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ORIGINAL ARTICLE

Donor hypo- and hypernatremia are predictors for increased 1-year mortality after cardiac transplantation

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Summary

Donor hypernatremia is known to be associated with initial graft dysfunction in liver transplantation. Controversial data exist regarding the impact of sodium dysregulation on patient survival after heart transplantation (HTX). The aim of this study was to investigate the influence of donor sodium levels on survival in a large cohort of heart transplant recipients from the Eurotransplant registry. From 1997 to 2005, all consecutive adult HTX performed in the Eurotransplant region were included into this study (n = 4641 patients). Multivariate analysis was applied to investigate possible clinical predictors for 1-year post-transplant survival after cardiac transplantation (donor sodium levels, donor age, donor cause of death, recipient age, primary disease, urgency status, cold ischemia time). In multivariate analysis, recipients receiving a donor heart with serum sodium level lower than 130 mmol/l or higher than 170 mmol/l had a 1.25-fold higher risk for 1-year post-transplant mortality than patients with normal donor sodium ranges (P = 0.007). Other independent risk factors for impaired 1-year survival were recipient age, the indication for transplantation and the urgency status of the recipient. Our study demonstrates that hyponatremia as well as hypernatremia show a strong U-shaped correlation with poor survival after cardiac transplantation. Accurate donor management to avoid electrolyte disorder seems to be crucial for ensuring good quality of donor hearts.

Introduction

Because of the increasing number of patients with end-stage congestive heart failure awaiting heart transplantation (HTX) and the limited number of suitable donor organs, expansion of donor criteria by using so called 'marginal' donor organs has become widely accepted over the last decade. Especially in kidney transplantation, donor pool expansion by introduction of 'old for old' programs has led to an increase in the number of transplantable donor organs [1]. Additionally, continuous progress in the treatment of recipients by alternative immunosuppressive regimens have resulted in good survival after HTX and therefore attempts have been made to extend donor criteria to expand the donor heart pool. However, accepting organs from expanded criteria donors could be associated with adverse outcome and is still a matter of debate, even in the field of cardiac retransplantation [2].

Several donor-derived risk factors, such as donor age, are well known to have an impact on recipient survival [3]. Brain death may result in disturbed electrolyte homeostasis leading to excessive sodium levels [4,5].

A review of the current literature reveals that the impact of hypernatremia on outcome after HTX is still debatable. Most publications report on liver transplantation and are of limited sample size; only few publications

were focused on HTX. Moreover, an established mechanism for organ damage attributable to elevated sodium levels is not defined.

In addition, hyponatremia can be also observed in brain-dead organ donors. As a possible explanation for this phenomenon, either of the cerebral salt wasting syndrome (CWS) or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been stated by recent publications, but the impact of hyponatremia on the clinical outcome after solid organ transplantation is still completely unclear [5–8].

The aim of this study was to analyse the influence of sodium level disturbances on survival after cardiac transplantation in a cohort of 4641 recipients within the Eurotransplant region.

Patients and methods

All consecutive isolated adult heart transplants (retransplantations excluded) performed between the period January 1, 1997 and December 31, 2005 in Eurotransplant were analysed ($n = 5297$). Clinical follow-up regarding the mortality data was complete in 4641 recipients, and these patients were amenable for statistical analysis.

Donor serum sodium levels at the time prior to organ procurement were analysed. Other laboratory parameters such as troponin levels or clinical information such as cardiac function or inotropic requirement were not included into the analysis as the amount of data reported to the registry was too low to allow significant analysis.

Statistical analysis

Demographic data on categorical variables are shown as absolute numbers as well as percentages. Statistical analysis was performed according to the practical guidelines for surgical studies by Klingler [9].

Concerning risk analysis regarding donor sodium levels, we first searched for threshold values. Thus, sodium levels were divided into 10 subgroups and then each category was tested in a Cox proportional hazards model for their association with the event indicator.

Kaplan–Meier survival analysis and log-rank testing was performed to evaluate clinical parameters on their possible influence on post-transplant survival. In a second step, a multivariate Cox proportional hazards model was applied to investigate independent predictors for 1-year mortality by means of hazard ratios (HR) and their 95% confidence intervals. Inclusion criteria for the multivardiate statistical analysis were statistical significance in the univariate statistical analysis and clinical relevance.

Covariates analysed for their influence on 1-year survival were donor age, donor-related cause of death, recipient age, primary disease, donor/recipient weight match, cold ischemic time and urgency status at the time of transplant.

A P-value <0.05 was considered to be statistically significant. SPSS software Version (SPSS Inc., Chicago, IL, USA) 12.0 was used for statistical analysis.

Results

Cox proportional hazards model revealed serum sodium levels of lower than 130 mmol/l and higher than 170 mmol/l as risk factors, this was found in 154 donors (3.3%). This constellation was defined as 'excessive donor sodium levels'. Cut off values used in previous reports were not found to show significant influence. There were no significant differences in demographic donor- and recipient-related variables among recipients with normal or excessive donor sodium levels (Table 1).

Table 1. Demographic data stratified by groups of donor sodium values ($n = 4641$).

	DS < 130 and DS ≥ 170 mmol/l ($n = 154$)	DS 130–169 mmol/l ($n = 4487$)	*P*-value
Donor age			
0–9 years	0 (0)	3 (0.1)	0.08
10–15 years	9 (9)	109 (2)	
16–49 years	113 (73)	3538 (79)	
50–59 years	26 (17)	714 (16)	
60 + years	6 (4)	123 (3)	
Donor cause of death cerebral vascular			
Accident	59 (38)	1780 (40)	0.3
Head trauma	70 (46)	1789 (40)	
Other	25 (16)	918 (20)	
Recipient age			
16–40 years	29 (19)	672 (15)	0.3
41–55 years	49 (32)	1662 (37)	
56–65 years	69 (45)	1884 (42)	
66 + years	7 (4)	269 (6)	
Primary disease			
CAD	46 (30)	1413 (32)	0.2
DCM	74 (48)	2332 (52)	
Other	34 (22)	742 (16)	
Urgency status			
Highly urgent	34 (22)	877 (20)	0.08
Urgent	116 (75)	3568 (79)	
Elective	4 (3)	42 (1)	
D/R weight match			
<0.8	18 (12)	454 (10)	0.5
0.8–1.2	117 (76)	3334 (74)	
≥1.2	19 (12)	699 (16)	
Cold ischemia time (h) mean	2.2	2.2	0.7

Values in parenthesis are expressed in percentage.
DS, donor sodium; D, donor; R, recipient; CAD, coronary artery disease; DCM, dilated cardiomyopathy.

One-year survival was significantly lower in the group with out-of-range donor sodium levels compared with recipients receiving a donor heart with normal donor sodium levels (1-year survival: 64% vs. 74%, log-rank $P = 0.007$). Actuarial survival within 1 year after transplantation is displayed in Fig. 1. The survival difference was mainly determined because of higher mortality within the first 3 post-transplant months.

Multivariate analysis

In the multivariate statistical analysis by means of the Cox proportional hazards model, isolated hyponatremia as well as hypernatremia were no significant risk factors because of the low number of affected donors. However, combined excessive donor sodium levels still revealed to be an independent predictor for 1-year survival [hazards ratio, HR: 1.25; 95% confidence interval (95% CI): 1.04–1.50; $P = 0.02$]. Additionally, other clinically relevant factors such as donor age (HR: 1.02 per year, 95% CI: 1.01–1.02, $P < 0.001$), recipient age (HR: 1.007 per year, 95% CI: 1.001–1.01, $P = 0.02$), indication for cardiac transplantation (dilated cardiomyopathy HR: 0.85, 95% CI: 0.75–0.98); other indications: HR: 1.26, 95% CI: 1.06–1.49, $P < 0.001$), urgency status (HR: 0.74 for elective vs. highly urgent, 95% CI: 0.63–0.86, $P < 0.001$) were found to be independent risk factors for mortality (Table 2). Donor and recipient weight mismatch and cold ischemia time failed to show statistical significance in the multivariate analysis.

Figure 2 shows the hazard ratios for 1-year mortality after HTX for the different categories of donor serum sodium. The association with 1-year mortality was lowest in donor serum sodium ranges from 135 to 144 mmol/l

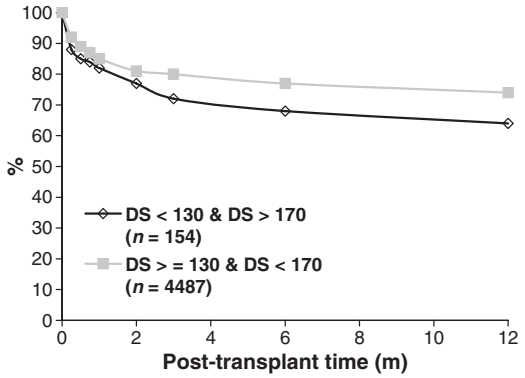

Figure 1 Actuarial 1-year survival (Kaplan–Meier survival analysis) in heart transplant recipients with normal (upper line) and excessive donor sodium levels (DS) (lower line). Actuarial 1-year post-transplant survival was 74% in recipients with normal donor sodium ranges and 64% in patients with hypo- or hypernatremia (log rank $P = 0.007$).

Table 2. Multivariate analysis for 1-year mortality.

Factor	HR	CI	*P*-value
Donor sodium levels			
130–169 mmol/l	1		0.02
<130 and ≥170 mmol/l	1.25	1.04–1.50	
Donor age (per year)	1.019	1.01–1.02	<0.0001
Donor cause of death			
Head trauma	1		0.4
CVA	0.94	0.81–1.09	
Other	1.05	0.89–1.24	
Recipient age (per year)	1.007	1.001–1.01	0.02
Primary disease			
CAD	1		<0.0001
DCM	0.85	0.75–0.98	
Other	1.26	1.06–1.49	
Urgency status			
Highly urgent	1		<0.0001
Urgent	0.80	0.44–1.49	
Elective	0.74	0.63–0.86	
Cold ischemia time (per minute)	1.002	0.96–1.04	0.9

HR, hazard ratio; CI, confidence intervals; CVA, cerebrovascular accident; CAD, coronary artery disease; DCM, dilated cardiomyopathy.

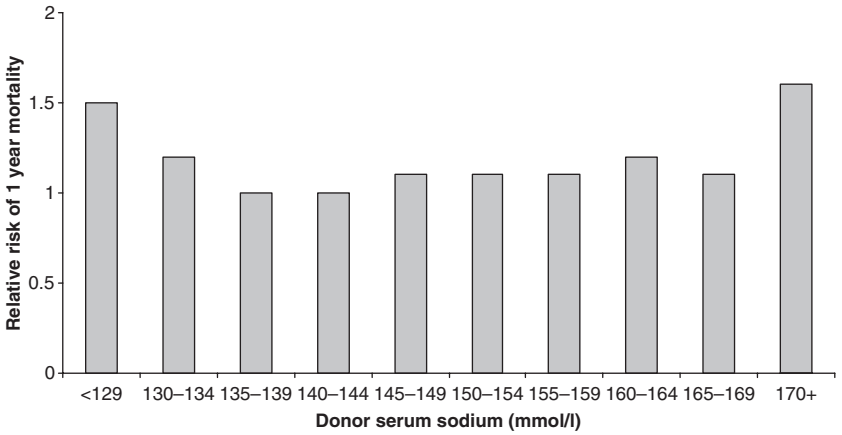

Figure 2 Hazards ratios for 1-year mortality after heart transplantation, for different donor serum sodium levels.

and highest in recipients with donor sodium ranges exceeding 170 mmol/l. Additionally, there was a clear U-shaped association of donor sodium levels and increased mortality in patients with out-of-range donor sodium levels.

Discussion

This study comprises the largest cohort ever analysed on the influence of donor sodium levels on early and intermediate survival after cardiac transplantation. Multivariate analysis revealed donor hypo- and hypernatremia to be independent predictors for 1-year survival indicating a 1.25-fold higher risk in recipients receiving a cardiac allograft from a donor with high or low donor sodium.

So far, the topic of donor sodium levels had been controversially discussed mainly in the field of liver transplantation. Several authors have reported hypernatremia to be a risk factor for adverse outcome after liver transplantation [10–16], however, most of these studies are retrospective analyses and the number of patients in these studies did not exceed more than several hundreds. On the other hand, some authors could not find an influence of donor sodium levels on outcome in liver transplantation [17–19], but the number of patients in these studies ranged from 35 to 336 and the study by Jawan *et al.* was based on an animal model in rats.

Only limited data have been reported concerning cardiac transplantation. Kaczmarek *et al.* could not find any impact of donor sodium levels on the outcome in their single-center analysis consisting of 336 heart transplant recipients, but the rather low donor sodium levels in their high-risk group (162 ± 6.6 mmol/l) was limiting their results [20]. In a second multicenter trial, the division of donor serum levels into four quartiles may have led to underestimation of extreme donor sodium levels [21].

Possible explanations for elevated donor sodium levels are the development of diabetes insipidus after brain death [4,5,22], excessive sodium infusions during a prolonged intensive care unit stay [8] resulting in severe cellular damage [12] and so called 'non optimal' management of organ donors [15].

Mechanisms claiming to be responsible for organ damage resulting from hypernatremia have been hypothesized in the current literature. Intracellular Na^+ accumulation caused by acidosis and H^+/Na^+ exchange during ischemia and the Ca^{2+} influx via Na^+/Ca^{2+} channels resulting in cellular Ca^{2+} overload during reperfusion have been stated as a major mechanisms resulting in reperfusion injury and might be aggravated by high donor sodium levels. [20,23,24]. However, these considerations concerning donor hypernatremia have not been supported by experimental studies so far. Another possible mechanism for adverse outcome after liver transplantation has been described in a study by Gonzales *et al.* [10]. A graft obtained from a hypernatremic donor may be damaged after being placed into the normotonic milieu of the recipient because of an increase of its intracellular water content caused by the persistence of the intracellular osmoles. Furthermore, the sodium efflux might be compromised as a consequence of the metabolic derangement during ischemia and reperfusion [10,25,26]. On the other hand, this theory could not be supported by the study by Jawan *et al.* performing experiments with hypernatremic rats as they did not find increased intracellular water content after a rather short period of hypernatremia of 3 h [17].

Hyponatremia is known to occur especially in patients with severe cerebral lesions and fast onset of brain death. CWS and SIADH are known syndromes in these patients. [6–8] However, in respect of these patients, a possible mechanism causing organ damage after transplantation has not been described so far. Therapeutic options for hypernatremia and other dysregulated systems as a consequence of cerebral death have been reported previously in the recent literature [5,11,16,27].

In a study of Totsuka *et al.*, donor sodium levels have been corrected by the use of vasopressin. The results of their prospective study reporting on 181 patients with severe hypernatremia were quite impressive as, after correction of donor hypernatremia before liver procurement, the amount of graft loss could be decreased significantly [11]. In addition to these convincing results, Van da Walker discussed the use of vasopressin or desmopressin even in the absence of diabetes insipidus in organ donors to decrease donor sodium levels [16].

Finally, our study demonstrated a clear U-shaped correlation of high- and also low donor sodium levels and its influence on 1-year mortality after cardiac transplantation. Although, according to the liver transplant study by Dawwas, this effect was mainly evident within the first 3 months after transplantation, indicating that hypo- and hypernatremia may predominantly affect initial graft function [19].

Limitations of this study are the retrospective setting and the use of registry data limiting the number of reported variables to the Eurotransplant registry. Donor sodium levels used for this analysis were those that had been reported to Eurotransplant not necessarily immediately before organ procurement, the latest available data had been analysed. Other parameters like inotropic support or detailed evaluation of heart function are not reported to the registry on a routine basis, so these variables were not analysed.

Regarding our results, hearts from hypo- or hypernatremic donors can be used for HTX only with great caution. However, the increase of relative risk for mortality was significant only in the extreme ranges of donor sodium levels. These extreme donor sodium levels are possibly a surrogate

parameter for non optimal donor management. It might be useful to examine these organs accurately for other risk factors, including echocardiographic evaluation and if possible coronary angiography [28]. If several additional risk factors for adverse outcome are present (e.g. estimated long ischemic time, older donor age) these organs can not be recommended even in the circumstances of donor shortage. Furthermore, experimental models are required for a better understanding of possible mechanisms of organ damage attributable to sodium dysregulation.

Authorship

DH: wrote paper. ER-U: analysed data. JS: analysed data. ED: collected data. HA: internal review. GL: designed study.

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