Hyponatraemia: a strong predictor of mortality in adults with congenital heart disease

Konstantinos Dimopoulos1,2*, Gerhard-Paul Diller1,2, Ricardo Petraco1, Evdokia Koltsida1, Georgios Giannakoulas1, Edgar Lik Tay1, Nicky Best3, Massimo F. Piepoli2, Darrel P. Francis4, Philip A. Poole-Wilson2, and Michael A. Gatzoulis1,2

1Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; 2National Heart and Lung Institute, Imperial College School of Medicine, London, UK; 3Department of Epidemiology and Public Health, Imperial College Faculty of Medicine, London, UK; and 4International Centre for Cardiocirculatory Health, St. Mary’s Hospital, London, UK

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Aims
We studied the prevalence of hyponatraemia and its prognostic implications in a large population of adult patients with congenital heart disease (ACHD).

Methods and results
A total of 1004 ACHD patients were retrospectively entered in this study (mean age 36.2 ± 14.4 years, 48.7% male). Cox regression was used to estimate mortality associated with hyponatraemia, adjusted for potential confounders using both multivariable regression and propensity score matching. Mean sodium concentration in this ACHD cohort was 137.6 ± 2.6 mmol/L. The overall prevalence of hyponatraemia in this cohort was 15.5% and was highest in congenitally corrected transposition (33.3%), after Fontan operation (29.6%), and in patients with Eisenmenger syndrome (22.0%). Predictors of hyponatraemia were worse functional class, cyanosis, higher serum creatinine levels, and treatment with diuretics. Patients were followed for a median of 4.1 years, during which there were 96 deaths. Hyponatraemia was a strong predictor of death, independent of age, previous surgery, functional class, systemic ventricular function, creatinine levels, and the use of diuretics (adjusted HR 2.82, 95% CI: 1.72–4.63, P < 0.0001).

Conclusion
Hyponatraemia is relatively common in ACHD. Hyponatraemia carries a three-fold higher risk of death in ACHD and is a simple, cheap but powerful marker of mortality.

Keywords
Congenital heart defects • Hyponatraemia • Sodium • Heart failure • Prognosis

Introduction
Hyponatraemia is common in patients with acquired congestive heart failure, usually the result of water retention in excess of sodium stores.1–3 It is an established prognostic marker in patients with acquired heart failure and ischaemic heart disease and is one of the seven variables included in the validated Heart Failure Survival Score which is currently used as a guide for listing patients for transplantation.4–7

In acquired heart failure, hypotonic hyponatraemia is the result of an increase in extracellular volume and redistribution of sodium in body compartments in conjunction with sodium retention and increase in total body sodium.2,3 Neurohormonal activation is considered important in the pathogenesis of hyponatraemia in these patients. Recent data suggest that significant neurohormonal activation is also present in adult patients with congenital heart disease (ACHD).8–11 We aimed to investigate the prevalence of hyponatraemia in a large population of ACHD patients and assess its relation to mortality.

Methods
Study subjects
Data on all ACHD patients attending our centre that had serum sodium levels measured between January 2000 and December 2005 were collected retrospectively. Diagnosis of congenital heart disease had been made by echocardiography, cardiovascular magnetic...
resonance, and/or cardiac catheterization. Patients with more than one diagnosis were classified according to the prevalent lesion. Demographic and clinical data were collected from dedicated clinical databases and clinical records. Cyanosis was defined as resting oxygen saturation < 90%. Systemic ventricular function was classified according to a 3-point semiquantitative scale into normal, mildly impaired, and moderately or severely impaired (due to inherent difficulties in applying quantitative measures such as ejection fraction across the spectrum of ACHD).13

Survival status and time of death was ascertained through the health service computer system, linked to the national database held by the Office of National Statistics. Approval by the local Ethical Committee was obtained for the study.

Statistical analysis
Analyses were performed using R version 2.8.1 (http://cran.r-project.org/) and the packages survival and Matchit and Amelia.13 Hyponatraemia was defined as sodium plasma concentration < 136 mmol/L.2 All variables entering the analyses were measured at baseline. Numerical values are presented as mean ± standard deviation and factor variables as percentage of total. Comparisons between groups were performed using Wilcoxon’s rank sum test or Fisher’s test as appropriate. Univariable and multivariable logistic regression was used to identify demographic and clinical predictors of hyponatraemia. Model selection was performed by minimisation of the Akaike information criterion (AIC).

Univariable Cox-regression analysis was used to assess the relation between hyponatraemia and the clinical endpoints of death. Verification of the proportional hazards assumption was performed assessing the correlation between the scaled Schoenfeld residuals and time.14 When evidence of violation of the proportional hazards assumption was found, additional analyses were performed using violating parameters as strata in the model. Unadjusted Kaplan–Meier survival curves were also plotted and difference in survival between patients with and without hyponatraemia was assessed using the Logrank test.

To explore the functional form of the relationship between sodium concentration as a continuous predictor and the risk of death, smoothing splines were applied in a separate Cox regression using AIC to select the degrees of freedom of the spline. Penalized splines were used (function pspline, package survival, which fits a comparatively small set of splines penalising the integrated second derivative).

A multivariable Cox model was also built using a limited number of clinically relevant covariates (n = 9) due to the limited number of events in our study. Multiple imputation was used to account for missing data (n = 10 imputed databases). To check the robustness of our findings, an alternative analysis of the relation between hyponatraemia and mortality was carried out using propensity score matching to adjust for baseline differences between the hyponatraemic and non-hyponatraemic groups. Propensity scores were computed using logistic regression with hyponatraemia as the dependent variable and baseline demographic and clinical variables as independent variables: age, sex, cyanosis, New York Heart Association (NYHA) functional class, previous palliative surgery, previous reparative surgery, systemic ventricular systolic function on a semiquantitative 3-level scale (normal, mild dysfunction, moderate–severe dysfunction), left-sided outflow tract obstruction/aortic stenosis, previous/current arrhythmia, treatment with diuretics, beta-blockers, angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), digoxin, warfarin, and aspirin. Parameters included were decided based on clinical criteria of relevance to the model. Propensity scores were used to perform 5:1 nearest neighbour matching (five non-hyponatraemic to one hyponatraemic patient) within a caliper of 0.10 standard deviations of the propensity score. Balance was verified by assessing standardized differences between groups for all variables in the matched cohort. A target of <10% standardized difference for all variables was set and achieved. Cox regression was used to compare mortality between the two groups in the matched cohort, combining matched sets into larger strata with propensity scores within the same quintile.

All P-values were two-sided and a P-value of < 0.05 was pre-specified as indicative of statistical significance.

Results

Patient population
In total, 1004 ACHD patients were analysed. Demographic and clinical characteristics of these patients are described in Tables 1 and 2. Patients with all major types of ACHD were included in the population. Mean age was 36.2 ± 14.4 years. Patients with a previous Fontan or Mustard-type operation were the youngest groups, whereas patients with atrial septal defects were the oldest. Nearly 40% of patients complained of symptoms at the time of assessment, and 14.1% were moderately or severely impaired (NYHA class 3 or above). Eisenmenger patients were the most symptomatic (51.3% in NYHA class 3 or more), followed by patients with ‘complex’ anatomy (28.6%) and congenitally corrected transposition of the great arteries (25%). Overall, 27.7% of patients were receiving treatment with diuretics.

Predictors of hyponatraemia among adults with different congenital heart defects
Mean sodium concentration in all ACHD patients was 137.6 ± 2.6 mmol/L and was lowest in patients with congenitally corrected transposition of the great arteries (136.2 ± 3.8 mmol/L) and those with Fontan operation (136.7 ± 3.9 mmol/L, Table 1). Eighty percent of ACHD patients had a sodium concentration below 140 mmol/L (Figure 1).

Hyponatraemia was present in 156 (15.5%) patients. In the congenitally corrected transposition of the great arteries and Fontan groups, one-third of patients were hyponatraemic (Figure 2). Hypo-natraemia was present in over 20% of patients with Eisenmenger syndrome or Ebstein anomaly of the tricuspid valve.

The risk of hyponatraemia was higher among patients with moderate or severe functional impairment (OR of hyponatraemia in NYHA class 3–4 compared with asymptomatic patients 1.61, 95% CI: 1.00–2.61, P = 0.049, prevalence in NYHA class 3–4 patients 21.7%). Hyponatraemia, however, was present even in asymptomatic (NYHA 1, 14.6%) and mildly symptomatic (NYHA 2, 15.5%) patients. Patients receiving diuretics (OR 1.47, 95% CI: 1.02–2.12, P = 0.036) and patients with higher plasma creatinine levels (OR for 1 mg/dL increase 2.04, 95% CI: 1.31–3.16, P = 0.001) were, as expected, at increased risk of hyponatraemia. Cyanotic patients also had a strong trend towards hyponatraemia (OR 1.49, 95% CI: 0.98–2.29, P = 0.06). On multivariable analysis, plasma creatinine level was the sole independent predictor of hyponatraemia.
Follow-up was complete for all patients. During a median follow-up of 4.1 years, a total of 96 patients died. The majority of deceased patients (55/96) belonged to the Eisenmenger (n = 16), ’complex diagnoses’ (n = 15), ’valvar’ disease (n = 12), and Mustard groups (n = 12). Thirty-five out of the 156 hyponatraemic patients died.
during this period (mortality rate 5.7%, 95% CI: 4.0–7.9), vs. 61/848 in the group without hyponatraemia (mortality rate 1.7%, 95% CI: 1.3–2.2). Five-year death rate in hyponatraemic patients was 21.6 vs. 7.5% in those without hyponatraemia (Log-rank P-value < 0.0001, Figure 3A). The difference in event rates between hyponatraemic and non-hyponatraemic patients was already evident after 1 year of follow up (2 vs. 10%, P < 0.0001).

On univariate Cox survival analysis, patients with hyponatraemia had a three-fold increase in the hazard of death (HR 3.26, 95% CI: 2.15–4.95, P < 0.0001). When treating plasma sodium levels as a continuous predictor, the hazard of death decreased with increasing concentrations up to a value of ≤136 mmol/L and appeared to remain constant thereafter (Figure 3B). Few ACHD patients had sodium levels above 141 mmol/L, resulting in confidence intervals too wide to determine prognostic effects.

After adjustment for other univariate predictors of death including age, cyanosis, previous surgery, functional class, systemic ventricular function, creatinine levels, use of diuretics, and previous arrhythmia, hyponatraemia remained a strong predictor of death (adjusted HR 2.59, 95% CI: 1.68–3.97, P < 0.0001). When use of diuretics and previous surgical repair were used as strata in the multivariable Cox model to account for violation of the proportional hazards assumption, results remained essentially unchanged (adjusted HR for hyponatraemia 2.62, 95% CI: 1.71–4.03, P < 0.0001). Similar results were obtained using propensity score analysis (HR 2.82, 95% CI: 1.72–4.63, P < 0.0001).

**Discussion**

Hyponatraemia is relatively common among ACHD patients. Patients with hyponatraemia tend to have more functional impairment, higher plasma creatinine levels, and be receiving diuretics. Hyponatraemia is associated with a three-fold increased risk of death in ACHD patients and this strong association is independent of renal function and the use of diuretics.

**Hyponatraemia: a common complication in adult patients with congenital heart disease**

The prevalence of hyponatraemia in ACHD patients with at least moderate functional impairment was comparable to that reported...
for older patients admitted in hospital for severe or decompensated acquired heart failure. However, while hyponatraemia is usually encountered in individuals with advanced acquired heart failure, we found a relatively high prevalence of hyponatraemia in asymptomatic (14.6%) and mildly symptomatic ACHD patients (15.5%). Moreover, a shift towards lower sodium concentrations was observed in this ACHD population, in which only one out of five patients had sodium levels above 140 mmol/L. This trend towards lower sodium levels reinforces recent observations of significant neurohormonal and autonomic activation even in asymptomatic ACHD patients, supporting the concept that subjective assessment of disease severity using the NYHA classification may underestimate the degree of impairment in ACHD.

Hyponatraemia appears to be a common feature of a spectrum of cardiac diseases that result in neurohormonal activation, which combined with vasopressin dysregulation results in defective water excretion. Hyponatremia with increased extracellular fluid volume (dilutional) is the most common type of hyponatraemia in acquired heart failure. Activation of the adrenergic and renin–angiotensin systems and reduction in glomerular filtration rate result in avid re-absorption of sodium and water at kidney level. Arginine vasopressin (AVP), also known as antidiuretic hormone, is produced in the hypothalamus and plays an important role in volume homeostasis. Serum AVP is chronically elevated in acquired heart failure and increases free water re-absorption by acting on the renal collecting duct as well as raising systemic vascular resistance.

The pathogenesis of hyponatraemia in ACHD is likely to be similar to that of acquired heart failure. Hyponatraemia, like neurohormonal activation, is a systemic manifestation of diseases that are included in the wide spectrum of ‘heart failure’ and have a chronic reduction in cardiac output as a unifying feature. Patients with congenitally corrected transposition of the great arteries, Fontan-type operations, and Eisenmenger syndrome had the highest levels of hyponatraemia and were associated, in turn, with severe reduction in systemic cardiac output through different pathophysiologic mechanisms, namely: failure of the right ventricle in the systemic circulation (a common complication of ccTGA after the third decade of life), univentricular circulation and limitation of pulmonary blood flow with cyanosis, respectively.

The relation between sodium levels and prognosis

Hyponatraemia defined as sodium concentration <136 mmol/L identified patients at a three-fold increased risk of death in our study. Patients with hyponatraemia (sodium concentration <136 mmol/L) had a three-fold increased mortality risk in our study. (B) Functional form of the unadjusted relationship between sodium concentration and the hazard of death (on a logarithmic scale) using smoothing splines with 4 degrees of freedom. The fitted spline function is plotted with pointwise standard errors.
ACHD cohort, both at mid and longer-term (Figure 3A). As no established cut-off for the definition of hyponatremia exists, we sought to assess the validity of the definition used in this study in relation to prognosis. The <136 mmol/L cut-off for defining hyponatremia in ACHD appears appropriate for prognostic purposes. In fact, a threshold effect was seen at 136 mmol/L, with no significant threshold effects above this cut-off for hyponatremia, but an increasing risk of death with increasing severity of hyponatremia in patients classified as hyponatremic (Figure 3B).

Hyponatremia remained a strong prognostic marker even after adjustment for other important parameters such as functional class and renal dysfunction. Thus, despite the strong relation between hyponatremia and both creatinine and NYHA class, the predictive power of hyponatremia goes beyond its relation to renal function or functional capacity.

Hyponatremia is an established predictor of outcome in patients with acquired heart failure, both hospitalized and non.30–32 Both the Heart Failure Survival Score—now used for risk stratification of candidates for cardiac transplantation—and the Seattle Heart Failure Model include sodium levels in their validated prediction models.4,5,33 Hyponatremia is also a strong predictor of outcome in ischaemic heart disease.34 Hyponatremia during the early phase of ST-elevation myocardial infarction was able to predict long-term outcome, independent of left-ventricular ejection fraction.

The prognostic power of hyponatremia in both congenital and acquired cardiac disease, we speculate, may relate, at least in part, with neurohormonal activation. Norepinephrine, atrial and brain natriuretic peptides, and endothelin-1 are independent markers of outcome in patients with acquired heart failure and ischaemic heart disease.35–38 Elevated AVP plasma levels are also associated with increased mortality in acquired heart failure.39

**Clinical implications**

Our findings have several clinical implications. Hyponatremia could be used as a cheap and simple but powerful prognostic marker in the clinical assessment and risk stratification of ACHD patients, either alone, or within a comprehensive risk score. Sodium levels could also be used to guide management. Correction of hyponatremia is associated with improved outcome in acquired heart failure and could be an index of adequacy of treatment. Finally, in hyponatremic patients, preference should be given to loop over thiazide diuretics, as the latter may decrease free water clearance.

**Limitations**

The ACHD cohort reported in this retrospective study consisted of patients who underwent mostly blood testing for clinical purposes and few as part of research protocols. It is conceivable, therefore, that more impaired patients were likely to undergo blood testing, introducing a bias in the analysis of the prevalence of hyponatremia, but not of the relation between hyponatremia and mortality. Furthermore, our patients are presented with the option to have their blood tests with us or locally. Thus, even though a selection bias cannot be excluded, this is likely to be marginal. Furthermore, our institution does not have an Accident and Emergency Department and patients are transferred to us from other hospitals once stable if acute decompensation had previously occurred. Thus, it is highly unlikely that the population reported here includes patients in acute heart failure. Last but not least, our study cohort is fairly representative of current ACHD practice, both in demographics and morphological/clinical characteristics, with 86% of patients being asymptomatic or mildly symptomatic at the time of blood sampling.30

Despite varied cardiac anatomy and physiology, ACHD patients seem to share common late pathophysiological mechanisms and, with longer follow-up, develop the clinical phenotype of the acquired chronic heart failure syndrome. Future prospective studies including ACHD patients not reaching routine tertiary care may shed additional light on the mechanisms of hyponatremia in ACHD and its potential role as a marker of disease progression and response to therapy.

**Conclusions**

Hyponatremia is relatively common in ACHD and is associated with a three-fold increased risk of death. Its prognostic impact is independent of renal function and use of diuretics. Plasma sodium concentration is a simple, cheap but powerful marker of mortality in ACHD and should be incorporated in the periodic assessment of these patients.

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**Conflict of interest:** none declared.

**References**

Hyponatraemia in ACHD


