

Haematocrit profoundly affects left ventricular diastolic filling as assessed by Doppler echocardiography

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Background The main determinants of diastolic function – pre- and afterload of the heart – are affected by the haematocrit, but the relation between haematocrit and diastolic function is unclear.

Objective To study the association between interindividual haematocrit values and diastolic function, by echocardiography.

Design In a cross-sectional survey, blood pressure, haematocrit values, and high-quality Doppler indexes of left ventricular filling were obtained in 1297 individuals, 25–74 years of age, and analysed by regression analyses.

Results Haematocrit and systolic blood pressure were strongly correlated ($r = 0.23$; $P < 0.0001$). Moreover, haematocrit was inversely correlated with the peak velocity of early left ventricular filling and with the peak velocity of early filling divided by late filling (E/A ratio; both $P < 0.005$). Left ventricular isovolumic relaxation time (IVRT) was positively associated with haematocrit ($r = 0.18$, $P < 0.001$). In individuals with an abnormal Doppler filling pattern ($E/A <_{50\text{years}} < 1$, $E/A >_{50\text{years}} < 0.5$, or $IVRT <_{30\text{years}} > 92$ ms, $IVRT_{30-50\text{years}} > 100$ ms or $IVRT >_{50\text{years}} > 105$ ms; $n = 119$), greater haematocrit values were observed than in those with normal diastolic parameters ($P < 0.001$). Conversely, individuals with an increased haematocrit ($> 50\%$ in men, $> 45\%$ in women; $n = 16$) had a greater risk of presenting with abnormal left ventricular filling (31.3%) compared with individuals with normal (12.1%; $n = 898$); or low ($< 40\%$ in men, $< 35\%$ in women: 10.5%, $n = 38$; $P = 0.07$) haematocrit. Strong and significant associations between haematocrit and Doppler indexes of left ventricular filling were confirmed after adjustment for multiple potential confounders including

blood pressure, antihypertensive medication and body mass index. Similarly, blood pressure and parameters of diastolic filling were strongly associated correlations that were not affected by inclusion of haematocrit values into the regression model.

Conclusion The data point to substantial adaptations of diastolic filling in response to both blood pressure and the characteristics of the medium that is propelled by the heart. Therefore, in addition to blood pressure values, the variability of haematocrit values should be considered when diastolic function is being evaluated by Doppler echocardiography. *J Hypertens* 18:1483–1489 © 2000 Lippincott Williams & Wilkins.

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Introduction

Chronic anaemia is related to a number of adaptations of the circulatory system [1]. Most notably, peripheral resistance decreases and heart rate and cardiac output increase substantially [2]. Such hyperdynamic circulation compensates, at least in part, for the reduced oxygen transport capacity of the anaemic blood. It may also increase cardiac preload in patients with severe

anaemia [3]. Given that left ventricular preload is an important determinant of the pattern of transmitral inflow during left ventricular filling [4–6], it is conceivable that anaemia – or even the variability of haematocrit values within the physiological range – may indirectly affect diastolic function; however, we are not aware of any study that has investigated this issue systematically. Such an association may be of specific

relevance to patients with arterial hypertension, as blood pressure values have been associated with both impaired diastolic filling and increased haematocrit [7,8], therefore we analysed the relation between Doppler indexes of left ventricular filling, haematocrit and blood pressure recorded in a large database of the third population-based MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg survey.

Participants and methods

Study population

The MONICA Augsburg study was conducted as a component of the international collaborative World Health Organization (WHO) MONICA project and investigated the cardiovascular risk factor profile of randomly selected individuals from the Augsburg population in cross-sectional surveys. Echocardiographic examinations were performed in a total of 845 men and 832 women, aged 25–74 years [9]. All gave written informed consent to participation in the study and underwent an interview relating to personal and family medical history, life style and nutrition, health behaviour, and psychosocial factors. Blood pressure was measured at the right arm and with the individual in a sitting position, using a random zero sphygmomanometer under standardized conditions.

Echocardiographic measurements

Doppler, two-dimensional, and two-dimensionally guided M-mode echocardiograms were performed in each participant by two expert sonographers using a commercially available echocardiograph (Hewlett Packard, Sonos 1500, Andover, Massachusetts, USA) with a 2.5 or 3.5 MHz transducer. M-mode tracings were recorded on a stripchart paper at a speed of 50 mm/s. To reduce interobserver variability, all these tracings were analysed by a single experienced cardiologist. Measurements for calculation of left ventricular mass from data acquired by M-mode-guided echocardiography were performed according to the guidelines of the American Society of Echocardiography.

Left ventricular mass (LVM) was calculated according to the formula [10]:

$$\text{LVM (g)} = 1.04[(\text{EDD} + \text{sWth} + \text{pWth})^3 - (\text{EDD})^3] - 13.6$$

where EDD is end-diastolic diameter and sWth and pWth are septal wall thickness and posterior wall thickness, respectively. It was indexed to body height raised to the power of 2.7, as LMV index (LMVI) in g/m [11]. Left atrial volume was traced at end-systole in the apical four-chamber view [12]. Doppler echocardiographic recordings were performed by pulsed-wave

Doppler with the sample volume at the tips of the mitral valve in the apical four-chamber view and registered at a paper speed of 100 mm/s. Early and late diastolic velocities, velocity time integrals, ratios of early and late velocities, and velocity time integrals were determined as reported previously [13]. Isovolumetric relaxation time (IVRT) was determined as the time interval between the end of the aortic outflow and the start of the mitral inflow signal. Doppler mitral profiles of sufficient quality were obtained in 1297 participants for the determination of diastolic filling velocities and in 970 for analysis of IVRT.

No systematic differences in terms of age, sex, body mass index (BMI) and systolic blood pressure were detected between participants with complete or with incomplete diastolic filling data. Diastolic dysfunction was defined as proposed by the European Study Group on Diastolic Heart Failure [14]. Specifically, an abnormal E/A ratio was considered to be present when $E/A_{<50\text{years}}$ was less than 1 or $E/A_{>50\text{years}}$ was less than 0.5, or when $IVRT_{<30\text{years}}$ was greater than 92 ms, $IVRT_{30-50\text{years}}$ was greater than 100 ms or $IVRT_{>50\text{years}}$ was greater than 105 ms.

Blood cell count

Blood was drawn from non-fasting individuals who were in a supine resting position for at least 30 min. A complete blood cell count was carried out in a Coulter STKS chamber (Coulter, Krefeld, Germany). Values of haematological variables were defined as low when the haematocrit was less than 40% in men and less than 35% in women. The upper range of normal haematocrit was set at 50% in men and 45% in women, based on the procedural manual of the clinical chemistry laboratory of this university. Categorization of the population into groups in whom the haematocrit was greater than, within, or less than two standard deviations of the sex-specific mean (men 38.5–50.1%, women 34–46%) revealed a range of normal haematocrit values that were comparable to those defined for our study. Accordingly, the sizes of the groups defined in Table 1 (low haematocrit, $n = 43$ compared with $n = 51$; normal haematocrit, $n = 1201$ compared with $n = 1187$; high haematocrit, $n = 16$ compared with $n = 22$) were only minimally affected, and the results of statistical tests were almost identical.

Statistical methods

Associations of haematocrit, haemoglobin and erythrocyte count with Doppler indexes of left ventricular filling were initially assessed by calculation of Pearson correlation coefficients. Mean values of continuous variables and percentages of categorical variables were obtained for groups of individuals with low, normal and high values for the haematological variables. Differences between groups were assessed univariately by

Table 1 Anthropometric and echocardiographic data by haematocrit group

Variable	Haematocrit (%)			P (ANOVA or χ^2)
	Low: M: < 40% W: <34% (n = 51)	Normal: M: 40–50% W: 35–45% (n = 1187)	High: M: > 50% W: >45% (n = 22)	
Sex (% female)	56.9	51.6	54.5	NS
Age (years)	50.1 $\pm$ 1.9	48.6 $\pm$ 0.4	53.5 $\pm$ 2.0	NS
Current smokers (%)	16	27	59	0.002
BMI (kg/m ²)	25.2 $\pm$ 0.4	26.4 $\pm$ 0.1	28.4 $\pm$ 0.8	0.006
Systolic blood pressure (mmHg)	129 $\pm$ 2.7	132 $\pm$ 0.6	144 $\pm$ 4	0.006
Hypertension* (%)	16	24	55	0.002
Medication for hypertension (%)	14	16	32	NS
LVMI (g/m ^{2.7})	38.3 $\pm$ 1.5	38.1 $\pm$ 0.3	41.4 $\pm$ 2.3	NS
End-diastolic diameter (mm)	29.4 $\pm$ 0.3	28.5 $\pm$ 0.1	27.3 $\pm$ 0.5	0.003
Fractional shortening (%)	34 $\pm$ 0.8	35 $\pm$ 0.2	36 $\pm$ 1.2	NS
Heart rate (beats/min)	70 $\pm$ 1.5	68 $\pm$ 0.3	75 $\pm$ 2.4	0.02
E _{max} (cm/s)	69 $\pm$ 2.0	64 $\pm$ 0.4	54 $\pm$ 3.1	0.0004
A _{max} (cm/s)	57 $\pm$ 2.4	55 $\pm$ 0.5	58 $\pm$ 3.6	NS
E/A ratio	1.32 $\pm$ 0.07	1.26 $\pm$ 0.01	0.96 $\pm$ 0.1	0.01
E/A ratio <1 (%)	29	32	64	0.006
IVRT [†] (ms)	71 $\pm$ 3.0	80 $\pm$ 0.6	90 $\pm$ 4.5	0.001
IVRT [§] >100 ms (%)	3	10	31	0.007
LA vol (ml)	43.0 $\pm$ 1.9	42.6 $\pm$ 0.4	42.9 $\pm$ 2.8	NS
Diastolic dysfunction [‡] (%)	10.5	12.1	31.3	0.07

Data are given as means $\pm$ SEM for continuous variables (*P* values indicate statistically significant differences between haematocrit groups by ANOVA) and as percentages for categorical variables (*P* values based on χ^2 statistic for homogeneity of haematocrit groups). *Defined as blood pressure at least 160/95 mmHg or individual taking current antihypertensive medication. [†]Number of individuals in whom IVRT could be assessed was 952. [§]Defined according to the criteria of the European Study Group on Diastolic Heart Failure [14] as: E/A_{<50years} ratio < 1 or E/A_{>50years} < 0.5; or IVRT_{<30years} > 92 ms, IVRT_{30–50years} > 100 ms or IVRT_{>50years} > 105 ms. NS, not significant; M, men; W, women; BMI, body mass index; LVMI, left ventricular mass index (indexed by height^{2.7}); E, E-wave; A, A-wave; IVRT, isovolumic relaxation time; LA vol, left atrial volume by planimetry in the four-chamber view.

analysis of variance or χ^2 tests. Differences in mean haematological values for individuals with and without diastolic dysfunction were evaluated by unpaired *t*-tests. Multivariate regression analyses adjusted the associations between haematological and left ventricular filling variables for the covariates age, sex, BMI, systolic blood pressure, antihypertensive treatment status (yes or no), heart rate, fractional shortening and LMV indexed to body height^{2.7}. Differences in Doppler indexes of left ventricular filling between the low, normal and high group were assessed using these fully adjusted models. *P* values < 0.05 were considered to be statistically significant.

Results

Univariate associations

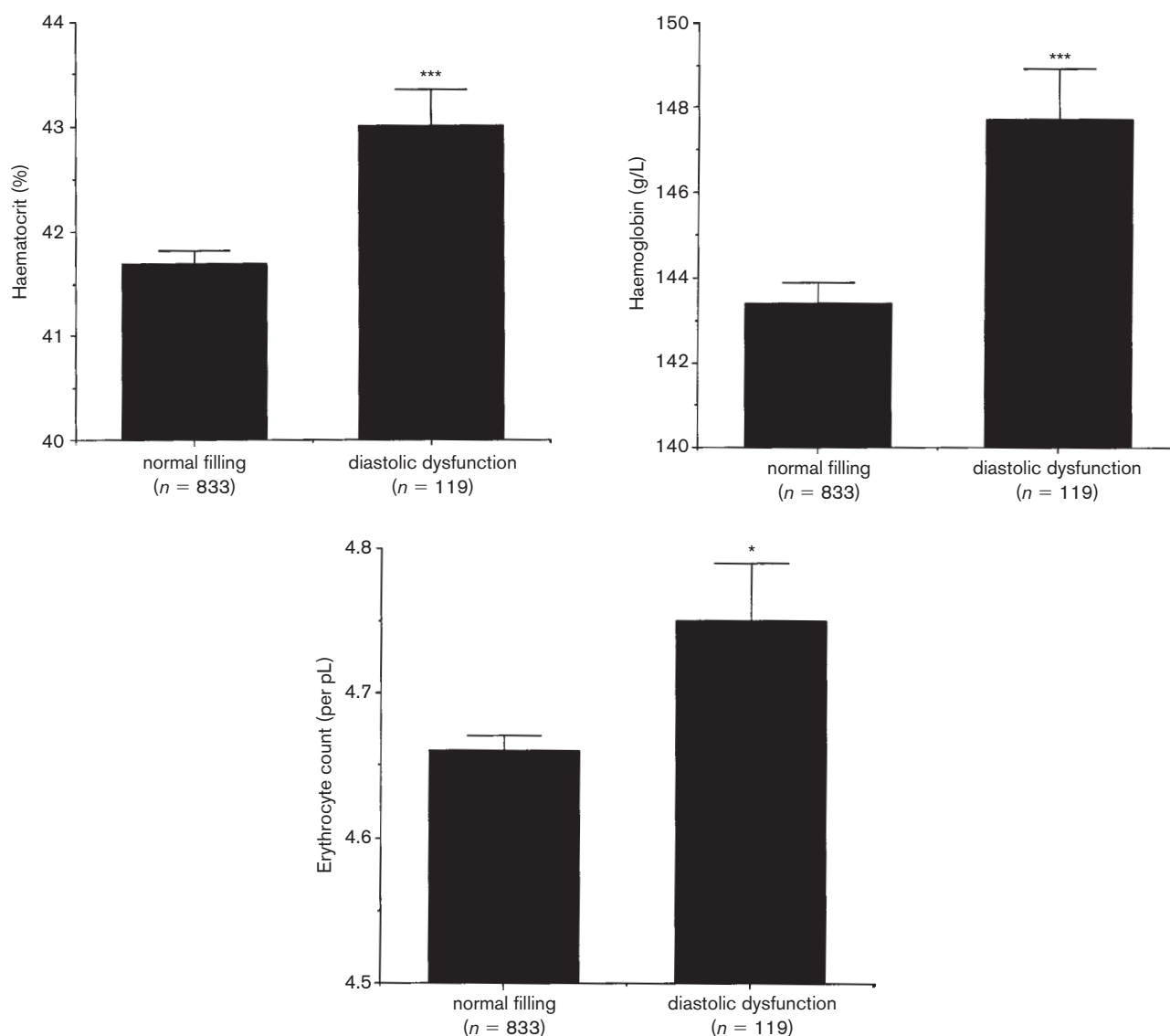
Table 1 presents anthropometric and echocardiographic data for individuals with low, normal, or high values of haematocrit. Similar to the observations of others [1,8], the prevalence of hypertension and the blood pressure values were markedly greater in individuals with high haematocrit levels. In addition, the peak velocity of early left ventricular filling (peak E-wave) and IVRT exhibited marked differences depending on the haematocrit. Moreover, the E/A ratio or the prevalence of an E/A ratio less than 1, or the prevalence of an IVRT greater than 100 ms varied significantly between individuals with high, normal or low haematocrit levels. No

difference between these groups was found with respect to fractional shortening or LMVI (Table 1).

The likelihood of displaying an abnormal Doppler pattern of filling of the left ventricle, as defined by the European Study Group on Diastolic Heart Failure [14], was 10.5% in individuals with a low haematocrit and 31.3% in those with an increased haematocrit (*P* = 0.07; Table 1). Conversely, in individuals with left ventricular diastolic dysfunction, the average haematocrit, haemoglobin concentration and erythrocyte count were significantly greater than the respective values in those without dysfunction (Fig. 1).

Blood pressure values were also associated with parameters of left ventricular diastolic filling. Compared with normotensive individuals (blood pressure less than 160/95 mmHg and not taking antihypertensive medications, *n* = 951), participants in the survey who were hypertensive (*n* = 309) were characterized by a decrease in the E-wave (61.1 cm/s compared with 64.5 cm/s; *P* < 0.0001), an increase in the A-wave (66.7 cm/s compared with 51.8 cm/s; *P* < 0.0001), a profound decrease in the E/A ratio (0.97 compared with 1.35; *P* < 0.0001), and an increase in IVRT (90.9 ms compared with 76.2 ms; *P* < 0.0001). The associations between haematocrit and peak E-wave and IVRT were observed in both normotensive (*r* = 0.21, *P* < 0.0001 and *r* = 0.15, *P* < 0.001, respectively) and hypertensive

Fig. 1



Haematological data (mean $\pm$ SEM) in individuals with normal or pathological left ventricular filling pattern. Diastolic dysfunction was defined according to the criteria provided by the European Study Group [14] as: E/A_{<50years} ratio < 1 or E/A_{>50years} < 0.5; or IVRT_{<30years} > 92 ms, IVRT_{30–50years} > 100 ms or IVRT_{>50years} > 105 ms. * $P < 0.05$; *** $P < 0.001$.

individuals ($r = 0.25$, $P < 0.001$ and $r = 0.11$, $P = 0.10$, respectively).

Multivariate associations

After adjustment for covariates – age, sex, BMI, systolic blood pressure, use of antihypertensive medication, heart rate, fractional shortening, and LMVI – the strong association between haematocrit values and peak E-wave velocity, integral of the E-wave, and peak velocity of early filling divided by late filling (E/A ratio) persisted (Table 2). Specifically, a 10% increase in the adjusted haematocrit accounted for a

decrease in peak E-wave of 8.0 cm/s ($P = 0.001$) and a decrease in the E/A ratio of 0.10 ($P = 0.006$). Similarly, IVRT was multivariately associated with haematocrit values (Table 2). Furthermore, adjusted haemoglobin concentration and erythrocyte count were inversely related to the peak E-wave and the E/A ratio in a highly significant fashion; however, the positive association with IVRT was less clearly significant (Table 2). For comparison, Table 2 displays respective associations for systolic blood pressure that were obtained from the full regression model, including haematocrit.

Table 2 Associations of haematocrit, haemoglobin concentration and erythrocyte count with echocardiographic parameters of left ventricular filling

Variable	Haematocrit (per 10% increase)	Haemoglobin (per 3 g/l increase)	Erythrocyte count (per 1/pl increase)	Systolic blood pressure (per 10 mmHg increase)
E _{max} (cm/s)	$\beta = -8.0$ $P = 0.001$	$\beta = -6.0$ $P = 0.001$	$\beta = -4.4$ $P = 0.001$	$\beta = 0.7$ $P = 0.003$
E/A ratio	$\beta = -0.10$ $P = 0.006$	$\beta = -0.08$ $P = 0.01$	$\beta = -0.08$ $P = 0.01$	$\beta = -0.02$ $P = 0.001$
IVRT (ms)	$\beta = 3.9$ $P = 0.03$	$\beta = 3.2$ $P = 0.04$	$\beta = 2.1$ NS	$\beta = 0.4$ NS

Data are results of multivariate regression analyses (adjusted for age, sex, body mass index, systolic blood pressure, antihypertensive treatment status, heart rate, fractional shortening and left ventricular mass indexed to body height^{2.7}), given as regression coefficients (β) and respective P values. E, E-wave; A, A-wave; IVRT, isovolumic relaxation time; NS, not significant.

When results from only those individuals with normal haematocrits were included in regression analyses, essentially identical associations were obtained (Table 3). Likewise, expansion of the model by further inclusion of covariates such as current smoking or end-diastolic diameter did not change the highly significant association of haematocrit and diastolic parameters. When the two sexes were analysed separately (Table 4), women revealed strong and highly significant correlations between haematological and Doppler left ven-

tricular filling parameters, whereas men (who were represented by a relatively narrow spectrum of haematocrit values) displayed similar trends for the associations, but these were not statistically significant. In formal statistical testing, the differences between men and women were significant for the peak E-wave ($P = 0.01$) and the E/A ratio ($P = 0.007$), suggesting a stronger relationship between haematocrit and diastolic filling parameters in women than in men. Moreover, categorization of the participants according to their taking or not taking antihypertensive medication revealed either significant associations or strong trends for the relationship between haematocrit and Doppler diastolic filling parameters in all subgroups tested. Lastly, after adjustment for multiple covariates, neither the size of the left atrium nor the peak A-wave were any longer significantly associated with haematocrit, haemoglobin concentration, or erythrocyte count (data not shown).

Discussion

Doppler indexes of left ventricular filling are widely used for the assessment of diastolic function. Here, we have demonstrated that variability in haematocrit, as occurs in the general population, is closely associated with these Doppler echocardiographic parameters. Specifically, an increase in haematocrit is associated with

Table 3 Associations of haematocrit, haemoglobin concentration and erythrocyte count with echocardiographic parameters of left ventricular filling

Variable	Haematocrit (per 10% increase)	Haemoglobin (per 3 g/l increase)	Erythrocyte count (per 1/pl increase)
E _{max} (cm/s)	$\beta = -6.9$ $P = 0.001$	$\beta = -6.0$ $P = 0.001$	$\beta = -4.5$ $P = 0.001$
E/A ratio	$\beta = -0.1$ $P = 0.02$	$\beta = -0.09$ $P = 0.006$	$\beta = -0.08$ $P = 0.02$
IVRT (ms)	$\beta = 1.6$ NS	$\beta = 1.8$ NS	$\beta = 2.8$ $P = 0.08$

Data are results of multivariate regression analyses (adjusted for age, sex, body mass index, systolic blood pressure, antihypertensive treatment status, heart rate, fractional shortening and left ventricular mass indexed to body height^{2.7}), given as regression coefficients (β) and respective P values for individuals with normal values of haematocrit (men 40–50%, women 35–45%), haemoglobin (men 133–177 g/l, women 117–157 g/l) and erythrocyte count (men 4.2–6.1/pl, women 3.6–5.2/pl). E, E-wave; A, A-wave; IVRT, isovolumic relaxation time; NS, not significant.

Table 4 Associations of haematocrit and systolic blood pressure with echocardiographic parameters of left ventricular filling after division of the participants into subgroups according to sex and use of antihypertensive medication

Variable	Men ($n = 575$)		Women ($n = 594$)		No antihypertensive drugs ($n = 1056$)		With antihypertensive drug use ($n = 204$)	
	Haematocrit (per 10% increase)	SBP (per 10 mmHg)	Haematocrit (per 10% increase)	SBP (per 10 mmHg)	Haematocrit (per 10% increase)	SBP (per 10 mmHg)	Haematocrit (per 10% increase)	SBP (per 10 mmHg)
E _{max} (cm/s)	$\beta = -4.0$ $P = 0.04$	$\beta = 0.9$ $P = 0.008$	$\beta = -10.2$ $P = 0.0001$	$\beta = 0.8$ $P = 0.02$	$\beta = -7.0$ $P = 0.001$	$\beta = 0.9$ $P = 0.004$	$\beta = -11.5$ $P = 0.002$	$\beta = 0.5$ NS
E/A ratio	$\beta = -0.005$ NS	$\beta = -0.03$ $P = 0.002$	$\beta = -0.17$ $P = 0.001$	$\beta = -0.01$ $P = 0.25$	$\beta = -0.08$ $P = 0.05$	$\beta = -0.02$ $P = 0.01$	$\beta = -0.15$ $P = 0.02$	$\beta = -0.02$ $P = 0.03$
IVRT (ms)	$\beta = 3.6$ NS	$\beta = 0.9$ $P = 0.09$	$\beta = 4.2$ $P = 0.08$	$\beta = -0.07$ $P = 0.86$	$\beta = 3.1$ $P = 0.09$	$\beta = 0.9$ $P = 0.01$	$\beta = 8.6$ NS	$\beta = -1.2$ NS

Data are results of multivariate regression analyses (adjusted for age, sex, body mass index, systolic blood pressure, heart rate, fractional shortening and left ventricular mass indexed to body height^{2.7}), given as regression coefficients (β) and respective P values. SBP, systolic blood pressure; E, E-wave; A, A-wave; IVRT, isovolumic relaxation time; NS, not significant.

an increased prevalence of Doppler patterns that suggest diastolic dysfunction, whereas anaemia has the opposite correlate.

Anaemia is known to cause a hyperdynamic circulation with decreased peripheral resistance, increased venous return and, thus, increased preload of the left ventricle [1,3,15]. In addition, haemodynamic changes of this nature are known to affect Doppler indexes of diastolic function [4–6,16]. For example, an increase in left atrial pressure changes the left ventricular filling velocity profile in a manner that may mimic the pattern of normal diastolic function, even when left ventricular relaxation is impaired [6,17]. Thus the association between haematocrit and transmitral inflow pattern, observed in the present study, is potentially mediated by circulatory adaptations at various values of haematocrit. In agreement with this hypothesis are the findings of smaller studies that reported enhanced early diastolic filling velocities in patients with severe anaemia and a hyperdynamic circulation despite concomitant left ventricular hypertrophy [18–20].

Although circulatory adaptations, including differences in left ventricular preload, are likely to explain the relationship between haematocrit and the pattern of transmitral inflow, we cannot exclude that myocardial or rheological alterations also contribute to this finding. Theoretically, different values of haematocrit might be associated with differences in left ventricular geometry, structure, morphology, systolic function, or blood viscosity. However, no associations were found between haematocrit values and late diastolic filling (A-wave), left ventricular systolic function (as measured by echocardiographic ejection fraction), or total LVM. Thus myocardial alterations appear less likely to explain the association between haematocrit and the pattern of transmitral inflow. Moreover, we are not aware of any study that has demonstrated that differences in blood viscosity at various values of haematocrit may affect the Doppler signals of diastolic function.

The present study reproduced the well-known associations between blood pressure and haematocrit (Table 1; [1,8]) and between blood pressure and diastolic function (see Results section; [7]). These associations, however, do not appear to explain the association between haematocrit and diastolic function. In fact, in the present study, hypertension had a stronger effect on late diastolic filling, probably secondary to left ventricular hypertrophy, whereas high values of haematocrit largely affected early diastolic filling (IVRT and E-wave). Moreover, the multivariate model that included systolic blood pressure, antihypertensive medication and haematocrit as independent variables demonstrated that both retained their significant relationship with echocardiographic parameters of diastolic function. Fi-

nally, the associations between haematocrit and diastolic function were observed in both normotensive and hypertensive individuals. Thus different and potentially additive mechanisms appear to explain the modulation of left ventricular filling in individuals with high blood pressure and high haematocrit levels.

No matter what the precise underlying mechanism may be, it is of interest that the variability of haematocrit values within the normal range was sufficient to produce significant alterations in the pattern of transmitral inflow. From a physiological point of view, this finding suggests that, even with normal haematocrit levels, the heart and the circulatory system adapt to subtle differences in the oxygen transport capacity of the blood. This notion may apply, not only to the pattern of transmitral inflow, but also to other haemodynamic parameters, including cardiac index, total peripheral resistance, or left ventricular geometry. In fact, we noted that haematocrit values, although largely in the normal range, were related inversely to cardiac index and positively to total peripheral resistance (data not shown). Moreover, as men and women are characterized by significant differences in average haematocrit values, some well-recognized sex-related cardiac adaptations may be secondary to differences in haematocrit. In this regard, we were able to reproduce recent observations [21,22] that sex, after adjustment for traditional covariates, may be a strong predictor of early filling velocity ($P < 0.0001$). However, when haematocrit values were included into the model, sex lost its significant association with early transmitral inflow velocity ($P > 0.1$). On the basis of the present findings, we therefore propose that future studies of left ventricular structure and function that compare groups with different haematocrit levels should take into consideration this potential covariate.

The present study was limited by its observational design. Because of this, associations between haematocrit values and Doppler echocardiographic parameters might be indirect and based, in part, on other covariates. In this respect, it should be noted that individuals with anaemia were on average younger and had lower BMI values and greater heart rates. Moreover, the associations between left ventricular filling parameters and haematocrit were not statistically significant in the subgroup of men. We cannot explain this sex-related difference, and speculate that, in women, the larger variability in haematocrit accounts for more pronounced associations. We considered sex and several additional anthropometric and left ventricular structural and functional parameters in multivariate regression analyses. Uniformly, these analyses confirmed highly significant associations between isovolumic relaxation and early diastolic filling of the left ventricle with haematological parameters, suggesting that at least these variables do

not explain the strong association with Doppler left ventricular filling indexes. A further limitation may be that determinants not recognized in this study might have influenced the results. Moreover, cardiovascular or severe general diseases might have affected blood cell count and diastolic function simultaneously and, thus, account for the reported associations. However, this consideration also appears to be unlikely, as exclusion of individuals with diabetes, atrial fibrillation, or prior myocardial infarction (data not shown), and limitation of the regression analyses to individuals with normal blood counts or normotension were without effect on the strong association between Doppler echocardiographically assessed patterns of transmitral inflow and haematocrit.

Potential clinical implications of the present observations relate to the frequent use of Doppler echocardiography for the non-invasive assessment of diastolic function, specifically in patients with arterial hypertension. In fact, diagnostic criteria for diastolic dysfunction are based largely on these techniques [14]. Thus it might be of relevance that Doppler echocardiography may underestimate or overestimate the extent of diastolic dysfunction in individuals with relatively low or relatively high haematocrit values.

We conclude that Doppler indexes of transmitral inflow are significantly associated with haematocrit values. Information on the red blood cell count may be important for the precise evaluation of diastolic function by echocardiography.

References

- 1 Duke M, Abelman WH. The hemodynamic response to chronic anemia. *Circulation* 1969; **39**:503–515.
- 2 Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. *Am Heart J* 1972; **83**:415–426.
- 3 Roy SB, Bhatia ML, Mathur VS, Virmani S. Hemodynamic effects of chronic severe anemia. *Circulation* 1963; **28**:346–356.
- 4 Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987; **10**:800–808.
- 5 Courtois M, Vered Z, Barzilai B, Ricciotti NA, Perez JE, Ludbrook PA. The transmitral pressure–flow velocity relation. Effect of abrupt preload reduction. *Circulation* 1988; **78**:1459–1468.
- 6 Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ. Influence of alteration in preload on the pattern of left ventricular diastolic filling as assessed by Doppler echocardiography in humans. *Circulation* 1989; **79**:1226–1236.
- 7 de Simone G, Greco R, Mureddu GF, Romano C, Guida R, Celentano A, *et al.* Relation of left ventricular diastolic properties to systolic function in arterial hypertension. *Circulation* 2000; **101**:152–157.
- 8 Smith WC, Lowe GD, Lee AJ, Tunstall-Pedoe H. Rheological determinants of blood pressure in a Scottish adult population. *J Hypertens* 1992; **10**:467–472.
- 9 Muscholl M, Hense HW, Broeckel U, Doering A, Riegger GAJ, Schunkert H. Alterations of left ventricular geometry and function in subjects with white coat hypertension: cross sectional survey. *BMJ* 1998; **317**:565–570.
- 10 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation* 1977; **55**:613–618.
- 11 Hense HW, Gneiting B, Muscholl M, Broeckel U, Kuch B, Doering A, *et al.* The associations of body size and body composition with left ventricular mass: impact for indexation in adults. *J Am Coll Cardiol* 1998; **32**:451–457.
- 12 Hirashi S, DiSessa TG, Jarmakani JM, Nakanishi T, Isabel-Jones J, Friedman WF. Two-dimensional echocardiographic assessment of left atrial size in children. *Am J Cardiol* 1983; **52**:1249–1257.
- 13 Muscholl M, Dennig K, Kraus F, Rudolph W. Echocardiographic and Doppler-echocardiographic characterization of left ventricular diastolic function. *Herz* 1990; **15**:377–392.
- 14 European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998; **19**:990–1003.
- 15 Guyton AC, Richardson TQ. Effect of haematocrit on venous return. *Circulation* 1961; **9**:157–164.
- 16 Hurrell DG, Nishimura RA, Ilstrup DM, Appleton CP. Utility of preload alteration in assessment of left ventricular filling pressure by Doppler echocardiography: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol* 1997; **30**:459–467.
- 17 Takagi S, Yokota M, Iwase M, Yoshida J, Hayashi H, Sotobata I, *et al.* The important role of left ventricular relaxation and left atrial pressure in the left ventricular filling velocity profile. *Am Heart J* 1989; **118**:954–962.
- 18 Kremastinos DT, Tsiapras DP, Tsetsos GA, Rentoukas EI, Vretou HP, Toutouzas PK. Left ventricular diastolic Doppler characteristics in beta-thalassemia major. *Circulation* 1993; **88**:1127–1135.
- 19 Satoh K, Masuda T, Ikeda Y, Kurokawa S, Kamata K, Kikawada R, *et al.* Hemodynamic changes by recombinant erythropoietin therapy in hemodialyzed patients. *Hypertension* 1990; **15**:262–266.
- 20 Bahl VK, Malhotra OP, Kumar D, Agarwal R, Goswami KC, Bajaj R, *et al.* Noninvasive assessment of systolic and diastolic left ventricular function in patients with chronic severe anaemia: a combined M-mode, two-dimensional, and Doppler echocardiographic study. *Am Heart J* 1992; **124**:1516–1523.
- 21 Benjamin EJ, Levy D, Anderson KM, Wolf PA, Plehn JF, Evans JC, *et al.* Determinants of Doppler indexes of left ventricular diastolic function in normal subjects (the Framingham Heart Study). *Am J Cardiol* 1992; **70**:508–515.
- 22 Mantero A, Gentile F, Gualtierotti C, Azzollini M, Barbier P, Beretta L, *et al.* Left ventricular diastolic parameters in 288 normal subjects from 20 to 80 years old. *Eur Heart J* 1995; **16**:94–105.