ORIGINAL RESEARCH

Cardiovascular adaptation to chronic anemia in the elderly: an echocardiographic study

Athanasios Aessopos, PhD*
Spyros Deftereos, PhD*
Dimitrios Farmakis, PhD*
Costas Corovesis, MD*
Stergios Tassiopoulos, PhD*
Maria Tsironi, PhD*
Dimitra Georgonikou, MD*
John Moyssakis, PhD†

From the *First Department of Internal Medicine, University of Athens Medical School, and the †Department of Cardiology, "Laiko" Hospital, Athens, Greece

(Original manuscript received Apr. 15, 2004; accepted in revised form Aug. 10, 2004)

Clin Invest Med 2004;27(5):265-73.

Abstract

Objective: To study the effects of chronic severe anemia on the aging heart.
Methods: We studied 41 elderly patients (mean age 69.8 yr, standard deviation [SD] 3.9 yr) suffering from chronic severe anemia (mean hemoglobin 6.3, SD 0.5 g/dL) with no history of cardiac disease, along with 63 healthy age- and sex-matched controls. Assessment included physical examination, electrocardiogram and Doppler echocardiography.
Results: Although heart rates were similar between patients and controls, arterial blood pressures were significantly lower in patients (mean pressure 92.7 mm Hg, SD 7.9, v. mean 102.1 mm Hg, SD 3.5; $p < 0.001$). No patient was found to have congestive heart failure. Patients with chronic anemia had larger diameters of the left (end-systolic 35.28, SD 4.20, v. 33.73, SD 2.08 mm, $p < 0.05$; end-diastolic 53.33, SD 4.55, v. 50.37, SD 2.10 mm, $p < 0.001$) and right ventricles (30.76, SD 3.98, v. 29.04, SD 2.04 mm; $p < 0.05$), and greater left-ventricular mass (277.64, SD 62.85, v. 212.91, SD 24.87 g; $p < 0.001$). Fractional shortening did not differ significantly (0.33, SD 0.04, v. 0.33, SD 0.03). The load-independent end-systolic index was lower in patients (2.67, SD 0.56, v. 3.87, SD 0.49 kdyn·m^2/cm^5; $p < 0.001$) along with end-systolic stress and total systemic resistance ($p < 0.001$) than controls, whereas the cardiac index was higher (4.31, SD 1.29, v. 2.73, SD 0.51 L/min/m^2; $p < 0.001$). Differences between the 2 groups in diastolic function indices and pulmonary arterial pressures were not statistically significant.
Interpretation: Chronic severe anemia is well tolerated by the aging heart. Neither congestive heart failure nor clearly evident left-ventricular dysfunction were encountered. The heart exhibited an adaptive potential through remodelling by means of the Frank–Starling mechanism and afterload reduction. However, the lower end-systolic index in patients suggests that ventricular performance was marginally compromised. This state of high output was achieved mainly by increased stroke volume, with little contribution from heart rate.

Résumé

Objectif : Étudier les effets de l'anémie sévère chronique sur le cœur vieillissant.
Méthodes : Nous avons étudié 41 patients âgés (âge moyen de 69,8 ans, écart type [ET] de 3,9 ans) atteints d'anémie sévère chronique (hémoglobine moyenne de 6,3, ET de 0,5 g/dL) qui n'avaient pas d'antécédents de maladie cardiaque, ainsi que 63 témoins en bonne santé jumelés en fonction de l'âge et du sexe. L'évaluation a inclus un examen physique, un électrocardiogramme et une échocardiographie Doppler.
Résultats : Même si les patients et les témoins avaient des fréquences cardiaques semblables, les tensions artérielles étaient beaucoup moins élevées chez les patients (tension moyenne de 92,7 mm Hg, ET de 7,9, c. moyenne de 102,1 mm Hg, ET de 3,5; $p < 0,001$). On n'a constaté la présence d'une insuffisance cardiaque globale chez aucun patient. Les patients atteints d'anémie chronique présentaient un diamètre plus important au ventricule gauche (télédiastolique de 35,28, ET de 4,20, c. 33,73, ET de 2,08 mm, $p < 0,05$; fin de diastole 53,33, ET de 4,55, c. 50,37, ET de 2,10 mm, $p < 0,001$) et au ventricule droit (30,76, ET de 3,98, c. 29,04, ET de 2,04 mm; $p < 0,05$) et un ventricule gauche de masse plus importante (277,64, ET de 62,85, c. 212,91, ET de 24,87 g; $p < 0,001$). La fraction de raccourcissement ne présentait pas de différence significative (0,33, ET de 0,04, c. 0,33, ET de 0,03). L'indice télédiastolique indépendant de la

charge était moins élevé chez les patients (2,67, ET de 0,56, c. 3,87, ET de 0,49 kdyn·m^2/cm^5; $p < 0{,}001$), tout comme la tension télédiastolique et la résistance systémique totale ($p < 0{,}001$) que chez les témoins, tandis que l'indice cardiaque était plus élevé (4,31, ET de 1,29, c. 2,73, ET de 0,51 L/min/m^2; $p < 0{,}001$). Les différences entre les deux groupes au niveau des indices de fonction diastolique et des tensions artérielles pulmonaires n'étaient pas statistiquement significatives.
Interprétation : Le cœur vieillissant tolère bien l'anémie sévère chronique. On n'a vu ni insuffisance cardiaque globale ni dysfonction clairement évidente du ventricule gauche. Le cœur a montré un potentiel d'adaptation par remodélisation grâce au mécanisme de Frank–Starling et à la réduction de la postcharge. L'indice télédiastolique moins élevé chez les patients indique toutefois que le rendement des ventricules a été légèrement compromis. Cet état de débit élevé a été produit principalement par une augmentation du volume d'éjection systolique et la fréquence cardiaque y a peu contribué.

Anemia reduces tissue oxygen delivery and causes a compensatory cardiovascular response. In chronic anemia, the heart undergoes structural changes in response to a persistently reduced hematocrit and in the end develops functional impairment. Gradually established anemia is known to lack structural or functional cardiac consequences until serum hemoglobin concentrations drop below 7 g/dL.[1,2] These results, however, are from studies performed on non-aged patients; the effect of advancing age on cardiovascular adaptation to anemia has not yet been studied. As the prevalence of anemia increases with age and as life expectancy in modern societies rises, knowledge of the effects of anemia on the aging heart grows in importance.[3–5]

The aim of the present study was to evaluate cardiac adaptation to chronic severe anemia in a group of elder individuals. To eliminate the potential cardiac effects of comorbidities, which are frequent in the elderly, only patients with recently established, chronic severe anemia alone were studied. Newly diagnosed chronic anemia constitutes the majority of cases admitted to hospitals for anemia investigation.

Methods

We recruited patients admitted to our department from January 2001 through June 2003 with recently established chronic anemia to the study.

Inclusion criteria were age > 65 years, severe anemia (defined as hemoglobin on admission ≤ 7 g/dL) and experiencing anemia-related symptoms for > 3 months. Exclusion criteria included a history of recurrent anemia episodes, cardiac disease (cardiomyopathy, valvular disease or coronary artery disease, as evidenced by history of angina or myocardial infarction; presence of q-waves indicative of old myocardial infarction in the electrocardiogram [ECG] or presence of hypokinetic or akinetic regions in the echocardiogram; atrial fibrillation; or aortic pressure gradient at cardiac Doppler results > 20 mm Hg or mitral regurgitation > 2 on a scale of 1–4) or arterial hypertension; diabetes mellitus; chronic obstructive pulmonary disease; renal, thyroid or hepatic disease; or other diseases that can affect the cardiac muscle or modify cardiac output via mechanisms irrelevant to anemia, such as metastatic tumours, leukemia or marked splenomegaly.

Recruiting an appropriately large sample was feasible because of the considerable number of individuals admitted to our department for investigation of anemia. Adhering to the described criteria, 41 patients were finally enrolled and 71 excluded (24 cases of cardiac disease; 13 of diabetes mellitus; 11 of chronic renal failure; 6 of chronic pulmonary obstructive disease; 5 of leukemia; 4 of hepatic disease; 4 of myelodysplastic syndromes; 3 of metastatic prostate cancer; and 1 of recurrent anemia from Weber–Osler–Rendu disease).

To serve as controls, 63 age- and sex-matched healthy individuals with normal hemoglobin concentrations (> 13 g/dL) admitted to the Ophthalmology Department of our hospital were recruited. They were all free of known diseases (with emphasis on cardiac illness) as suggested by history, clinical examination, ECG, echocardiography and basic laboratory investigations. They were taking no cardioactive medications, and their blood pressure was below 140/90 mm Hg.

Patients underwent history-taking and a physical examination focusing on cardiovascular symptoms. Standard 12-lead ECG, chest radiography and Doppler echocardiography studies were performed before any therapeutic intervention; control subjects under-

went the same investigations. At the echocardiographic study, arterial blood pressure, right-arm pressure (measured by a mercury manometer) and heart rate were recorded, along with systolic blood pressure, which was used to calculate left-ventricular (LV) end-systolic stress. The study protocol was approved by the institutional committee on human research, and all patients and control subjects gave informed consent.

Echocardiography

Complete M-mode, 2-dimensional and Doppler (pulsed-wave, continuous-wave and colour) echocardiography was performed with the patient at rest, using an Aloca ProSound SSD 5500 Pure HD diagnostic ultrasound system (Aloca Co., Ltd., Tokyo), with transducer operating at 2.0–3.5 MHz. All echo-Doppler studies were carried out by the same cardiologist, whereas the tracings were interpreted by 2 independent cardiologists who were unaware of patients' data.

Cardiac dimensions were measured by M-mode, according to the recommendations of the American Society of Echocardiography (ASE); 2-dimensional echocardiography was used wherever M-mode measurements were considered unreliable.[6,7] Left ventricular mass was calculated with the ASE-cube formula as corrected by Devereux and colleagues.[8] All measurements were indexed to body surface area, to correct for differences in body constitution.

The pattern of LV remodelling was estimated by relative wall thickness. This index evaluates the LV hypertrophy response with respect to LV dilatation and is calculated as (intraventricular septum thickness + posterior wall thickness) ÷ (LV end-diastolic diameter).[9–11]

Systolic LV function was evaluated by the shortening fraction, ejection fraction and end-systolic index. The end-systolic index, expressed as the ratio of end-systolic stress to the index of LV volume in systole, is independent of preload and afterload, and has proved useful for anemic patients.[12–14] Left-ventricular volumes and, subsequently, stroke volume, ejection fraction and cardiac output were estimated by the method of discs, following ASE recommendations and using apical 2- and 4-chamber views.[15] Stroke volume and cardiac output were indexed to body surface area. End-systolic wall stress (ESS, in kdyn/cm^2) and total peripheral resistance index (TPRI, in dyn·s·m^2/cm^5) were calculated[16] with the formulas

$$ESS = (0.334 \cdot sP \cdot LVESD) \div [pW(1 + pW/LVESD)]$$

$$TPRI = [80(mP - 3)] \div CI$$

where sP = systolic blood pressure, in mm Hg
LVESD = LV end-systolic diameter, in mm
pW = posterior wall thickness, in mm
mP = mean arterial pressure (diastolic pressure + 1/3 of pulse pressure), in mm Hg
and CI = cardiac index, in L/min/m^2

Diastolic LV function was assessed by pulsed-Doppler recording of mitral inflow velocities from 3 consecutive cardiac cycles. Measurements, obtained with standard methods, included peak early (E) and atrial (A) diastolic flow velocities, E/A ratio, deceleration time of E, and isovolumic relaxation time.[7,17]

Pulmonary-artery pressure was assessed by peak systolic right-ventricular-to-right-atrial pressure gradient (TG, for tricuspid gradient), provided by tricuspid-valve continuous-wave Doppler tracing in the presence of tricuspid regurgitation. This is considered the most reliable noninvasive method of estimating pulmonary-artery pressure.[18] Measurements were obtained at maximal velocity jet; TG was calculated according to the simplified Bernoulli equation. Apical 4-chamber and parasternal short- and long-axis views were recorded while the subject suspended breathing at the end of a normal expiration; 3 cardiac cycles were averaged. Increased pulmonary-artery pressure was defined as a TG > 30.0 mm Hg.[19]

Statistical analysis

Statistical analysis was performed with the SPSS 10.0 statistical software package (SPSS Inc., Chicago, Ill.). Continuous variables are expressed as mean and standard deviation (SD). Student's *t* test was used to compare variables between patients and controls. A p value > 0.05 was considered statistically significant.

Results

Common symptoms for all patients were reduced activity, fatigue and dyspnea on exertion. These symptoms were present for the 3–5 months preceding the

study. Signs of congestive heart failure were absent; there was no lower-limb edema, jugular-vein distention or hepatojugular reflux; gallop rhythm and lung rales were similarly absent. A systolic ejection murmur over the cardiac apex and base was a constant finding in all the patients. Despite anemia, the resting heart rate did not differ significantly between patients and controls. Systolic, diastolic and mean arterial blood pressures were lower in the patient group. Chest radiography revealed a marginally increased cardiothoracic index in 60% of the patients, but signs of pulmonary venous congestion, interstitial edema or pleural effusion were absent in all cases. None of the patients was receiving cardioactive medication. Hemoglobin concentrations were 5.0–7.0 g/dL in patients and 13.0–14.6 g/dL in controls. Baseline characteristics of patients and controls are shown in Table 1. Encountered causes of anemia are reviewed in Table 2. In total, 36 patients were found to have iron-deficiency anemia and 5, megaloblastic anemia.

Electrocardiograms were normal in all control subjects and in 33 patients (80%). Left-ventricular hypertrophy, indicated by voltage and ST–T changes, was present in 1 patient; incomplete right bundle branch block in 3; and left anterior hemiblock in 2. Premature atrial beats were detected in 5 patients, whereas 10 had nonspecific ST–T abnormalities or T-wave flattening.

Structural echocardiographic parameters of patient and controls are presented in Table 3. All M-mode measurements were higher in patients than in controls. Relative cardiac wall thickness was also higher in the patient group, yet remained within normal limits (that is, <0.44).

Functional echocardiographic and Doppler parameters are presented in Table 4. Although shortening and ejection fractions were similar between the 2 groups, the end-systolic index was lower in the patient group. Cardiac and stroke indexes were significantly higher in patients than in controls ($p<0.001$). In contrast, total systemic resistance and end-systolic stress were lower in the patient group.

As for LV diastolic indices, E and A were higher in the patient group ($p<0.001$), whereas the E/A ratio and E deceleration and isovolumic relaxation times did not differ significantly between the groups.

TG was measurable in 30 of 41 patients (73%) and in 43 of 63 controls (68%). Mean TG values were 27.75 (SD 2.67) mm Hg and 26.56 (3.53) mm Hg, respectively, which were not significantly different. Marginal TG elevation was observed in 6 patients (range 30.3–32.5, mean 31.4 mm Hg) and 12 controls (range 31.3–31.8, mean 31.5 mm Hg).

Discussion

In this study, we elaborated on cardiovascular adaptation to anemia in the elderly. Its major novel aspect was to characterize previously identified cardiovascular changes in response to anemia in these patients (increased left and right ventricular diameters and wall thickness, LV mass, stroke volume, cardiac index and reduced systemic vascular resistance), but without the expected increase in heart rate. No clear indication of heart failure was identified, but a lower

Table 1: Baseline characteristics of patients and controls

Characteristic	Subjects; mean (and SD)*		*p* value
	Patients, *n* = 41	Controls, *n* = 63	
Age, yr	69.8 (3.9)	69.4 (4.5)	0.865
Males, no. and %	17, 41.5%	32, 50.8%	0.823
Smoking, no. and %	15, 36.6%	22, 34.9%	0.431
Body surface area, m^2	1.77 (0.17)	1.83 (0.18)	0.098
Heart rate, beats/min	81 (13)	78 (3)	0.162
Arterial BP, mm Hg			
Systolic	121.5 (12.0)	135.1 (4.8)	<0.001
Diastolic	78.3 (6.7)	85.7 (3.5)	<0.001
Mean	92.7 (7.9)	102.1 (3.5)	<0.001
Hemoglobin, g/dL	6.3 (0.5)	13.9 (0.5)	<0.001

*unless specified as number and %. BP = blood pressure; SD = standard deviation

Table 2: Causes of anemia in the patient group, *n* = 41

Cause	Patients	%
Gastroduodenal ulcer	7	17
Hemorrhoids	6	15
Hiatus hernia	5	12
Diverticulitis	5	12
Vitamin B_{12} deficiency	5	12
Polyps of the stomach and colon	3	7.3
Nonmetastatic stomach cancer	2	4.9
Nonmetastatic colon cancer	2	4.9
Ulcerative colitis	1	2.5
Unidentified cause	5	12

(load-independent) end-systolic index suggested that ventricular performance may have been marginally compromised.

The response of the cardiovascular system to both acute and chronic anemia has been thoroughly investigated in young adults. The textbook description of the physiological effects of anemia on the cardiovascular system include reduced oxygen delivery to the tissues, initiating a sympathetic response that contributes to an increase in cardiac index, contractility, heart rate and stroke volume, with a reduction in systemic vascular resistance. The associated reduction in blood viscosity contributes to these effects by reducing vascular resistance and facilitating venous return, thereby optimizing preload. Therefore, the primary effect of anemia is reduced oxygen delivery to tissue; compensatory responses include active and passive mechanisms to improve it. In chronic severe anemia, hemodynamic and echocardiographic studies in non-aged individuals have shown that adaptation of the heart includes mainly hypertrophy and enlargement of the left ventricle, increased heart rate and cardiac output.[16,20–23] Recent experimental evidence suggests that anemia-related hypertrophy is accompanied by microvascular angiogenesis, which optimizes oxygen delivery to the myocardium.[24] This may result from the increase in vascular endothelial growth factor that has been observed in anemic patients.[25]

Symptom development depends on the severity of the anemia, its rate of establishment, and the underlying cardiac condition.[20,21] In the absence of heart disease, cardiac structural or functional abnormalities begin to appear when the hemoglobin concentration falls to below 7–10 g/dL,[1,2] although some individuals can tolerate levels as low as 4 g/dL without developing congestive heart failure.[1,26] In the presence of heart disease, however, anemia may seriously affect the cardiac status, and it has been suggested that in such cases the hemoglobin level should be kept above 10 g/dL.[27]

The aged heart has been shown to undergo metabolic and structural changes that may render it prone to deconditioning. De Souza[28] reported an age-related increase in both collagen concentration and intermolecular cross-linking of collagen in myocardium, and

Table 3: Mean structural echocardiographic parameters (and SD)

Parameter	Patients, $n = 41$	Controls, $n = 63$	p value
Left atrium			
Diameter, mm	43.35 (5.60)	36.97 (2.61)	< 0.001
Index, mm/m^2	24.81 (4.83)	20.35 (2.53)	< 0.001
Left ventricle			
ES diameter, mm	35.28 (4.20)	33.73 (2.08)	0.031
Index, mm/m^2	20.18 (3.52)	18.54 (1.99)	0.011
ED diameter, mm	53.33 (4.55)	50.37 (2.10)	< 0.001
Index, mm/m^2	30.49 (3.81)	27.71 (2.89)	< 0.001
Posterior wall, mm	11.01 (1.08)	9.71 (0.56)	< 0.001
Index, mm/m^2	6.27 (0.86)	5.42 (0.64)	< 0.001
Intraventricular septum, mm	11.04 (1.87)	10.03 (0.50)	0.002
Index, mm/m^2	6.26 (1.24)	5.52 (0.62)	0.001
Mass, g	277.64 (62.85)	212.91 (24.87)	< 0.001
Index, g/m^2	158.37 (36.75)	116.89 (16.33)	< 0.001
Relative wall thickness, mm	0.41 (0.06)	0.39 (0.02)	0.015
Right ventricle			
Diameter, mm	30.76 (3.98)	29.04 (2.04)	0.013
Index, mm/m^2	17.32 (2.79)	16.0 (2.04)	0.013
Wall thickness, mm	4.02 (1.54)	2.46 (1.51)	< 0.001
Index, mm/m^2	2.29 (0.97)	1.37 (0.86)	< 0.001

ED = end-diastolic; ES = end-systolic; SD = standard deviation

Table 4: Mean functional Doppler echocardiographic parameters (and standard deviations), by group

Parameter	Patients, $n = 41$	Controls, $n = 63$	p value
Systolic indices, LV			
Fractional shortening	0.33 (0.04)	0.33 (0.03)	0.244
Ejection fraction	0.54 (0.05)	0.56 (0.03)	0.155
Stroke index, mL/m^2	52.73 (12.90)	35.0 (6.05)	< 0.001
Cardiac index, L/min/m^2	4.31 (1.29)	2.73 (0.01)	< 0.001
ES stress, kdyn/cm^2	77.67 (19.78)	97.28 (8.87)	< 0.001
ES index, kdyn·m^2/cm^5	2.67 (0.56)	3.87 (0.49)	< 0.001
Total systemic resistance index, dyn·s·m^2/cm^5	1.79 (0.50)	3.01 (0.57)	< 0.001
Diastolic indices, LV			
Peak E velocity, m/s	78.51 (20.70)	59.63 (10.98)	< 0.001
Peak A velocity, m/s	93.46 (23.18)	72.14 (10.13)	< 0.001
$\frac{\text{peak E velocity}}{\text{peak A velocity}}$	0.88 (0.22)	0.83 (0.13)	0.155
Deceleration, ms	178.99 (24.38)	171.74 (10.66)	0.111
Isovolumic relaxation time, ms	80.56 (9.16)	79.09 (5.37)	0.358
Peak systolic tricuspid BP gradient, mm Hg	27.75 (2.67)	26.56 (3.53)	0.100

BP = blood pressure; ES = end-systolic; LV = left ventricle; SD = standard deviation

suggests that the collagen accumulation increases heart muscle stiffness, which affects myocardial function. Molecular alterations in the levels of the myocyte Na^+/Ca^{2+} exchanger protein, the sarcoplasmic reticulum Ca^{2+} pump and phospholamban (an inhibitor of sarcoplasmic reticulum calcium transport) have also been reported.[29] However, several studies[30–34] of normal, non-anemic, elder individuals failed to show an age-related decrement in cardiac output, stroke volume or ejection fraction at rest. During exercise, a decreased heart rate response was noted, compensated by cardiac dilatation and increased stroke volume.[31] Nonetheless, when the above age-related changes are combined with an additional pathological condition affecting the heart, LV systolic or diastolic dysfunction may develop and lead to congestive heart failure. Our study addressed the impact of chronic anemia on elderly patients, selected to be free of other serious pathology or disease.

The cause of anemia in the majority of the cases we studied was iron or vitamin deficiency. Although the exact onset of anemia could not be determined, it was possible to deduce from the medical history that it had not been present for long, as patients' symptoms never exceeded 5 months. It is believed that sustained high-output state in elder individuals can lead to congestive heart failure.[30,35] Although our patients presented with reduced activity, fatigue and dyspnea on exertion, clinical indications of congestive heart failure were not present. Despite their markedly low hemoglobin concentrations (5.0–7.0 g/dL) and uniformly elevated cardiac output, none had findings of congestive heart failure upon clinical examination. Compatible with the clinical picture was an absence of signs of pulmonary congestion in chest radiographs.[36]

ECGs revealed premature atrial beats, nonspecific ST–T changes, mild conduction disturbances and signs of ventricular hypertrophy in a few of our patients. Although other signs persisted until discharge, premature atrial beats subsided during the study patients' hospitalization. Similar findings have also been reported in previous studies of patients with chronic anemia;[21] these abnormalities appeared when hemoglobin fell below 7 g/dL, and vanished after its restoration to normal concentrations.[1,21] Typical ischemia findings were not encountered in our study. Similarly, during acute drops in hemoglobin to levels as low as 5 g/dL, no signs of ischemia were detected in recent ECG studies of otherwise healthy persons.[37]

A more detailed and global structural and functional cardiac evaluation was provided by the echocardiographic Doppler study. The increased venous blood return and ventricular preload led to the ventricular enlargement observed in the patient group. As indicated by the increased LV mass, this in turn resulted in LV hypertrophy to compensate for the increased end-diastolic wall stress. Relative wall thickness, which expresses the relationship between LV hypertrophy and LV dilatation, remained within normal limits in the patient group, implying that LV mass increased in parallel to LV diameter. The fact that this index was higher in patients suggests that hypertrophy prevails slightly over dilatation, a beneficial response for this elder population, expressed as an eccentric LV hypertrophy pattern.[11] The mean cardiac index in the patient group was 1.6 times that of controls. In contrast, arterial blood pressures, total systemic vascular resistance and end-systolic wall stress were lower compared with controls, who were similar in terms of demographic characteristics.

Interestingly, heart rate was not significantly different between patients and controls. Such a response is in contrast to the sympathetic stimulation reported in young individuals with chronic anemia,[16] in whom heart rate was found to contribute to the hyperdynamic state. Cardiac output elevation in our anemic population was therefore accomplished mainly by an increase in LV end-diastolic volume, which leads to increased stroke volume and cardiac output by means of the Frank–Starling mechanism. This finding can be attributed to the decreased cardiovascular response to catecholamines reported in the elderly.[1,31] Previous studies[38–41] have shown an age-related decrease in the inotropic, chronotropic and arterial vasodilating effects of catecholamine stimulation, both at rest and on exertion. Furthermore, in acute normovolemic hemodilution (ANH) general anesthesia, affecting the sympathetic nervous system, blunts the increase in heart rate and cardiac output.[42] As a consequence, anesthetized patients respond to ANH with a smaller increase in cardiac index than unanesthetized patients. Similarly, beta-blockade impairs the cardiovascular response to he-

modilution,[43] whereas beta-adrenergic stimulation restores the oxygen extraction reserve following acute hemodilution.[44] In addition, the weakening of sympathetic modulation in the elderly may affect the redistribution of cardiac output that occurs during anemia. Increased sympathetic activity accounts for the systemic or local redistribution of cardiac output in favour of organs with high metabolic oxygen requirements and lower capacity to increase oxygen extraction, i.e., the heart and brain.[44,45]

Systolic function indexes, ejection fraction and shortening fraction did not differ significantly between patients and controls. However, the end-systolic index, which is independent of load and a more appropriate LV contractility index for anemic patients, was lower in the patient group. This finding, combined with the fact that ejection fraction was not elevated in patients despite their increased cardiac output state, may indicate that in anemic elder individuals systolic cardiac function may already be slightly compromised.

In regard to diastolic LV function, it should be noted that the routinely used Doppler indexes might be misleading in elder anemic individuals. Both the age-related changes in LV compliance and the increased LV preload may affect the measurements obtained.[46] Thus, the impact of diastolic dysfunction on Doppler diastolic indexes may be overridden. The higher E and A values in our patient group may represent the effect of the high output state, whereas the lack of significant difference in the E/A ratio, E deceleration time and isovolumic relaxation time cannot easily be evaluated.

Peak systolic tricuspid pressure gradient was not significantly increased in the patient group. The borderline or slightly elevated TG values found in some of our patients and controls should be expected because of their advanced age.[47] These results indicate a good pulmonary vascular response and sufficient coupling of LV function to the high output state and are in accordance with the lack of congestive heart failure or obvious systolic or diastolic LV dysfunction in the patient group. Aging is associated with reduced striated muscular mass; hence, muscular activity in the elderly requires less blood flow than in young individuals.[48,49] Thus, the decreased oxygen demands of peripheral tissues in combination with the gradual development of anemia allowed the aging heart to undergo an efficient adaptation.

The purpose of this study was to evaluate the resting clinical and echocardiographic status of elder patients suffering from chronic anemia. The presence of cardiac symptoms in all subjects during exercise indicates that more serious functional changes might have been uncovered, had patients been stressed. Two further potential limitations are relevant to our work: first, the presence of occult coronary artery disease might not have been detected by the applied methodology; and second, TG was not measurable in all patients and controls. However, the demographic characteristics of the 2 study groups are similar and the frequency of thse situations is expected to be comparable. On the other hand, individuals with increased pulmonary pressure usually present tricuspid regurgitation, and cases with immeasurable TG very probably had low pulmonary pressure. Continuation of this study to evaluate cardiovascular changes after correction of the anemia would have been of interest; unfortunately, many of our patients were from places all over Greece, and distances made their follow-up extremely difficult.

In conclusion, recently established chronic severe anemia, in the absence of cardiac comorbidity, was well tolerated by the older individuals without development of congestive heart failure, even in patients with hemoglobin as low as 5.0 g/dL. Despite its age-related changes, the heart exhibited an adaptive potential at hemoglobin levels under 7.0 g/dL, through remodelling via the Frank–Starling mechanism and afterload reduction. Nevertheless, in light of the marginally compromised cardiac function encountered herein, congestive heart failure may easily develop in patients with coexistent heart abnormalities or other systemic conditions that affect cardiac function. This may also be the case in the presence of recurrent anemia, or anemia that remains untreated for periods longer than those examined in this study.

These issues should be taken under consideration during anemia treatment. In the case of element deficiency in elder anemic patients without a history of heart disease, correction of the hemoglobin level might not need to be achieved rapidly from a cardiovascular perspective. Target hemoglobin values could be reached more slowly, by means of element substi-

tution therapy. If, however, transfusion is required, care should be taken to avoid volume overload, a complication that may easily develop in an aged heart that is prone to deconditioning.

References

1. Rosenthal DS, Braunwald E. Anemia and cardiovascular disorders. In: Braunwald E, editor. *Heart disease*. 6th ed. Philadelphia: W.B. Saunders; 1999. p. 1744-9.
2. Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 2000;58(3):1325-35.
3. Mitrache C, Passweg JR, Libura J, Petrikkos L, Seiler WO, Gratwohl A, et al. Anemia: an indicator for malnutrition in the elderly. *Ann Hematol* 2001;80:295-8.
4. Carmer R. Anemia and aging: an overview of clinical, diagnostic and biological issues. *Blood Rev* 2001;15: 9-18.
5. Harman D. Aging: overview. *Ann N Y Acad Sci* 2001; 928:1-21.
6. Sahn DJ, De Maria A, Kisslo J, Weyman A. The committee on M-mode standardization of the American Society of Echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58:1072-83.
7. Feigenbaum H. Echocardiographic evaluation of cardiac chambers. In: *Echocardiography*. 5th ed. Philadelphia: Lea & Febiger; 1994. p. 134-73.
8. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450-8.
9. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, et al. A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. *N Engl J Med* 1996;334:809-14.
10. Rossi MA, Carillo SV. Cardiac hypertrophy due to pressure and volume overload: distinctly different biological phenomena? *Int J Cardiol* 1991;31:133-41.
11. Abernethy WB, Choo JK, Hutter AM. Echocardiographic characteristics of professional football players. *Am Coll Cardiol* 2003;41:280-4.
12. Spann JF, Carabello BA, Gash AK, Denenberg BS, Donner RM, Maurer AH, et al. Assessment of systolic ventricular muscle function in man: the end systolic index. *Herz* 1984;9:255-69.
13. Taketani S, Sawa Y, Ichikawa H, Ohtake S, Nishimura M, Kawaguchi N, et al. Change of c-Myc expression and cardiac hypertrophy in patients with aortic valve replacement. *Ann Thorac Surg* 2001;71(4):1154-9.
14. Taniguchi K, Kawamaoto T, Kuki S, Masai T, Mitsuno M, Nakano S, et al. Left ventricular myocardial remodeling and contractile state in chronic aortic regurgitation. *Clin Cardiol* 2000;23:608-14.
15. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards Subcommittee. *J Am Soc Echocardiogr* 1989;2:358-67.
16. Bahl VK, Malhotra OP, Kumar D, Agarwal R, Goswami KC, Bajaj R, et al. Non-invasive assessment of systolic and diastolic left ventricular function in patients with chronic severe anemia: a combined M-mode, two-dimensional, and Doppler echocardiographic study. *Am Heart J* 1992;124:1516-23.
17. Lubien E, DeMaria A, Krishnawamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction — comparison with Doppler velocity recordings. *Circulation* 2002;105:595-601.
18. Chan KL, Currie PJ, Seward JB, Hagler DJ, Mair DD, Tajik AJ. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery disease. *J Am Coll Cardiol* 1987;9:549-54.
19. Aessopos A, Farmakis D, Taktikou H, Loukopoulos D. Doppler-determined peak systolic tricuspid pressure gradient in persons with normal pulmonary function and tricuspid regurgitation. *J Am Soc Echocardiogr* 2000;13:645-9.
20. Graettinger JS, Parsons RL, Campbell JA. A correlation of clinical and hemodynamic studies in patients with mild and severe anemia with and without congestive heart failure. *Ann Intern Med* 1963;58:617-26.
21. Duke M, Abelmann WH. The hemodynamic response to chronic anemia. *Circulation* 1969;39:503-15.
22. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. *Am Heart J* 1972;83:415-26.
23. Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. *Am Heart J* 1992; 124:424-7.
24. Rakusan K, Cicutti N, Kolar F. Effect of anemia on cardiac function, microvascular structure, and capillary hematocrit in rat hearts. *Am J Physiol Heart Circ Physiol* 2001;280:H1407-14.
25. Martin C, Yu AY, Jiang BH, Davis L, Kimberly D, Hohimer AR, et al. Cardiac hypertrophy in chronically anemic fetal sheep: increased vascularization is associated with increased myocardial expression of vascular endothelial growth factor and hypoxia-inducible factor 1. *Am J Obstet Gynecol* 1998;178(3):527-34.
26. Brannon ES, Merrill AS, Warren JV, Stead EA. The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. *J Clin Invest* 1945;24:332-6.
27. Wu W, Rathore S, Wang Y, Radford M, Krumholz H. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345:1230-4.
28. De Souza RR. Aging of myocardial collagen. *Biogerontology* 2002;3:325-35.

29. Lakatta EG, Sollott SJ. Perspectives on mammalian cardiovascular aging: humans to molecules. *Comp Biochem Physiol A Mol Integr Physiol* 2002;132:699-721.
30. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 2001;104:2996-3007.
31. Rodeheffer RJ, Gerstenblith G, Becker LC, Fleg JL, Weisfeldt ML, Lakatta EG. Exercise cardiac output is maintained with advancing age in healthy human subjects: cardiac dilatation and increased stroke volume compensate for a diminished heart rate. *Circulation* 1984;69:203-13.
32. Proper R, Wall F. Left ventricular stroke volume measurements not affected by chronologic aging. *Am Heart J* 1972;83:843-5.
33. Gerstenblith G, Frederiksen J, Yin FC, Fortuin NJ, Lakatta EG, Weisfeldt ML. Echocardiographic assessment of a normal adult aging population. *Circulation* 1977;56:273-8.
34. Aldrich HA, Roman MJ, de Simone G, Alderman MH, Devereux RB. Relation of age to left ventricular structure, function, and systemic hemodynamics in normotensive and hypertensive employed adults. *Am J Geriatr Cardiol* 1992;1:29-42.
35. Sokolow M, McIlroy MB, Cheitlin MD. Cardiac failure. In: *Clinical cardiology*. 5th ed. Norwalk, CT: Appleton & Lange; 1990. p. 296-339.
36. Badgett RG, Lucey CR, Mulrow CD. Can the clinical examination diagnose left-sided heart failure in adults? *JAMA* 1997;277(21):1712-9.
37. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998;279:217-21.
38. Lakatta EG, Gerstenblith G, Angell CS, Shock NW, Weisfeldt ML. Diminished inotropic response of aged myocardium to catecholamines. *Circ Res* 1975;36:262-9.
39. Guarnieri T, Filburn CR, Zitnik G, Roth GS, Lakatta EG. Contractile and biochemical correlates of beta-adrenergic stimulation of the aged heart. *Am J Physiol* 1980;239:H501-8.
40. Yin FC, Raizes GS, Guarnieri T, Spurgeon HA, Lakatta EG, Fortuin NJ, et al. Age associated decrease in ventricular response to hemodynamic stress during beta-adrenergic blocade. *Br Heart J* 1978;40:1349-55.
41. Yin FCP, Weisfeldt ML, Milnor WR. The role of aortic input impedance in the decreased cardiovascular response to exercise with aging in the dog. *J Clin Invest* 1981;68:28-38.
42. Ickx BE, Rigolet M, Van der Linden PJ. Cardiovascular and metabolic response to acute normovolemic anemia. *Anesthesiology* 2000;93:1011-6.
43. Nozaki J, Kitahata H, Tanaka K, Kawahito S, Oshita S. The effects of acute normovolemic hemodilution on left ventricular systolic and diastolic function in the absence or presence of beta-adrenergic blockade in dogs. *Anesth Analg* 2002;94(5):1120-6.
44. Crystal GJ, Salem MR. Beta-adrenergic stimulation restores oxygen extraction reserve during acute normovolemic hemodilution. *Anesth Analg* 2002;95:851-7.
45. van Bommel J, Trouwborst A, Schwarte L, Siegemund M, Ince C, Henny P. Intestinal and cerebral oxygenation during severe isovolemic hemodilution and subsequent hyperoxic ventilation in a pig model. *Anesthesiology* 2002;97:660-70.
46. Andren B, Lind L, Hedenstierna G, Lithell H. Left ventricular diastolic function in a population sample of elderly men. *Echocardiography* 1998;15:433-50.
47. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797-802.
48. Evans WJ. What is sarcopenia? *J Gerontol A Biol Sci Med Sci* 1995;50:5-8.
49. Ginet J. Physical and sports activities and aging: how to delay the state of dependence. *Bull Acad Natl Med* 1995;179:1493-502; discussion 1502-3.

Medical subject headings: anemia; aging heart; elderly; left ventricular remodelling; high output state

Correspondence to: Dr. Athanasios Aessopos, 17 Agiou Thoma St., Athens 115 27, Greece; fax 30 210 777 1161; aaisopos@cc.uoa.gr; deftereo@otenet.gr