Haematocrit levels and left ventricular geometry: results of the MONICA Augsburg Echocardiographic Substudy

Jan Stritzke[a], Björn Mayer[a], Wolfgang Lieb[a,b], Andreas Luchner[c], Angela Döring[d], Hans-Werner Hense[e] and Heribert Schunkert[a,*]

Background **Extreme alterations in blood count such as anaemia or polycythemia are known to cause circulatory changes and, if these alterations persist, adaptations of cardiac geometry.**

Objectives **To investigate further the association between haematocrit levels and left ventricular geometry in a population-based sample.**

Methods **We examined 687 women and 648 men, aged 25–74 years, participating in the third population-based MONICA Augsburg study. Anthropometry, blood pressure, laboratory measurements and M-mode echocardiography were obtained using standardized methods.**

Results **Haematocrit levels were inversely related to end-diastolic diameters ($P<0.001$). By contrast, septal and posterior wall thickness displayed parabolic association curves with nadirs at physiological haematocrit levels ($P<0.001$). These associations remained significant after adjustment for age, sex, body fat, hypertension, diabetes mellitus, cardiovascular disease, heart failure, serum creatinine, and were likewise found for haemoglobin levels or numbers of erythrocytes. These correlations appeared to be secondary to changes in blood pressure and stroke volume that correlated either positively (blood pressure) or inversely (stroke volume) with haematocrit levels. Consequently, a concentric pattern of left ventricular hypertrophy, i.e. a relative wall thickness of 0.45 or greater, was significantly more prevalent in subjects with high haematocrit levels than in those with intermediate haematocrit levels. By contrast, an eccentric left ventricular hypertrophy, i.e. relative wall thickness less than 0.45, was more common in subjects with low haematocrit levels.**

Conclusion **In the general population, the variability of haematocrit levels and its haemodynamic consequences translates to distinct patterns of left ventricular geometry.** ***J Hypertens*** **25:1301–1309 © 2007 Lippincott Williams & Wilkins.**

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[a]Medizinische Klinik II, [b]Institut für Humangenetik, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, [c]Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Regensburg, [d]GSF Nationales Forschungszentrum für Umwelt und Gesundheit, Institut für Epidemiologie, Neuherberg and [e]Institut für Epidemiologie und Sozialmedizin, Universitätsklinikum Münster, Münster, Germany

Correspondence to Heribert Schunkert, Medizinische Klinik II, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany
Tel: +49 451 500 2501; fax: +49 941 500 6437;
e-mail: heribert.schunkert@innere2.uni-luebeck.de

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Introduction

Chronic anaemia is related to a number of adaptations of the circulatory system [1]. Most notably, low blood viscosity and hypoxic vasodilatation result in a decrease of peripheral resistance. Moreover, anaemia-induced sympathetic activation increases the heart rate as well as cardiac output [2,3]. Such hyperdynamic circulation compensates at least partly for the reduced oxygen transport capacity of the anaemic blood. As a consequence the heart is faced with an increased volume load, and left ventricular geometry may be reshaped if anaemia persists chronically [4,5].

On the other hand, the heart of patients presenting with a morbidly raised number of red blood cells, such as polycythemia, may face an elevated afterload because of the high viscosity of the blood and increased peripheral resistance [6,7]. Cardiac strain may thus be elevated in patients with high haematocrit levels [8]. The correction of anaemia or polycythemia, respectively, has been shown partly to reverse haemodynamic adaptations as well as secondary changes in cardiac geometry [9–11].

It is not known, however, whether the variability of haematocrit levels within a healthy population-based sample may affect the geometry and mass of the left ventricle. Moreover, the interaction of haematocrit and blood pressure in the mediation of these effects has not been studied thus far.

Methods

Study population

The MONICA Augsburg study was carried out as a component of the international collaborative World

* For the MONICA investigators. The MONICA Augsburg study was initiated by Ulrich Keil and co-workers.

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Health Organization MONICA project. It investigated the cardiovascular risk factor profile of randomly selected subjects of the Augsburg population in cross-sectional surveys. The third survey took place from October 1994 to June 1995. The study design, sampling frame, and data collection have been described in detail elsewhere [12,13]. Briefly, 6640 individuals aged 25–74 years were randomly sampled by a two-stage, age and sex-stratified cluster sampling from the population registry. A total of 4856 men and women (response rate 74.9%) participated in the study. For logistical reasons, only 2376 participants residing within or close to the city of Augsburg were offered an additional echocardiographic examination. The 825 men and 852 women who agreed to be examined had the same sex distribution as the non-responders, but they differed in the following ways: they were younger (on average by 3.2 years; $P < 0.001$), their body mass index was lower (by 0.7 kg/m^2; $P < 0.001$), and their systolic blood pressure was lower (by 3.0 mmHg; $P < 0.001$) [14,15].

All participants underwent an interview relating to personal and family medical history, lifestyle and nutrition, health behaviour, and psychosocial factors [16,17]. Blood pressure was measured using a random zero manometer under strictly standardized conditions at the right arm. The mean of the second and third measurement was used for the present analyses [15]. Arterial hypertension was considered as systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 90 mmHg or greater, or the current intake of antihypertensive medication. Diabetes mellitus was determined by the individual's history or the intake of antidiabetic medications. Cardiovascular disease was determined by a history of myocardial infarction or stroke. Renal failure was assumed with serum creatinine greater than 1.2 mg/dl.

Echocardiographic measurements

Two-dimensionally guided M-mode echocardiograms were performed on each subject by two expert sonographers on a commercially available echocardiograph (Sonos 1500; Hewlett Packard, Andover, Massachusetts, USA) with a 2.5 or 3.5 MHz transducer following standardized protocols [14,18–20]. M-mode tracings were recorded on a stripchart paper at 50 mm/s. To reduce inter-reader variability, all M-mode tracings were analysed by a single cardiologist. As a result of technically inadequate echocardiographies, 156 men and 104 women were excluded from further analyses. Measurements of left ventricular diameter (end-diastolic diameter; EDD), septal wall thickness (SWT) and posterior wall thickness (PWT) were performed at end-diastole according to the guidelines of the American Society of Echocardiography [21]. Relative wall thickness (RWT) was calculated as the ratio of (SWT + PWT) and EDD. Left ventricular mass (LVM) was calculated according to the formula:

$$\mathrm{LVM\,(g)} = 0.8[1.04([\mathrm{EDD} + \mathrm{SWT} + \mathrm{PWT}]^3 - \mathrm{EDD}^3)] + 0.6$$

as described by Devereux and Reichek [22,23]. The rank correlation for 144 duplicate measurements by the two sonographers was 0.91 for the determination of LVM. All measurements were indexed to fat-free body mass [24,25]. Left ventricular hypertrophy (LVH) was defined as a ratio of LVM over fat-free mass of more than 4.1 g/kg [14,26], an eccentric geometry was assigned to cases with a concomitant RWT below 0.45, and a concentric hypertrophy was assigned to cases with a RWT of 0.45 or greater. The left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were determined using the Teichholz equations [27]:

$$\mathrm{LVEDV\,(ml)} = [7/(2.4 + \mathrm{LVEDD})] * \mathrm{LVEDD}^3$$
$$\mathrm{LVESV\,(ml)} = [7/(2.4 + \mathrm{LVESD})] * \mathrm{LVESD}^3$$

where LVEDD is the left ventricular end-diastolic diameter and LVESD is the left ventricular end-systolic diameter.

Using LVEDV and LVESV, the left ventricular stroke volume [SV (ml) = LVEDV − LVESV] and ejection fraction [EF = (LVEDV − LVESV)/LVEDV] were calculated. A systolic cardiac dysfunction was assumed with an ejection fraction of less than 45%.

Bioelectrical impedance analysis

Fat-free mass was determined by the measurement of bioelectrical impedance with a body composition analyser TVI-10 (Danziger Medical Technology, Heidelberg, Germany) as previously reported in great detail [24,25]. Body fat was calculated as the difference between total body mass and fat-free mass.

Statistical methods

A total of 648 men and 687 women had a complete set of data for echocardiography, BIA measurements, haematological parameters and the other variables. Male and female study participants were compared with regard to their baseline characteristics using mean values and standard deviations of haematological, anthropometric, blood pressure and echocardiographic variables. Differences were assessed with unpaired *t*-tests for continuous and chi-squared tests for categorical variables. The echocardiographic variables SWT and PWT, EDD and end-systolic diameter (ESD), and LVM were indexed to the fat-free body mass [24,25]. The strength of the linear association between the haematological and the other variables was assessed by computation of Pearson's coefficients of correlation for men and women separately.

Chronic severe anaemia [3,5] as well as polycythemia [8] result in an increase in wall thickness. In other words, published reports provide evidence that LVH may occur at both ends of the haematocrit spectrum. We therefore hypothesized that the associations between the haematological variables and the left ventricular wall thickness and mass were curvilinear rather than strictly linear. Therefore, we fitted second-order regression models that included, for example, haematocrit as a linear and, in addition, as a squared term as independent (predictor) variables. SWT, PWT, EDD, ESD, LVM and RWT were the dependent variables. In our analyses, haematocrit was used as values centred around the respective median, that is, as the deviation of the crude measurement value from the sex-specific median value. The centred haematocrit value (HCT) was computed as ($HCT_{crude} - 0.44$) in men and as ($HCT_{crude} - 0.40$) for women, where 0.44 and 0.40 represent the respective medians. Centred variables were preferred because of their superior statistical properties in the second-order regression modeling. We ran the regression models pooling male and female participants because fat-free mass-indexed LVM is known to be similar in men and women of this study group [24,25] and as we used sex-specific medians for the generation of the centred haematological variables. First, regression models were computed including HCT and HCT^2 including only sex and age as covariates (model 1), whereas in a second step body fat, hypertension, diabetes mellitus, cardiovascular disease, heart failure and serum creatinine were also included (model 2). In addition, we fitted linear regression analyses with SWT, EDD and stroke volume (each indexed for fat-free mass) as dependent and HCT, HCT^2, systolic blood pressure, age, sex, body fat, diabetes mellitus, cardiovascular disease, heart failure and serum creatinine as independent variables (Fig. 2b). Finally, the prevalence of eccentric and concentric LVH was assessed in groups with low (women < 35, men < 40), intermediate (35–44 and 40–48, respectively), and high (> 44 and > 48, respectively) haematocrit. The prevalence odds ratios were also calculated adjusting for age, sex, body fat, and hypertension in multiple logistic regression models. All analyses were performed using SPSS version 12.0.1 for Windows (SPSS Inc., Chicago, Illinois, USA).

Table 1 Characteristics of study sample

	Men ($N = 648$)	Women ($N = 687$)
Clinical and anthropometric characteristics		
Age (years)	48.9 ± 13.8	49.2 ± 13.4
Weight (kg)	82 ± 11	68 ± 12
Fat-free mass (kg)	60 ± 6	44 ± 4
Fat mass (kg)	22 ± 7	25 ± 9
Body mass index (kg/m^2)	26.8 ± 3.3	26.3 ± 4.6
Body surface area (m^2)	1.97 ± 0.14	1.72 ± 0.14
Systolic blood pressure (mmHg)	136 ± 19	130 ± 21
Diastolic blood pressure (mmHg)	83 ± 12	78 ± 11
Hypertension (%)	41.5	30.6
Diabetes mellitus (%)	3.9	2.9
Heart failure (%)	3.4	2.8
Cardiovascular disease (%)	5.4	1.7
Renal failure (%)	2.0	0.6
Current smoker (%)	30.6	25.2
Laboratory parameters		
Erythrocyte count	4.92 ± 0.36	4.47 ± 0.34
Haemoglobin (g/dl)	153 ± 10	137 ± 10
Haematocrit (%)	0.44 ± 0.03	0.4 ± 0.03
Haematocrit level		
Low (%)	3.5	3.9
Intermediate (%)	90.0	90.4
High (%)	6.5	5.7
MCV (fl)	90 ± 4	89 ± 4
MCH (pg)	31.1 ± 1.5	30.7 ± 1.7
MCHC (g/l)	345 ± 6	343 ± 6
HDL-cholesterol (mg/dl)	47.9 ± 14.1	60 ± 16
LDL-cholesterol (mg/dl)	146 ± 41	138 ± 44
Total cholesterol (mg/dl)	233 ± 43	230 ± 44
Serum creatinine (mg/dl)	0.84 ± 0.15	0.67 ± 0.13
Echocardiographic variables		
SWT (mm)	11.16 ± 2.13	9.92 ± 1.96
PWT (mm)	9.17 ± 1.4	8.21 ± 1.41
EDD (mm)	50 ± 4	45.8 ± 4.1
ESD (mm)	32.6 ± 4.3	29.4 ± 3.8
RWT	0.41 ± 0.09	0.4 ± 0.09
LVM (g)	189 ± 47	140 ± 37
SWT/FFM (mm/kg)	0.19 ± 0.04	0.23 ± 0.05
PWT/FFM (mm/kg)	0.15 ± 0.03	0.19 ± 0.04
EDD/FFM (mm/kg)	0.84 ± 0.09	1.05 ± 0.11
ESD/FFM (mm/kg)	0.55 ± 0.08	0.68 ± 0.09
LVM/FFM (g/kg)	3.17 ± 0.77	3.21 ± 0.83
SV (ml)	76 ± 17	63 ± 15
SV/FFM (ml/kg)	1.28 ± 0.29	1.45 ± 0.34

EDD, Left ventricular end-diastolic diameter; ESD, left ventricular end-systolic diameter; FFM, fat-free mass; HDL, high-density lipoprotein; LDL, low density lipoprotein; LVM, left ventricular mass; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; PWT, posterior wall thickness; RWT, relative wall thickness; SWT, septal wall thickness; SV, stroke volume.

Results

Correlation analyses between haematological and echocardiographic variables

The clinical, anthropometric and laboratory variables as well as echocardiographic parameters of male and female study participants are shown in Table 1. In total, 90.1% of study participants presented with haematocrit levels within the normal range (women 35 to 44; men 40 to 48); low haematocrit levels were found in 3.8% and high haematocrit levels in 6.1%. Correlation analyses between haematological and echocardiographic variables were carried out for both sexes separately. Highly significant negative correlations were observed between haematocrit, haemoglobin, and red blood count with indexed left ventricular EDD and left ventricular ESD in both sexes (Table 2). By contrast, the associations with fat-free mass-indexed SWT and PWT were consistently positive. The correlation coefficients were, however, relatively weak and clearly significant only in women. The opposite directions of the associations of haematological variables with wall thickness on the one hand, and ventricle diameters on the other hand, resulted in pronounced and highly significant correlations between RWT and haematological parameters.

Associations within linear regression models

To study these associations in more detail we investigated whether the relationships between haematocrit levels and echocardiographic variables were better

Table 2 Coefficients of the correlation between haematocrit, haemoglobin, erythrocyte count and echocardiographic variables

	Men ($N=648$)			Women ($N=687$)		
	HCT	HB	RBC	HCT	HB	RBC
EDD/FFM	−0.10 (0.008)	−0.11 (0.004)	−0.13 (<0.001)	−0.13 (0.005)	−0.14 (<0.001)	−0.11 (0.004)
ESD/FFM	−0.08 (0.03)	−0.08 (0.04)	−0.08 (0.03)	−0.16 (<0.001)	−0.017 (<0.001)	−0.15 (<0.001)
SWR/FFM	0.09 (0.02)	0.06 (0.13)	0.03 (0.46)	0.19 (<0.001)	0.16 (<0.001)	0.17 (<0.001)
PWT/FFM	0.09 (0.02)	0.07 (0.09)	0.02 (0.7)	0.17 (<0.001)	0.15 (<0.001)	0.21 (<0.001)
RWT	0.15 (0.003)	0.12 (0.002)	0.09 (0.02)	0.25 (<0.001)	0.23 (<0.001)	0.23 (<0.001)
LVM/FFM	0.06 (0.155)	0.04 (0.283)	0.01 (0.751)	0.12 (0.001)	0.09 (0.022)	0.14 (<0.001)

HB, Haemoglobin; HCT, haematocrit; RBC, red blood cell count. For explanation of echocardiographic variables see Table 1. Pearson's correlation coefficients, respective *P* values in parentheses.

reflected by a curvilinear correlation. For this purpose, we fitted multiple linear regression models including second-order terms for haematocrit. As displayed in Table 3, the squared haematocrit values (reflecting a curvilinear relationship) were significantly related to fat-free mass-indexed SWT, PWT and LVM in both sexes. By contrast, the second-order term did not contribute to EDD and ESD, indicating that the variance of this parameter is sufficiently explained by a linear term. A significant curvilinear association was also found between haematocrit and RWT (Table 3). Interestingly, in both models no significant interaction of sex on RWT ($P=0.233$) and indexed LVM ($P=0.742$) was found, indicating that the mechanisms of adaptation to haemodynamic changes in both sexes are comparable.

Table 3 Regression coefficients (β) and respective *P*-values in parentheses, and explained variance (R^2) of regression models including hematocrit (HCT) and squared values of hematocrit (HCT^2). Men and women, age 25 to 74 years

		Model 1[a]		Model 2[b]	
		β	*p*	β	*p*
Hemodynamic variables					
RRsyst	HCT	104	<0.001	23	0.055
	HCT^2	324	0.250	77	0.744
		$R^2=0.25$		$R^2=0.65$	
SV/FFM	HCT	−1.03	0.001	−1.05	<0.001
	HCT^2	1.37	0.823	2.95	0.620
		$R^2=0.10$		$R^2=0.16$	
Echocardiographic variables					
SWT/FFM	HCT	0.17	<0.001	0.15	<0.001
	HCT^2	1.35	0.065	1.18	0.100
		$R^2=0.46$		$R^2=0.49$	
PWT/FFM	HCT	0.11	<0.001	0.11	<0.001
	HCT^2	1.58	0.003	1.50	0.004
		$R^2=0.46$		$R^2=0.48$	
EDD/FFM	HCT	−0.50	<0.001	−0.25	0.007
	HCT^2	−0.02	0.992	0.02	0.990
		$R^2=0.54$		$R^2=0.61$	
ESD/FFM	HCT	−0.41	<0.001	−0.21	0.007
	HCT^2	−0.68	0.690	−1.14	0.462
		$R^2=0.36$		$R^2=0.48$	
RWT	HCT	0.49	<0.001	0.37	<0.001
	HCT^2	3.23	0.028	3.50	0.017
		$R^2=0.23$		$R^2=0.27$	
LVM/FFM	HCT	1.56	0.018	−0.03	0.959
	HCT^2	36.70	0.006	32.05	0.013
		$R^2=0.29$		$R^2=0.35$	

[a] Including age and sex; [b] Including age, sex, body fat, hypertension, diabetes mellitus, cardiovascular disease, heart failure, serum creatinine; RRsyst indicating systolic blood pressure; For explanation of echocardiographic variables see Table 1.

These more complex relationships between haematocrit levels and wall thickness as well as left ventricular dimensions are graphically displayed in Fig. 1. We plotted the results of model 2 for each of four echocardiographic variables relating to hypothetical 50-year old men and women without hypertension, diabetes mellitus, cardiovascular disease and heart failure, with body fat and serum creatinine values corresponding to the median of the entire study sample. By respective adjustments, the shape of these correlations is independent of age, sex, body fat and creatinine level. The parabolic associations become obvious, and it is most pronounced for RWT. On the other hand, the EDD (and the ESD alike, not shown) decrease with increments of the haematocrit. These associations were consistent and were also found in further statistical analyses with different indexations of echocardiographic variables (e.g. indexation of PWT, SWT, EDD and ESD by body height or indexation of LVM by body surface area; data not shown).

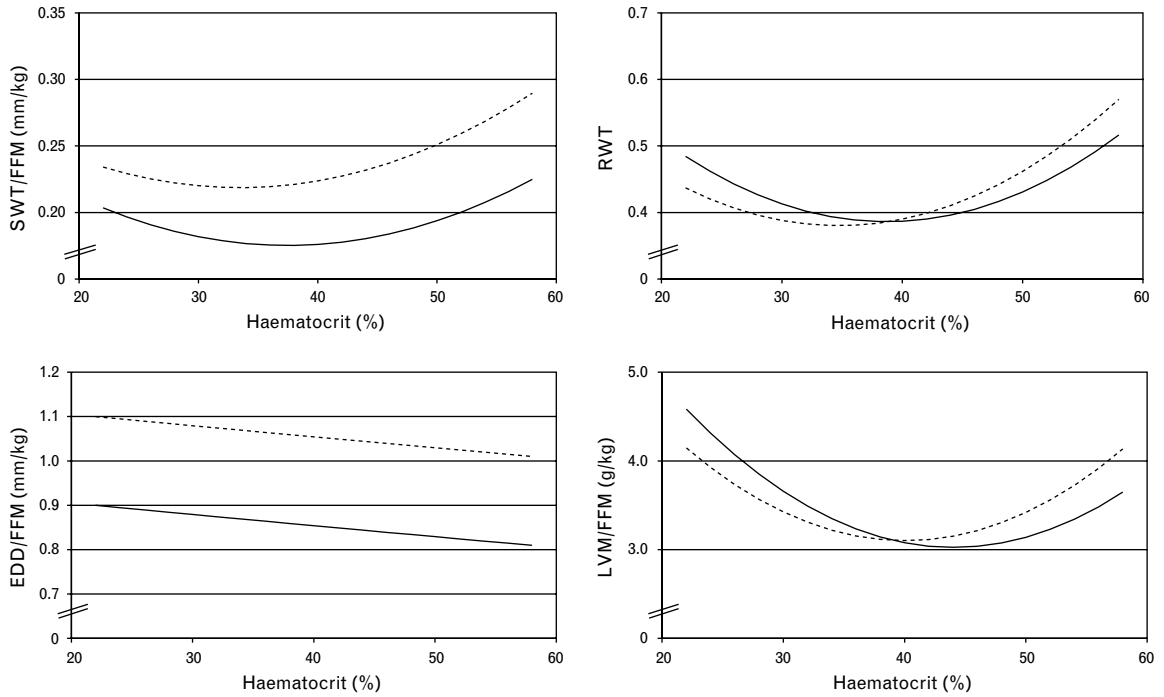
Influence of blood pressure

In addition, associations between haematocrit levels and haemodynamic variables were analysed (Fig. 2). Decreasing haematocrit levels were related to increasing stroke volumes, consistent with an increased volume load in this condition. By contrast, increasing haematocrit levels were related to an increase in systolic blood pressure, i.e. increased afterload. In order to clarify these interactions in more detail, we also display the relationship between systolic blood pressure with left ventricular geometry and stroke volume. The pronounced effects related to low haematocrit (i.e. increase in stroke volume) or high haematocrit (i.e. increase in blood pressure) may thus partly explain the relationship between haematocrit levels and left ventricular geometry.

Prevalence of eccentric and concentric hypertrophy

We finally assessed the prevalence of eccentric and concentric LVH in subjects with low, intermediate and high haematocrit. Crude analyses confirmed our expectation that eccentric LVH was more common in

Fig. 1



Relationships between haematocrit levels, wall thickness, end-diastolic demensions and left ventricular mass. Results of linear regression model 2 (Table 3) were plotted separately for hypothetical 50-year-old men and women without hypertension, diabetes mellitus, heart failure or a history of cardiovascular disease with body fat (men 22.1 kg, women 24.7 kg) and serum creatinine levels (men 0.84 mg/dl, women 0.67 mg/dl) corresponding to the median of the entire study sample. For explanation of echocardiographic variables see Table 1. EDD, End-diastolic diameter; FFM, fat free mass; LVM, left ventricular mass; RWT, relative wall thickness; SWT, septal wall thickness. – – – – Women; ——— men.

individuals with low haematocrit. In contrast, concentric LVH was more prevalent in those with high haematocrit levels (Fig. 3). Multivariable analyses confirmed these results: the adjusted prevalence odds ratios for eccentric LVH was 4.58 (95% confidence interval 1.70–12.29; $P = 0.003$) comparing low with intermediate levels and the adjusted prevalence odds ratios for concentric LVH was 2.00 (1.04–3.86; $P = 0.037$) comparing high with intermediate haematocrit levels.

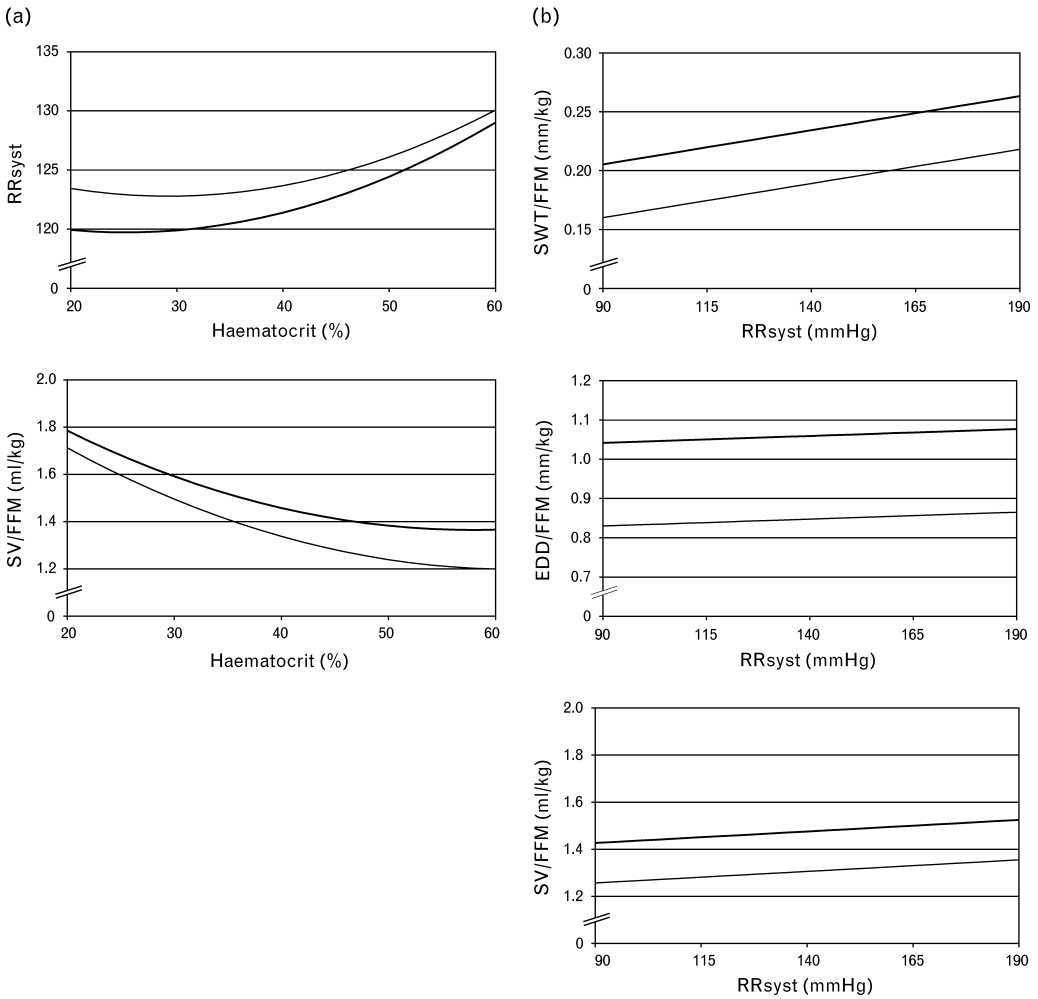
Discussion

Chronic anaemia as well as polycythemia are related to a number of adaptations of the circulatory system [1,6,7]. It is not known, however, whether the variability of haematocrit levels within the general population may affect the geometry and mass of the left ventricle. Here we demonstrate, first, a linear inverse relationship between left ventricular diameters and haematocrit, second, a curvilinear relationship between left ventricular wall thickness and haematocrit, and furthermore an elevated risk of LVH at the upper and lower end of the haematocrit distribution curve in a population-based sample.

Pathophysiology

The differential relationships between haematocrit and left ventricular dimension and wall thickness are best explained as a response to either volume or pressure overload of the heart. The linear inverse relationships between haematocrit and left ventricular end-diastolic as well as end-systolic dimensions are likely to reflect the increasing volume load with decreasing haematocrit [28]. Pressure load, on the other hand, is likely to be determined by the linear association between haematocrit and systolic blood pressure (Fig. 2) and other mechanisms affecting afterload (e.g. viscosity), resulting in an increased left ventricular wall thickness at high haematocrit levels. The association of haematocrit and left ventricular wall thickness may, however, be even better described as a parabolic relationship. This finding is a good agreement with the concept that, at one end of the spectrum, increasing haematocrit levels augment (systolic) pressure load and consecutively increase wall thickness [7]. At the lower spectrum of haematocrit levels increased left ventricular dimensions may augment wall stress and therefore result in increased left ventricular wall thickness. As a consequence, the lowest values for LVM as well as the lowest values for RWT were observed at physiologically 'normal' haematocrit levels. Interestingly, Narayan *et al.* [29] reported recently on associations of haemoglobin delivery with left ventricular structure and function in hypertensive patients. They also found negative but weak or insignificant correlations of haemoglobin level and EDD.

Fig. 2



Relationships between haematocrit levels, haemodynamic variables and left ventricular dimensions. Results of linear regression models were plotted separately for hypothetical 50-year-old men and women without hypertension, diabetes mellitus, heart failure or a history of cardiovascular disease with body fat (men 22.1 kg, women 24.7 kg) and serum creatinine levels (men 0.84 mg/dl, women 0.67 mg/dl) corresponding to the median of the entire study sample. For explanation of echocardiographic variables see Table 1. EDD, Left ventricular end-diastoic diameter; RRsyst, systolic blood pressure; SV, stroke volume; SWT, septal wall thickness. ——— Women; ——— men.

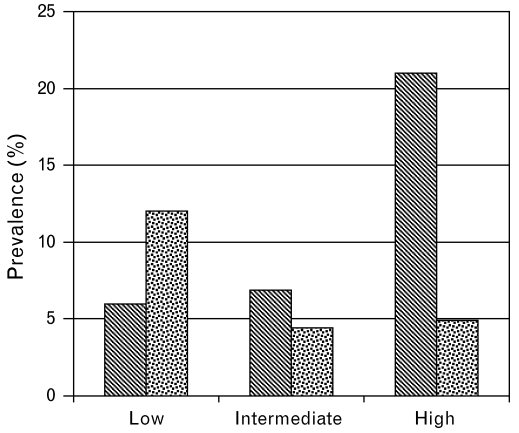
Anaemia and left ventricular geometry and function

Anaemia may result in a reduction in afterload as a result of a decrease in systemic vascular resistance [30]. In parallel, an increase in preload may occur as a result of an increase in venous return [2]. Finally, left ventricular function may be enhanced in anaemic individuals because of increased sympathetic activity and ionotropic factors that may also lead to an increase in cardiac work [3,31]. Together, these mechanisms of haemodynamic compensation result in elevated wall stress, which may finally result in an adaptive increase in wall thickness, as observed in individuals with low haematocrit levels [32].

Anaemia is commonly found in patients with chronic heart failure [33], and is then related to a poor outcome [34]. Witte *et al.* [33] reported a prevalence of 34% in patients with chronic heart failure. The aetiology of the condition is only partly understood [35,36]. Emerging evidence suggests that the correction of anaemia, for example with erythropoietin and iron, may improve cardiac function and effectively reduce symptoms in patients with chronic heart failure [37,38].

Likewise, chronic renal disease may cause anaemia and LVH. Here the correction of anaemia resulted in an increase in the left ventricular ejection fraction and a decrease in the left ventricular end-diastolic diameter and LVM [39,40]. The present findings strengthen the notion that alterations in haematocrit, even within the physiological range, affect left ventricular geometry and potentially function. Consequently, the data support

Fig. 3



Prevalence of eccentric and concentric left ventricular hypertrophy (LVH) within subjects with low, intermediate and high haematocrit. Concentric LVH; eccentric LVH.

therapeutic attempts to correct anaemia in patients with heart or renal failure. Available animal studies have also indicated that beyond the effect on erythropoiesis, erythropoietin also has multiple paracrine autocrine functions that coordinate local responses to injury by maintaining vascular autoregulation and attenuating both primary (apoptotic) and secondary (inflammatory) causes of cell death [41–43].

Polycythemia and left ventricular geometry and function

On the other hand, the hearts of patients presenting with a morbidly increased number of red blood cells, such as polycythemia, may face an elevated afterload as a result of the high viscosity of the blood and increased peripheral resistance [6,7]. Cardiac strain may thus be elevated in patients with high haematocrit levels [8]. In conjunction with the lower diameters, a raised RWT predominates in individuals with high haematocrit levels. In line with these observations, Bertinieri *et al.* [44] demonstrated that isovolumic haemodilution in hypertensive polycythemic patients reduces both systolic and diastolic blood pressure. A common cause of polycythemia is elevated erythropoietin levels, e.g. as a result of chronic hypoxemia. LVH is common in transgenic mice with high haematocrit levels because of an overexpression of the erythropoietin gene [45]. In patients, chronic obstructive pulmonary disease may frequently cause elevated haematocrit levels. Future studies will be required to understand whether this adaptive change contributes to subsequent cardiac alterations, and in particular right ventricular hypertrophy or LVH.

Anaemia and polycythemia result in different cardial adaptation patterns

In the current study, we demonstrated that subjects within the low range of haematocrit (<35 for women and <40 for men) display an increased risk of eccentric LVH and, vice versa, those in the upper range (>44 for women and >48 for men) were predisposed to concentric LVH. These associations support the potential clinical relevance of our findings. By comparison, the increase in the adjusted risk of LVH in individuals within the upper haematocrit range, approximately a doubling of the prevalence, compares with the risk observed with mild to moderate hypertension [19]. As haematocrit and blood pressure are known to be associated, (e.g. the correlation coefficient was $r=0.25$; $P<0.001$, in the present sample), it is of interest that this risk is still discernible after adjustment for blood pressure levels. At the other end of the spectrum, in subjects within the lower range of haematocrit, a doubling of the prevalence of eccentric LVH was observed. Of note is the fact that the extreme end of the spectrum, namely anaemia, has already been identified as a preventable factor contributing to eccentric LVH in patients with renal failure [46]. In the present population approximately 1.3% presented with elevated creatinine levels, such that renal failure does not appear to be mandatory for the left ventricular dilatation seen in such patients.

Limitations

Some limitations of the present study need to be considered. First, we report on associations in a rather complex biological system with multiple interactions. For example, blood pressure, body fat composition, age, and sex affect both cardiac geometry as well as haematocrit levels [25,26,47–49]. It is thus difficult to establish causal relationships using the present cross-sectional study design. Nevertheless, the associations reported were consistent and robust against multiple adjustments in a variety of models. Moreover, the reported findings are in line with the pathophysiological implications of relatively high or low haematocrit levels hypothesized before commencing these analyses.

In conclusion, this study demonstrates that the variability of haematocrit levels occurring in the general population is significantly associated with left ventricular geometry. Our findings suggest a linear inverse association between haematocrit and left ventricular dimensions throughout the entire spectrum of haematocrit levels. The association between left ventricular wall thickness and haematocrit levels appears more complex. As hypothesized, we observed an increased wall thickness, particularly in individuals with relatively high haematocrit levels, whereas at the lower end of the haematocrit spectrum, the observed increase in left ventricular wall thickness was less pronounced. These relationships contribute independently to the explanation of differences in left ventricular geometry and may be of clinical interest with regard to recent initiatives to normalize haematocrit levels in patients with mild anaemia and renal or congestive heart failure.

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