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Reducing cardiac after-load by lowering blood viscosity in patients with familial hypercholesterolemia – A pilot study. Possible mechanism for occurrence of anemia in chronic heart failure patients?

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SOUHRN

Anemie je přítomna u více než 40 % pacientů s chronickým srdečním selháním, zvláště u těch se sníženou ejekční frakcí; příčina této souvislosti dosud není známa. Hematokrit se významným způsobem podílí na viskozitě plné krve, která do velké míry ovlivňuje celkovou periferní rezistenci, jež musí srdce překonávat. Snížení viskozity krve by tedy mohlo zmenšit dotížení selhávajícího srdce. Pro pacienty s homozygotní familiární hypercholesterolemií (HFH) jsou charakteristické výrazně zvýšené hodnoty cholesterolu lipoproteinů o nízké hustotě (LDL) a předčasný rozvoj ischemické choroby srdeční. Doporučený způsob léčby tohoto onemocnění představuje selektivní aferéza LDL cholesterolu u pacientů s HFH k odstranění LDL z krevního oběhu; současně bylo prokázáno, že se tak snižuje viskozita plné krve. Koncentrace natriuretického peptidu typu B (BNP) ukazují plnicí tlaky srdce a jsou ovlivňovány převážně dotížením. Hodnota BNP byla měřena u čtyř po sobě následujících pacientů s HFH před léčbou selektivní LDL aferézou a po ní. Zjistili jsme, že 20% snížení viskozity krve těchto pacientů LDL aferézou vedlo ke snížení hodnot BNP o 40 %. U pacientů s chronickým srdečním selháním by anemie mohla představovat kompenzační mechanismus organismu snižující dotížení selhávajícího srdce snížením viskozity krve.

Keywords:
Anemia
Blood viscosity
BNP
Heart failure
Hypercholesterolemia

ABSTRACT

Anemia is present in more than 40% of the patients with chronic heart failure (CHF), especially in those with reduced ejection fraction. The etiology is not yet understood. Hematocrit is a major determinant of whole blood viscosity, which is an important factor of the total peripheral resistance for the heart. Therefore, lowering blood viscosity may reduce after-load for the failing heart. Patients with homozygous familial hypercholesterolemia (HFH) are characterized by markedly elevated low-density lipoprotein (LDL) cholesterol levels and premature ischemic heart disease. Selective LDL-cholesterol apheresis in HFH patients to remove LDL from the circulation is the recommended treatment of this condition and has been shown to reduce whole blood viscosity. The level of B-type Natriuretic Peptide (BNP) is a parameter of filling conditions in the heart and is predominantly induced by cardiac after-load. BNP was measured in 4 consecutive HFH patients before and after treatment with selective LDL-apheresis. We observed that 20% reduction of blood viscosity by LDL-apheresis in these patients resulted in 40% lower levels of BNP. In chronic heart failure patients anemia might be a compensatory mechanism of the organism in order to reduce after-load for the failing heart by lowering blood viscosity.

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Introduction

In approximately half of the patients with chronic heart failure, especially in those with reduced ejection fraction, normocytic anemia is present [1,2]. Most studies have shown an inverse linear relationship between hematocrit or hemoglobin levels and survival: the SOLVD trial (Studies of Left Ventricular Dysfunction) reported a 2.7% increase in the adjusted risk of death per 1% reduction in hematocrit and the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) trial described a 3% increase in risk for each 1% decline in hematocrit [3,4]. The etiology is not yet understood. Several clinical trials have been performed in recent years with erythropoietin or other erythropoiesis stimulating drugs in order to reduce anemia in CHF patients, but until now these studies have failed to show improved cardiovascular outcome [5,6]. A clear explanation why treatment of anemia in patients with congestive heart failure (CHF) does not improve cardiovascular prognosis has not yet been found. We and others [7,8] hypothesized that an increase of the hematocrit-level in CHF patients will raise blood viscosity, which according to Poisseuille's Law enhances the peripheral resistance, against which the failing heart has to work. According to the law of Poisseuille ($Q = ((\Delta P \cdot \varpi \cdot r^4)/8 \cdot l) \times 1/\eta$), in which η represents blood viscosity, cardiac after-load has a vascular and a viscous component and blood flow will be enhanced by reducing its viscosity. Therefore, anemia in CHF patients might be a physiological adaptation mechanism to reduce workload for the failing heart.

Homozygous familial hypercholesterolemia (HFH) is a rare inborn error of metabolism caused by mutations in both alleles encoding for the LDL-receptor. The majority of these patients die untreated before the age of 20 yrs of ischemic heart disease as a result of markedly increased LDL-cholesterol levels; ischemic heart disease is reflected in diastolic and/or systolic dysfunction. Since drug treatment is not always possible or insufficient to lower LDL-cholesterol, LDL can be removed extra-corporally by plasmapheresis or preferably by selective LDL-apheresis [9–11]. Earlier studies have demonstrated, that LDL apheresis in these patients reduces whole blood viscosity significantly and this effect has been attributed to the reduction in acute phase proteins (fibrinogen and CRP) and the effects of LDL-lowering itself [12].

Aim of our study is to determine the influence of lowering blood viscosity by selective LDL-apheresis on cardiac after-load in patients with homozygous familial hypercholesterolemia by comparing the level of B-type Natriuretic Peptide (BNP) before and after LDL-apheresis; BNP has been shown to be predominantly influenced by cardiac after-load [13]. This conceptual approach in patients with premature cardiac dysfunction might give physiological insight in why occurrence of anemia could be considered a physiological adaptation mechanism in CHF patients.

Patients and methods

After obtaining written informed consent and being in accordance with The Helsinki Declaration, a pilot-study was performed in 4 consecutive patients with homozygous familial hypercholesterolemia. They underwent cardiac investigations during 2 consecutive treatments with LDL-apheresis. In Table 1 the clinical history, medication and laboratory investigations at baseline are depicted for each individual patient. All patients also underwent transthoracic Doppler-echocardiography (TTE) at baseline. Further determination of cardiac hemodynamics consisted of measurement of BNP-levels immediately before and after LDL-apheresis, as well as simultaneous measure-

Table 1 – Baseline characteristics of patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Female	Female	Male
Age	30 yrs	36 yrs	28 yrs	50 yrs
BSA	1.56 m^2	2.00 m^2	1.76 m^2	1.91 m^2
Clinical history	CABG 1993; PTCA 2007; moderate AS	CABG 1986; moderate/ severe AS; LVH	No cardiac history	CABG 1992; ICD 2005
LV ejection fraction (by TTE)	68%	60%	65%	48%

AS – aortic valve stenosis; BSA – body surface area; CABG – coronary artery bypass surgery; ICD – implantable cardiac defibrillator; LVH – left ventricular hypertrophy; TTE – transthoracic echocardiography.

Table 2 – Measurement of blood viscosity, BNP and LDL before and after 0.5 and after 2.5 h.

	Visc before 0.5 h [mPa·s]	Visc after 0.5 h [mPa·s]	Visc after 2.5 h [mPa·s]	BNP before 0.5 h [pg/ml]	BNP after 0.5 h [pg/ml]	BNP after 2.5 h [pg/ml]	LDL before 0.5 h [mmol/L]	LDL after 0.5 h [mmol/L]
Patient 1	7.87	6.62	6.7	70.5	40.5	46	8.23	3.17
Patient 2	6.77	4.79	5.35	59.5	36	56	7.68	2.35
Patient 3	7.37	5.26	6.69	144.5	90	93	10.16	3.54
Patient 4	11.5	10.54	10.37	319	187	147.5	6.01	1.4

BNP – B-type Natriuretic Peptide; LDL – low density lipoprotein cholesterol; Visc – viscosity at shear rate 4.04 s^{-1}.

Table 3 – Relative change from baseline for blood viscosity, BNP and LDL-cholesterol.

	Relative change from baseline (+95% CI)	*P*-value
Viscosity	–20.5268 (–36.7433, –4.3103)	0.027
Viscosity (after 2.5 h)	–13.72354 (–22.4051, –5.0419)	0.015
BNP	–40.28614 (–43.6696, –36.9027)	< 0.0001
BNP (after 2.5 h)	–32.0370 (–64.0068, –1.0112)	0.046
LDL-cholesterol	–68.18660 (–78.5873, –57.7859)	< 0.0001

BNP – B-type Natriuretic Peptide.

ment of blood pressure and heart frequency. Laboratory investigations before and after LDL-apheresis consisted of: hematocrit, fibrinogen and hs-CRP. Whole blood viscosity was measured within 30 minutes after withdrawal of blood at different shear rates (0.87, 1.182, 1.607, 2.19 and 4.04 s^{-1}) with the Contraves LS 30, which is considered to be the standard for measurement of whole blood viscosity at low shear rate [14]. All cardiac investigations and blood withdrawals were done while the patient was in supine position. Two and a half hours after LDL-apheresis blood was withdrawn again for determination of hematocrit, BNP and whole blood viscosity. The Student t-test was used to test whether the relative changes from baseline were significant. *P*-values < 0.05 were considered statistically significant.

Results

In Table 1 the baseline characteristics of the patients are demonstrated. Only patient 4 revealed significant reduction of systolic LV-function on transthoracic Doppler--echocardiography.

Table 2 depicts measurement results of blood viscosity, BNP and LDL-cholesterol before and 0.5 and 2.5 h after LDL-apheresis, respectively. Finally, in Table 3, the relative change from baseline is depicted for blood viscosity, BNP and LDL-cholesterol immediately after LDL-apheresis and after 2.5 h. Heart rate, blood pressure as well as hematocrit remained constant before and after LDL-apheresis.

Discussion

The significant reduction of BNP-level by lowering blood viscosity with selective LDL-apheresis in these HFH patients demonstrates the important effect of blood viscosity on cardiac after-load.

During the last three decades, the biological role and potential clinical application of the natriuretic peptides as reflection of increased intra-cardiac pressure in chronic heart failure have been extensively investigated [15]. Toischer et al. [13] showed that BNP is predominantly induced by afterload, which made it a good measurement parameter for our study, in which afterload according to Poisseuille's Law is being changed by lowering blood viscosity. The importance of blood viscosity for cardiac after--load has been shown in earlier studies, in which the role of blood viscosity has been demonstrated in the pathophysiology of hypertension and left ventricular hypertrophy [16,17]. Animal studies showed that in normal or incipient failing hearts almost all BNP is produced in the atria [18]. This might be true for our patients as well; the decrease of filling pressures in the atria can be explained by the lower blood viscosity, which will have more impact in the atria than in the ventricles because of the lower shear rates in the atria. In our limited study, the relative reduction of BNP was higher than the relative reduction of whole blood viscosity. Blood is a non-Newtonian fluid, which means that its viscosity changes when the shear rate varies. At lower shear rates blood viscosity shows a steep rise (Figure 1). In chronic heart failure low flow state exists, which will enhance the role of blood viscosity in this clinical situation. This may also explain, why reduction in BNP-level in our patients was more evident, when baseline BNP-level was higher

The reduction of BNP-level is not due to elimination of this peptide itself by the apheresis, because after 2.5 h the BNP level still remains significantly reduced. Considering the half-life of BNP to be 23 min [14], BNP-level should have returned to baseline if the apheresis would have eliminated the BNP-peptide. Furthermore, the highly selective apheresis with binding of the apoB, should not cause elimination of other proteins.

The recurrence of paroxysmal atrial fibrillation is related with increased levels of BNP [19]. Therefore, the demonstrated effect of blood viscosity on cardiac hemodynamics in our study is consistent with the finding that occurrence of post-operative atrial fibrillation after cardiac surgery is correlated with the amount of blood transfusion [20]. Not a linear but a logarithmic relationship exists between blood viscosity and the hematocrit [21]; this is again especially true at low shear rate. Besides hematocrit inflammatory proteins, especially fibrinogen and CRP, increase blood viscosity; the BNP level in our patients changed, whereas the hematocrit remained con-

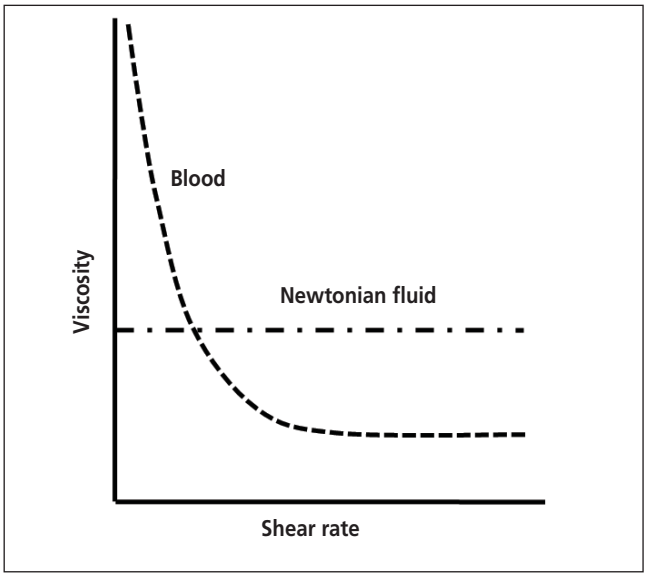

Fig. 1 – Newtonian fluids have a constant viscosity at all shear rates. However, blood is a non-Newtonian fluid, reason why its viscosity rises sharply at low shear rate.

stant. This could be the explanation why NT-proBNP-levels appeared to be not only correlated with hematocrit level in CHF patients [22]. Also inflammatory activity and even LDL-cholesterol-levels should be considered if blood viscosity would be the determining factor of physiological adaptation [6,7,14,22]. On the other hand in patients with high inflammatory activity (endocarditis, rheumatoid arthritis) according to the rheological view [23], anemia occurs to compensate for the increased blood viscosity by the high levels of acute phase proteins.

From this pilot-study we postulate that lowering blood viscosity decreases filling pressures in the heart, as expressed by BNP levels. Our pilot-study is in accordance with the recently published meta-analysis about the effect of statin therapy on heart failure events [24]. Further studies should confirm whether a decrease of 20% in viscosity corresponds with a 40% reduction in BNP and whether the occurrence of anemia (or bone marrow "dysfunction" [22]) in CHF patients [25] should be considered as a physiological adaptation mechanism for the failing heart. Probably an optimal hematocrit exists for each CHF patient and other determinants of blood viscosity should be taken into account. Lower levels of anemia might reflect more adaptation to more severe heart failure and hence are associated with worse outcome.

Conflict of interest
None declared.

Funding body
None.

Ethical statement
I declare, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

Informed consent
I declare, on behalf of all authors that informed consent was obtained from all patients participating in this study.

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