
<td>24 (20–27)</td>
<td>23 (20–26)</td>
</tr>
<tr>
<td>End-systolic volume index (mL/m²)—median (IQR)</td>
<td>105 (85–130)</td>
<td>107 (82–131)</td>
<td>128 (102–163)</td>
<td>137 (104–171)</td>
</tr>
<tr>
<td>QRS duration (ms)—median (IQR)</td>
<td>160 (150–170)</td>
<td>160 (151–174)</td>
<td>161 (152–180)</td>
<td>160 (154–180)</td>
</tr>
<tr>
<td>Interventricular mechanical delay (ms)—median (IQR)</td>
<td>52 (33–71)</td>
<td>50 (31–68)</td>
<td>45 (30–64)</td>
<td>51 (30–65)</td>
</tr>
<tr>
<td>Mitral regurgitation area—a—median (IQR)</td>
<td>0.15 (0.09–0.26)</td>
<td>0.17 (0.07–0.28)</td>
<td>0.25 (0.17–0.38)</td>
<td>0.29 (0.17–0.39)</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min/1.73 m²)—median (IQR)</td>
<td>65 (51–77)</td>
<td>65 (52–78)</td>
<td>56 (43–70)</td>
<td>53 (42–66)</td>
</tr>
<tr>
<td>Use of an ACE-inhibitor or an ARB (%)</td>
<td>172 (97)</td>
<td>186 (98)</td>
<td>173 (94)</td>
<td>166 (92)</td>
</tr>
<tr>
<td>Use of a beta-blocker (%)</td>
<td>144 (81)</td>
<td>136 (72)</td>
<td>116 (63)</td>
<td>132 (73)</td>
</tr>
<tr>
<td>Use of spironolactone (%)</td>
<td>96 (54)</td>
<td>118 (62)</td>
<td>101 (55)</td>
<td>101 (56)</td>
</tr>
<tr>
<td>High-dose loop diuretics (%)</td>
<td>65 (37)</td>
<td>62 (33)</td>
<td>91 (49)</td>
<td>98 (54)</td>
</tr>
<tr>
<td>Use of digoxin (%)</td>
<td>70 (40)</td>
<td>89 (47)</td>
<td>75 (41)</td>
<td>75 (41)</td>
</tr>
</tbody>
</table>

*aThe area was calculated as the area of the colour-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimetres.*
Discussion

This analysis of the CARE-HF study demonstrates that NT-proBNP measured before device implantation retains its prognostic value in patients with chronic HF treated with CRT. However, measurement of NT-proBNP, 3 months after implantation, reflecting the effect of CRT and other treatments and changes in the underlying disease, is a stronger predictor than baseline NT-proBNP of subsequent outcome. Potentially of greatest interest is the observation that patients with less markedly elevated NT-proBNP benefited similarly in relative terms to those patients with higher levels.

Cardiac resynchronization therapy in patients with different stages of disease

The CARE-HF study enrolled patients with HF in NYHA class III (94%) or IV (6%) at the start of the run-in period. However, NYHA class has a large subjective element and is not fixed. In CARE-HF, the pre-randomization assessment indicated that 22% of patients had improved with medical treatment alone and had...
no or only mild symptoms (NYHA class I or II). The severity of symptoms appeared a poor guide to therapeutic effect. N-terminal pro-brain natriuretic peptide is a more objective measure of cardiac dysfunction than symptoms or echocardiographic ejection fraction and a much stronger predictor of prognosis. Outcome according to symptom severity and plasma concentration of NT-proBNP should be viewed in the context of other cornerstone HF trials. The annual mortality rates of patients assigned to the control group of CARE-HF with above median NT-proBNP were 7.4% and 17.7%, respectively. In the MERIT-HF trial, the COMPANION trial enrolled mainly patients in NYHA class III. Subset analysis of this trial demonstrated an extension of the time to death or rehospitalization and a trend for improved mortality by CRT in the small proportion of patients in NYHA class IV (14%).

Figure 2 Mode of death in patients with CRT dependent on baseline NT-proBNP. (A) Shows the proportions of sudden death, death from pump failure, and death from other causes. (B) Gives the absolute rates of deaths. In CRT patients with <median baseline NT-proBNP levels, the proportion of sudden death was 41% (absolute rate 5%), and the proportion of death from pump failure was 27% (absolute rate 3%). Amongst CRT patients with ≥median baseline NT-proBNP levels, the proportion of sudden death was lower (29%), but the absolute rate was higher (15%).

Concern exists that patients with advanced disease may not benefit from CRT, as the procedure of device implantation may have an adverse effect on cardiac or renal function and, thereby, worsen short-term outcome. However, this analysis suggests that high-risk patients with above median NT-proBNP have a similar gain in mortality expressed in relative terms. The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial evaluated the effects of CRT alone or combined with a defibrillator. Similar to the CARE-HF trial, the COMPANION trial enrolled mainly patients in NYHA class III. Subset analysis of this trial demonstrated an extension of the time to death or rehospitalization and a trend for improved mortality by CRT in the small proportion of patients in NYHA class IV (14%).

The effect of CRT on survival has not been established in patients with milder stages of disease. However, in the CONTAK-CD trial, which assessed the efficacy of CRT in symptomatic HF patients with malignant ventricular tachyarrhythmias, CRT induced LV reverse remodelling but no improvement in symptoms or exercise capacity in a subgroup of 263 patients in NYHA class I and II. Similarly, in the MIRACLE-ICD II study, which evaluated the effects of CRT on disease progression in NYHA II patients with an indication for an ICD, CRT did not alter exercise capacity but improved cardiac structure and function.

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The absolute and relative risk of sudden death in relation to the severity of the disease

Considerable confusion exists about proportional and absolute risk of sudden death in patients with HF. It is widely recognized that sudden death is the commonest mode of death in patients with mild symptoms. Less well appreciated is that the rate of sudden death is higher in patients with more severe symptoms of HF, even though the proportion of patients who die suddenly is lower. In other words, the rate of death due to both, pump failure and arrhythmias, increase with worsening HF, but the rate
of pump failure death increases faster, thus reducing the proportion of patients who die suddenly. Defibrillators can prevent sudden death in patients with HF, but may not improve overall survival when pump failure death is likely.\(^\text{17}\) This hypothesis is supported by an analysis of the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) revealing a survival benefit from a defibrillator in NYHA class II patients but not in NYHA class III patients.\(^\text{18}\) However, our data demonstrate that CRT reduces the risk of dying from pump failure in high (as well as low) risk patients, and that a substantial proportion of high-risk patients die suddenly. Accordingly, for many patients who are not at high risk of dying from non-cardiac disease, CRT-D(defibrillator) may be preferred to CRT alone even if symptoms and LV dysfunction are severe. Nevertheless, another approach could be to leave the D out, wait for a positive response to occur, and then discuss with the patient to potentially upgrade to a CRT-D device. Some patients might prefer to die suddenly than slowly through a protected pump failure death.

**N-terminal pro-brain natriuretic peptide predicts outcome irrespective of cardiac resynchronization therapy**

Our data indicate that NT-proBNP predicted all-cause mortality, sudden death, and death from pump failure, whether they were assigned to CRT or the control group. Similar results have been demonstrated previously with neurohormonal antagonists that are known to improve survival in patients with HF.\(^\text{9,19}\) As mortality rates remain substantially higher in patients with high baseline NT-proBNP levels even if they receive CRT, patients with high NT-proBNP levels should be monitored more carefully to ensure optimal device function and pharmacological treatment.

**N-terminal pro-brain natriuretic peptide at 3 months**

Few data exist about the prognostic significance of changes in NT-proBNP. An analysis of the Val-HeFT study demonstrated that changes in BNP at 4 months of follow-up were associated with corresponding changes in morbidity and mortality.\(^\text{19}\) Maeda et al.\(^\text{20}\) evaluated the prognostic value of BNP before and 3 months after optimization of medical therapy in an observational trial of 102 patients and reported that follow-up values predicted mortality better than baseline values. Our data are entirely consistent with these findings and support a role for monitoring patients with HF using NT-proBNP to evaluate the likely outcome after treatment.

**Limitations**

Our analyses used all-cause mortality and different modes of death as endpoints, although there are many other possible endpoints, which are positively influenced by CRT. Although the level of missing data was modest for most variables included in the statistical modelling, there was substantial missing data for the mitral regurgitation index. However, multiple imputation techniques that enable the inclusion of data from all subjects in the statistical modelling were unchanged for sudden death and death from HF, and consistent with the non-imputed model for the outcome of all-cause mortality.

**Conclusion**

N-terminal pro-brain natriuretic peptide is a powerful marker of prognosis in patients who are being considered for CRT. However, within the general range of values observed in CARE-HF, NT-proBNP is not a useful method to select patients because the relative benefit of CRT appears similar in patients regardless of their level of NT-proBNP. Our data argue strongly that the survival benefit of CRT applies similarly to patients with different stages of disease. Measurement of NT-proBNP, 3 months after implantation, was a better predictor of prognosis than baseline values, suggesting a role for NT-proBNP in monitoring the effect of CRT. The effects of CRT on survival in patients with asymptomatic LV dysfunction or mild HF remain to be determined and are being addressed in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT trial).

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**References**

A 51-year-old man was referred to our institution for NYHA functional class II dyspnea. His medical history had no chest trauma or chest pain, but was significant for a continuous cardiac murmur known since his childhood but never explored. He had no fever and biological disorder.

An echocardiography showed a large communication between the right vasa saliva sinus of the aortic root and the right ventricle (RV) outflow tract with significant left-to-right shunt (Panel A). The RV and pulmonary artery were moderately dilated, left ventricular ejection fraction was normal, and aortic and pulmonary valves were tricuspid with no valvular disease. There were no other cardiac defects. Cardiac catheterization showed no evidence of pulmonary hypertension, coronary angiography revealed normal coronary disease, and aortography showed the shunt to the RV (Panel B). Chest-computed tomography scans confirmed the isolated aorto-right ventricular fistula (Panel C) with normal sizes of aortic root and ascending aorta. Because of right cavities dilation with dyspnea, the patient had been successfully operated on for fistula (Panel D) closure.

Aorto-right ventricular fistulas are very rare entities. The target area is the bottom of the right coronary cusp which is the closest aortic zone from the pulmonary infundibulum. Most of them are consequence of valsalva aneurysm rupture, chest trauma, endocarditis of native or prosthetic valves, or aortic dissection. To our knowledge, only four cases without these aetiologies had been published. We report an exceptional case of isolated congenital aorto-right ventricular fistula in an adult.