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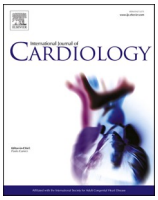

Bioactive adrenomedullin as a marker of congestion and disease progression in patients with a systemic right ventricle

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ABSTRACT

Background: Adults with a systemic right ventricle (sRV) are at a high risk for heart failure (HF) hospitalization and mortality. Bioactive adrenomedullin (bio-ADM) has been proposed as a marker of congestion and prognosis in patients with cardiovascular disease. We aimed to evaluate the association between bio-ADM and mortality and HF events in sRV patients.

Methods: Plasma bio-ADM was measured by a novel immunoassay in plasma of 85 sRV patients. A composite endpoint of all-cause mortality and HF events was used as outcome. HF events were defined as onset or progression of HF signs or symptoms requiring hospitalization, initiation or intensification of therapy. Multivariable Cox regression analyses were performed to evaluate the association between bio-ADM and outcome.

Results: The mean age of the patients was 37 ± 9 years and 65% were male. Patients with higher plasma bio-ADM concentrations were more often treated with diuretics ($p = 0.007$), possibly because of signs and/or symptoms of congestion. During a median follow-up of 10.2 years, 33.7% of the patients reached the endpoint. After adjustment for age and N-terminal pro B-type natriuretic peptide (NT-pro BNP), higher bio-ADM levels were associated with a higher risk of the composite endpoint (hazard ratio: 2.09 [95%-confidence interval: 1.15–3.78]). Bio-ADM improved risk prediction when added to NT-proBNP and age (C-statistic improved from 0.748 to 0.776 [$p = 0.03$]).

Conclusions: Bio-ADM can be considered as a marker of congestion and independent predictor of death and HF events in adult patients with a sRV. Moreover, in terms of risk prediction, it has added value to NT-proBNP.

1. Introduction

Adults with a systemic right ventricle (sRV) are at a high risk for heart failure (HF) hospitalization and mortality [1] which might be related to their increased susceptibility for congestion. Bioactive adrenomedullin (bio-ADM), a neurohormonal peptide expressed in different cells and organs, has been proposed as a marker of congestion and has been related to clinical outcomes in patients with cardiovascular disease [2,3]. Experimental studies have shown the same amount of bio-ADM expression in the right and left ventricle [4]. Moreover, bio-ADM is increasingly expressed in the right ventricle of rats with hypoxia induced pulmonary artery hypertension (PAH) [5]. Higher bio-ADM plasma concentration was associated with poor outcomes in patients with idiopathic PAH and patients with atrial septal defects and PAH [6]. However, less is known about this biomarker in patients with a systemic right ventricle.

We aimed to evaluate the correlation between bio-ADM and other biomarkers and its association with mortality and HF events in patients with a sRV. Moreover, we investigated the additional value of bio-ADM to NT-proBNP in these patients.

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2. Methods

2.1. Study population

The study investigated 86 patients born with a transposition of the great arteries (TGA) who have had an atrial switch operation according to Mustard (76%) or congenitally corrected transposition of the great arteries (ccTGA) (24%). The data were collected from a prospective cohort of clinically stable adults at the Erasmus Medical Centre between April 2011 and April 2013. Exclusion criteria included age < 18 years, pregnancy, renal dysfunction, and inability to provide informed consent.

2.2. Ethical considerations

This study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participants.

2.3. Study measurements

Patients underwent clinical examination, electrocardiography, transthoracic echocardiography, and venous blood sampling. Blood sampling was done at the day of inclusion in the study. The samples of 85 patients were available and transferred to the laboratory within 2 h from withdrawal. Samples were exposed to only 1 freeze–thaw cycle. Bio-ADM was measured in Ethylenediamine tetraacetic acid plasma samples using the immunoluminometric assay sphingotest® bio-ADM® (Sphingotec GmbH, Hennigsdorf, Germany) as described previously [7]. The laboratory performing the biomarker measurement was blinded to clinical and demographic data of the patients.

2.4. Study events

The study's endpoint was a composite of all-cause mortality and HF events. HF events were defined as symptoms requiring hospital admission, initiation or change in medications.

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) depending on the distribution. Categorical variables are presented as cases (percentage). Trends between adrenomedullin tertiles and baseline characteristics were tested with linear regression for continuous variables or the Mantel-Haenszel test for categorical variables. The Kaplan-Meier estimator was used to derive survival curves and adrenomedullin tertiles were compared using the log rank test. Multivariable survival analyses was performed using cox-proportional hazards regression in which biomarker levels were log-2 transformed. Missing values were imputed using multiple imputation with 10 imputed datasets and 25 iterations. Statistical analysis was performed using SPSS Statistics (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) and R version 4.0.5 (packages 'Survival', 'mice' and 'ggplot2'). A two-sided *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. Eighty-six patients (65% male) were included in this study (mean age 37 ± 9 years). Although 70% of the patients had at least a moderately dysfunctional sRV, most patients were in New York Heart Association (NYHA) class I (83%). Less than a third of the patients were under treatment with angiotensin converting enzyme inhibitors (ACE—I). Patients with higher plasma bio-ADM concentrations were similar to those with lower concentrations in respect to baseline characteristics except that they were more often treated with diuretics ($p = 0.007$).

3.2. Correlation of bio-ADM with other biomarkers

Bio-ADM had no significant correlation with other measured biomarkers.

3.3. Bio-ADM as predictor of events

During a median follow-up of 10.2 years (interquartile range:9.7–10.5), 33.7% of the patients had either died (9 patients) or had HF events (27 patients). Fig. 1 shows that patients in the highest tertile of bio-ADM had worse outcome compared to the other two tertiles regarding the composite endpoint of all-cause mortality or HF events. Higher bio-ADM was associated with a higher risk of this composite endpoint based on univariable Cox regression (Table 2; HR 2.41 (1.39–4.17) and this remained statistically significant when adjusted for age and NT-proBNP, HR 2.09 (95%-CI: 1.15–3.78).

3.4. Added value of bio-ADM in predicting outcome

Two strong predictors of outcome were age and NT-proBNP (C-statistics 0.748). Adding bio-ADM significantly improved risk prediction as shown by an increase in C-statistic from 0.748 to 0.776 (*p*-value 0.034).

4. Discussion

In this study, we evaluated plasma concentrations of bio-ADM in clinically stable patients with a systemic right ventricle due to transposition of the great arteries. Despite their relatively young age (37 years) their mortality or heart failure events within 10 years were considerable. This emphasizes the importance of finding early markers for prognosis and disease progression in these patients in order to intensify follow-up and start HF treatment at an earlier stage. Our finding of more diuretic use in patients with higher plasma bio-ADM concentrations suggests that they had more signs and symptoms of congestion. This is supported by previous studies showing the strong association between bio-ADM and symptoms and signs of congestion [2]. In experimental studies, it has been shown that bio-ADM is expressed in the right ventricular myocardium, and canines who have HF express more bio-ADM in their myocardium [3]. Moreover, it has been shown that treatment with ACE-I decreases bio-ADM expression in the myocardium [3]. These previous findings are in favour of our hypothesis that bio-ADM may act as a marker of congestion due to RV failure (which could be either a subpulmonary RV or a subaortic RV). We therefore argue that bio-ADM could be used as an early marker of disease progression in patients with a sRV. In conclusion, considering the added value of bio-ADM in predicting outcomes in patients with a sRV, this marker might provide clinical value that could guide intensification of follow-up and potentially more aggressive treatment, although the potential benefits of such an approach need to be prospectively tested in a bio-ADM guided trial.

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CRediT authorship contribution statement

Mohammad Mostafa Ansari Ramandi: Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Paul M. Hendriks:** Data curation, Formal analysis, Writing – original draft, Writing – review &

Table 1
Baseline characteristics of the patients based on the bio-ADM tertiles.

	Complete, n(%)	All patients (n = 86)	Tertile 1 (n = 29)	Tertile 2 (n = 28)	Tertile 3 (n = 28)	p - value
Patient characteristics						
Age, years	86 (100)	37 ± 9	35 ± 8	36 ± 11	38 ± 7	0.359
Sex, male (%)	86 (100)	56 (65)	23 (79)	16 (57)	17 (61)	0.138
Age at initial repair, years	64 (98)	–	0.74 (0.52–2.8)	0.73 [0.26–3.7]	0.97 [0.55–5.6]	0.265
Concomitant heart defect, (%)	86 (100)					
Ventricular septal defect		27 (31)	7 (24)	7 (25)	12 (43)	0.750
Pulmonary outflow tract obstruction		12 (14)	3 (10)	3 (11)	5 (18)	0.494
NHYA class ≥ II, (%)	86 (100)	15 (17)	4 (14)	5 (18)	6 (21)	0.448
Body mass index, kg/m^2	84 (98)	24.8 ± 4.0	23 ± 3	25 ± 3	26 ± 4	0.191
Systolic blood pressure, mmHg	83(97)	125 ± 14	125 ± 15	126 ± 15	123 ± 13	0.921
Diastolic blood pressure, mmHg	83 (97)	79 ± 12	78 ± 11	81 ± 12	77 ± 12	0.772
Heart rate, beats/min	84 (98)	72 ± 13	68 ± 12	70 ± 12	77 ± 12	0.651
Oxygen saturation > 90%, (%)	78 (91)	76 (97)	25 (100)	27 (100)	24 (96)	0.206
Cardiac medication use, (%)	86 (100)					
ACE-inhibitor		26 (30)	8 (28)	8 (29)	10 (36)	0.506
ARBs		5 (6)	1 (3)	2 (7)	2 (7)	0.546
B-blocker		19 (22)	4 (14)	9 (32)	6 (21)	0.474
Diuretics		17 (20)	2 (7)	5 (18)	10 (36)	0.007*
Antiarrhythmic		13 (15)	3 (10)	2 (7)	8 (29)	0.060
Anticoagulants		19 (22)	4 (14)	3 (11)	11 (39)	0.020*
Electrocardiography						
QRS duration, msec	69 (80)	114 [105–130]	117 [106–126]	111 [101–137]	114 [105–132]	0.222
Rhythm, (%)	86 (100)					0.822
Sinus rhythm		59 (68)	21 (72)	18 (64)	19 (68)	
Pacemaker rhythm		17 (20)	6 (21)	7 (25)	4 (14)	
Atrial fibrillation		4 (5)	0 (–)	2 (7)	2 (7)	
Other		6 (7)	2 (6)	1 (2)	3 (11)	
Device implantation, (%)	86 (100)					0.313
Pacemaker		17 (20)	5 (17)	5 (18)	6 (21)	
ICD		9 (10)	2 (7)	4 (14)	4 (14)	
Echocardiography						
sRV dimensions						
End-diastolic basal dimension, mm	57 (66)	59.6 ± 8.4	61.3 ± 7.5	58.2 ± 9.1	58.9 ± 8.9	0.461
End-diastolic annulus, mm	67 (78)	47.1 ± 8.6	46.7 ± 7.7	46.5 ± 10.1	49.2 ± 7.2	0.167
End-systolic area, cm^2	81 (95)	30.7 ± 7.9	32.3 ± 7.1	30.0 ± 7.7	30.9 ± 8.0	0.221
End-diastolic area, cm^2	81 (95)	41.0 ± 9.2	43.9 ± 9.7	39.9 ± 8.4	39.7 ± 8.2	0.345
sRV systolic function						
≥Moderately impaired, n (%)	86 (100)	60 (70)	22 (76)	16 (57)	22 (79)	0.998
TAPSE, mm	45 (52)	13 ± 3	12.4 ± 2.5	14.4 ± 3.2	12.4 ± 2.9	0.185
RV fractional area change, n (%)	81 (95)	25.4 ± 8.2	26.2 ± 6.7	25.3 ± 8.7	22.8 ± 7.3	0.344
Tricuspid regurgitation	86 (100)					0.600
None		12 (14)	2 (8)	1 (4)	5 (22)	
Mild		46 (53)	14 (56)	16 (61)	10 (43)	
Moderate		24 (28)	8 (32)	8 (31)	6 (26)	
Severe		4 (5)	1 (4)	1 (4)	2 (9)	
Subpulmonary LV dimensions						
LV end-diastolic diameter, mm/m^2	51 (79)	–	41.6 ± 7.2	40.1 ± 7.5	43.6 ± 11.1	0.728
LV end-systolic diameter, mm/m^2	49 (75)	–	25.3 ± 5.4	22.4 ± 6.9	29 ± 11.3	0.762
Subpulmonary LV function						
≥ Moderately impaired, n (%)	86 (100)	2 (2)	0	0	2 (7)	0.410
Laboratory						
Hemoglobin, mmol/L	81 (94)	9.5 [9.2–10.0]	9.6 [9.3–10.2]	9.4 [9.2–9.8]	9.4 [8.7–9.8]	0.370
RDW, %	81 (94)	13.1 [12.6–13.7]	12.6 [12.3–13.0]	13.3 [12.8–13.7]	13.6 [12.9–14.1]	0.913
eGFR, mL/min/1.73m^2	84 (98)	90 [81–90]	90 [89.5–90]	87 [80–90]	89 [78–90]	0.951
NT-proBNP, pmol/L	85 (99)	30.9 [17.7–58.2]	26.1 [15.9–42.1]	24.1 [17.6–58.4]	39.3 [25.9–91.6]	0.699
Hs-troponin-T, ng/L	85 (99)	6.0 [1.5–9.5]	6.1 [2.6–8.6]	4.7 [2.1–10.2]	6.7 [3.8–13.4]	0.810
GDF-15, ng/L	84 (98)	623 [501–886]	532 [467–639]	634 [481–871]	882 [643–1393]	0.103
Hs-CRP, mg/L	85 (99)	1.8 [0.8–3.5]	1.2 [0.45–2.75]	0.9 [0.5–3.1]	2.6 [1.8–5.3]	0.548
Galectin-3, ng/mL	85 (99)	12.7 [11.2–15.0]	12.0 [10.1–13.1]	12.3 [11.1–14.1]	13.8 [12.5–17.5]	0.468
Bio-ADM, pg/mL	85 (99)	16.1 [12.3–23.7]	10.8 [10.8–12.3]	16.2 [15.0–18.7]	26.3 [23.6–32.1]	N/A

ACE Angiotensin converting enzyme, ARB Angiotensin receptor blockers. Bio-ADM Bioactive adrenomedullin, CRP C reactive protein, eGFR Estimated glomerular filtration rate, GDF Growth differentiating factor, Hs High sensitivity, ICD Implantable cardioverter defibrillator, LV Left ventricle, NT-proBNP N-terminal pro B-type natriuretic peptide, NYHA New York heart association, RDW Red cell distribution width, RV Right ventricle, sRV Systemic right ventricle, TAPSE Trans annular plane systolic excursion.
1st tertile: 10.8–13.9 pg/mL, 2nd tertile: 13.9–20.5 pg/mL, 3rd tertile: 20.5–59.1 pg/mL.
*p value <0.05 significant for trend evaluated by Mantel-Haenszel test for categorical values and linear regression for numeric values.
Values are presented as numbers (percentage), mean ± standard deviation and median (IQR).

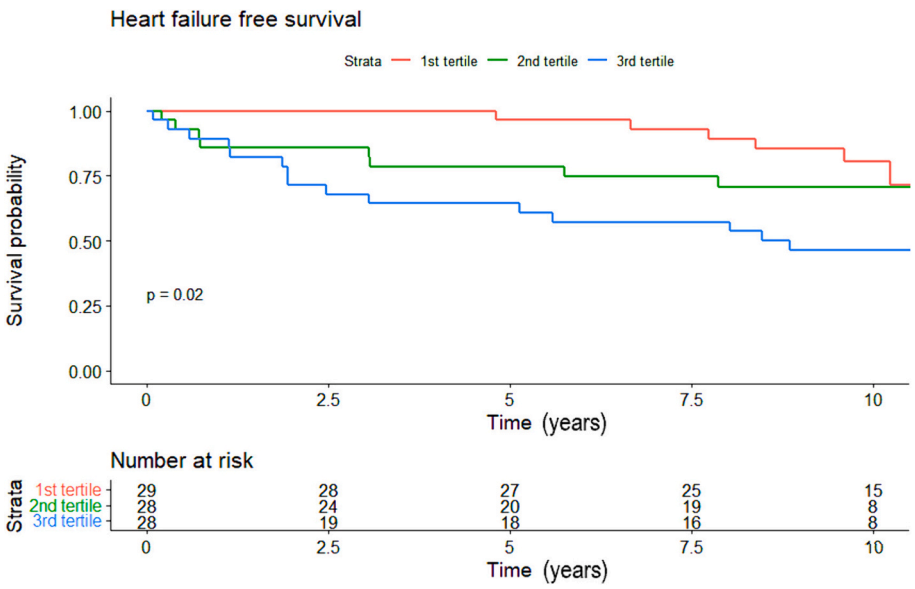

Fig. 1. Heart failure free survival stratified according to bioactive adrenomedullin tertiles.
1st tertile: 10.8–13.9 pg/mL, 2nd tertile: 13.9–20.5 pg/mL, 3rd tertile: 20.5–59.1 pg/mL.

Table 2
Cox regression analysis for composite endpoint of mortality or heart failure events.

	HR (95%-CI)	p-value
Log2-Bio-ADM	2.41 (1.39–4.17)	0.002
Log2-Bio-ADM + age + sex	2.39 (1.35–4.22)	0.003
Log2-Bio-ADM + age + NT-proBNP	2.09 (1.15–3.78)	0.015

Bio-ADM Bioactive adrenomedullin, CI Confidence interval, HR Hazard ratio, NT-proBNP N-terminal pro B-type natriuretic peptide.

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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