Letter to the Editor

Prognostic value of anemia in predicting sudden death of patients with diastolic heart failure

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Abstract

It has been reported that anemia is a prognostic predictor in patients with diastolic heart failure (DHF), however, the relationship between anemia and sudden death in those patients is still unclear. We prospectively studied 357 stable DHF patients and the proportion of anemic patients was 39% of the study population. During the mean follow-up period of 3.6 ± 1.7 years, 30 (8.4%) patients died suddenly. Importantly, the Cox proportional-hazards regression analysis showed that lower hemoglobin level was significantly associated with the development of sudden death in the multivariate model ($P < 0.001$). Anemia may be an important therapeutic target to reduce sudden death in DHF patients.
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Mild to moderate anemia is common in patients with chronic heart failure (CHF) and it causes a poor prognosis [1]. Patients with diastolic heart failure (DHF) account for 30–50% of CHF patients, whose prognosis is poor as compared with those with systolic dysfunction [2]. Recently, it was reported that anemia is associated with the increased mortality in patients with DHF [3]. However, little is known regarding the association between anemia and the development of sudden death.

In February 2000, we started prospectively a hospital-based CHF registry called the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) in order to analyze characteristics and prognosis of patients with CHF [4]. Of 1278 patients included in the CHART registry, 357 patients with DHF are the subjects of the present study. The diagnosis of heart failure and DHF was based on the criteria of the Framingham study and the report by Vasan et al. [5,6].

We excluded patients who were receiving hemodialysis, those who had uncorrected valvular dysfunction, and those with malignant neoplasm/gastrointestinal disease at the entry. Anemia was defined as hemoglobin (Hb) <12 g/dl in women and <13 g/dl in men using the World Health Organization (WHO) definition [7]. The end points were all-cause mortality and cause-specific mortality. Sudden death was the summation of *sudden cardiac death,* (witnessed sudden death with or without documented ventricular fibrillation, death within 1 hour of new symptoms, or nocturnal death with no prior history of worsening symptoms), *survived ventricular fibrillation*, and *implantable cardioverter-defibrillator (ICD) discharge*.

Baseline characteristics of the subjects were shown in Table 1. The mean Hb level was 13.0 ± 2.1 g/dl and patients with ischemic etiology, left ventricular hypertrophy accounted for 28%, 54% of the study population, respectively. Anemic patients were more severely symptomatic and were also associated with higher age, higher level of B-type natriuretic peptide (BNP), lower body mass index (BMI), lower glomerular filtration rate calculated using the simplified Modification of Diet in Renal Disease formula and

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lower usage rate for beta-blocker or angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB). The numbers who reached the endpoints are also shown in Table 1. During the mean follow-up period of 3.6 ± 1.7 years, 30 (8.4%) patients died suddenly. To investigate detailed relationship between anemia and the mortality, multivariate Cox proportional-hazards regression analysis was conducted as shown in Table 2. Low Hb level, high BNP level, diabetes, and male gender were significantly associated with the increased mortality in patients with DHF and the usage of ACEI/ARB was significantly associated with increased survival in those patients. Importantly, it also revealed that Hb level was the only independent factor which was significantly associated with the development of sudden death. Adjusted survival curves showed that the all-cause mortality of anemic patients was significantly higher than that of non-anemic patients as shown in Fig. 1. Anemic patients in the present study had the significant increased risk

Table 1
Baseline characteristics of the study population and events

	Overall (N=357)	Anemic (N=140)	Non-anemic (N=217)	p
Patients' characteristics				
Age	67.7 ± 13.4	72.0 ± 11.5	64.9 ± 13.9	<0.001
Male	62.5%	61.4%	63.1%	0.75
BMI	23.6 ± 3.6	22.4 ± 3.7	24.4 ± 3.4	<0.001
Patients' symptom				
NYHA	1.97 ± 0.58	2.10 ± 0.60	1.89 ± 0.55	0.001
Laboratory data				
Hemoglobin (g/dl)	13.0 ± 2.1	11.1 ± 1.4	14.3 ± 1.3	–
eGFR (ml/min/1.73 m²)	87.2 ± 33.2	77.3 ± 34.3	93.6 ± 30.9	<0.001
BNP (pg/ml)	204.9 ± 287.0	260.9 ± 327.3	168.8 ± 251.9	0.005
Echocardiography				
LVDD (mm)	51.2 ± 8.3	50.7 ± 7.6	51.5 ± 8.7	0.38
LVEF (%)	63.1 ± 10.4	63.0 ± 9.9	63.2 ± 10.7	0.91
Medical history				
Ischemic etiology	27.7%	30.0%	26.3%	0.45
LV hypertrophy	54.1%	60.0%	50.2%	0.07
Hypertension	50.4%	50.0%	50.7%	0.90
Diabetes	20.7%	20.0%	21.2%	0.78
Hyperlipidemia	14.8%	12.9%	16.1%	0.39
Atrial fibrillation	43.1%	43.6%	42.9%	0.89
Ventricular tachycardia	13.2%	15.0%	12.0%	0.42
Medical treatment				
Beta blocker	29.7%	20.0%	35.9%	<0.001
ACEI/ARB	71.4%	65.0%	75.6%	0.03
Status				
All-cause death	90	52	38	
Sudden death	30	19	11	

Values are presented as mean ± standard deviation or %. *P* value refers to comparisons between anemic or non-anemic patients using *t* test for continuous variables and χ^2 tests for categorical variables.
Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; DD = end-diastolic diameter; EF = ejection fraction; eGFR = estimated glomerular filtration rate; LV = left ventricular; NYHA = New York Heart Association functional class.

Table 2
Results of multivariate Cox proportional-hazards regression analyses

Events	Factor	HR	95%C.I.			p
All-cause mortality	Hb (per 1 g/dl increase)	0.75	0.68	–	0.84	<0.001
	BNP (per 1 pg/ml increase)	1.01	1.01	–	1.01	<0.001
	Diabetes	2.36	1.46	–	3.82	<0.001
	Male	1.98	1.21	–	3.22	0.006
	ACEI/ARB	0.59	0.37	–	0.93	0.02
Sudden death	Hb (per 1g/dl increase)	0.67	0.57	–	0.79	<0.001

Cox proportional-hazards regression analyses were conducted with following covariates; male gender, age, BMI, ischemic etiology, LVH, NYHA, hypertension, diabetes, hyperlipidemia, atrial fibrillation, ventricular tachycardia, BNP, eGFR, Hb, LVEF, LVDD, usage of beta blocker or ACEI/ARB. Age, BMI, BNP, eGFR, Hb, LVDD, and LVEF are entered as continuous variables in the multivariate model.
Abbreviations: C.I. = confidential interval; Hb = hemoglobin; HR = hazard ratio; other abbreviations as in Table 1.

even in the incidence of sudden death as well as in the all-cause mortality.

We demonstrated that low Hb level was significantly associated with the poor prognosis in patients with DHF and that its association was evident even in the development of sudden death. Anemia is common in patients with DHF as well as CHF, and the proportion of anemic patients in the study population was 38% [3]. A subgroup analysis of the CHARM trial reported that anemia was associated with older age, worse functional class, diabetes and renal dysfunction [3]. Anemic patients in the present study were also associated with older age, worse functional class, renal dysfunction and lower BMI. These revealed that a risk stratification by anemia and the associated factors may be promising strategy to improve the survival of those patients. Although Silverberg et al. showed that the use of erythropoietin improved ejection fraction, functional class, and peak oxygen consumption in patients with NYHA class III–IV heart failure, it is still controversial whether the rise of Hb level improves the prognosis of CHF patients [8]. These results suggest that further investigation is necessary to elucidate the optimal Hb target, even if treatment of anemia is beneficial in patients with CHF.

In conclusion, Hb level may be a useful predictor for sudden death in patients with DHF. It is necessary to investigate what treatment is the most effective for preventing the sudden death in patients with DHF.

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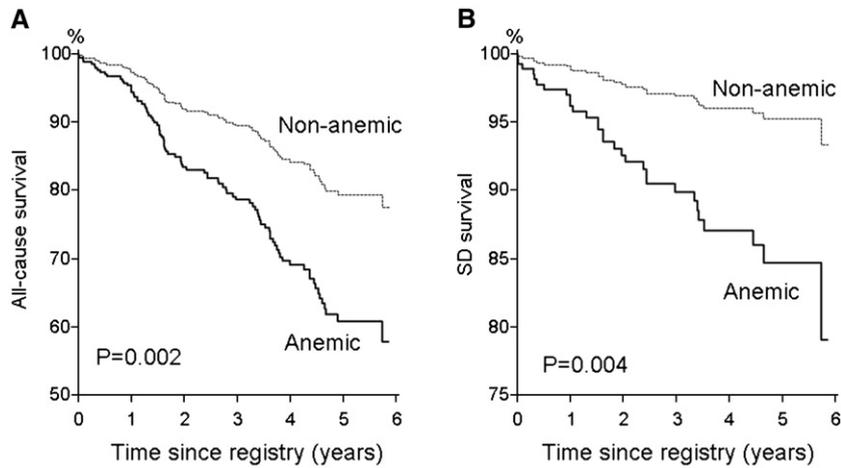
Fig. 1. Cumulative survival curves for all-cause (A) and sudden death mortality (B) in relation to anemia. SD=sudden death.

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