Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/crvasa

Original research article

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?

Gheorghe A.M. Pop [a,*], *Menko-Jan de Boer* [a], *Anton F. Stalenhoef* [b]

[a] *Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands*
[b] *Department of Internal Medicine, Division of Vascular Medicine, Radboud University Medical Center, Nijmegen, The Netherlands*

ARTICLE INFO

Article history:
Received 14 July 2015
Received in revised form
15 September 2015
Accepted 5 October 2015

Keywords:
Blood viscosity
BNP
Heart failure
Anemia
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.

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

* *Corresponding author at*: Department of Cardiology, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 243614153; fax: +31 243540537.
E-mail address: Gheorghe.Pop@Radboudumc.nl (Gheorghe A.M. Pop).

http://dx.doi.org/10.1016/j.crvasa.2015.10.001

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 ($Q = ((\Delta P \cdot \pi \cdot r^4)/8 \cdot l) \times 1/\eta$), 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 as to 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 measurement 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 min 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 hour after LDL-apheresis blood was withdrawn again for determination of hematocrit, BNP and whole blood viscosity. 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.

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%

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