Enalapril therapy and cardiac remodelling in sickle cell disease patients

Carmen S.P. LIMA[1,2], Osvaldo M. UETI[2], Adriana A. UETI[2], Kleber G. FRANCHINI[2], Fernando F. COSTA[1,2], Sara T.O. SAAD[1,2]

[1]Haematology and Haemotherapy Centre; [2]Department of Internal Medicine, Faculty of Medical Sciences, State University of Campinas, Campinas, São Paulo, Brazil.

Introduction — Angiotensin-converting enzyme inhibitors (ACEi) have been successfully used for patients with cardiac dysfunction after myocardial infarction.

Objective — The aim of the present study was to investigate cardiac effects of ACEi in sickle cell disease (SCD) patients, as there are no previous reports regarding these effects.

Methods — Enalapril was administered to 9 SCD patients with microalbuminuria. Nine SCD patients without microalbuminuria, matched according to age, diagnosis and levels of haemoglobin, haematocrit and foetal haemoglobin did not receive enalapril and were followed up as the control group during the same period of study. Echocardiograms were performed before the study entry and after 36 months of follow-up.

Results — At 36 months of follow-up, significant increases in left ventricular mass, left ventricular mass index, posterior left ventricular wall thickness in end-diastole, interventricular septal wall thickness in end-diastole, and aortic root diameter values were seen in untreated, but not in enalapril-treated patients. No major changes were seen in left ventricular systolic diameter, diastolic dimension and ejection fraction, and left atrial diameter, in both groups, along the observational period.

Conclusion — The results of this study suggest that enalapril prevents cardiac remodelling in SCD patients. However, a large trial concerning the response to enalapril in patients with SCD should be carried out to further clarify this issue.

Keywords: *sickle cell disease – ACEi – enalapril – cardiac remodelling.*

Introduction

Moderate to severe anaemia associated with sickle cell disease (SCD) causes a high output state that can lead to cardiac hypertrophy followed by cardiac enlargement and congestive heart failure[1-3]. Left ventricular volume load and dilation, ventricular dysfunction and sudden death are reported in SCD patients[1-5]. In addition, diastolic dysfunction is an independent risk factor for death in SCD patients[6].

Angiotensin-converting enzyme inhibitors (ACEi) have been successfully used for the treatment of sickle cell nephropathy; reducing urinary protein excretion, normalising serum albumin, and apparently retarding renal failure in SCD patients[7-10]. On the other hand, ACEi are able to decrease remodelling in patients with cardiac dysfunction after anterior myocardial infarction[11].

To the best of our knowledge, there are no reports regarding the cardiac effects of ACEi in SCD patients, this, therefore, was the aim of the present study.

Methods

From January 2002 to April 2005, 9 adult patients with SCD in attendance at the Haematology and Haemotherapy Centre, with microalbuminuria, were enrolled for enalapril treatment.

The diagnosis of SCD was based on clinical, familial, and laboratory data, using haemoglobin electrophoresis methods and high-pressure liquid chromatography (Variant II Hemoglobin Testing System).

Address for correspondence: Carmen S. P. Lima, MD, PhD, Department of Internal Medicine, Faculty of Medical Sciences, State University of Campinas, Rua Alexander Fleming, 181, Cidade Universitária "Zeferino Vaz", Barão Geraldo, Campinas, São Paulo, Brazil. CP: 6111, Cep.: 13083-970. E-mail: carmenl@fcm.unicamp.br

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Haplotype and α-thalassaemia were investigated as described elsewhere[12]. Complete blood counts were performed using an Advia Hematology System 120 (Bayer Diagnostics, Tarrytown, NY, USA). Microalbuminuria was measured by a nephelometric method in nocturnal 12-hour urine[13]. Glomerular filtration rate (GFR) was estimated by 51Cr-EDTA[14,15]. Nine SCD patients without microalbuminuria, matched according to diagnosis, age, and levels of haemoglobin (Hb), haematocrit (Ht) and foetal haemoglobin (F Hb), did not receive enalapril and were considered as control subjects. None of the patients or control subjects were on chronic transfusion therapy. Four patients from the enalapril group and 2 patients from the control group were using hydroxyurea, at a dose of 20 to 30 mg/Kg /day. The study protocol was in accordance with the Helsinki Declaration and was approved by the local Ethics Committee.

The dose was 5 mg of enalapril, administered once a day, as previously reported[8]. Doses varying from 7.5 mg to 20 mg were administered to a single patient, who developed systolic blood pressures (BP) of over 120 mm Hg during follow-up.

Cardiac evaluation was performed before study entry and once a year in treated patients and after 36 months of follow-up in control subjects. BP was measured with a standard mercury sphygmomanometer after 5 minutes of rest in a half-sitting position. Systolic pressure and diastolic pressure were calculated as the average of three measurements taken with a 5-minute interval. Mean blood pressure (MBP) was calculated as the diastolic blood pressure plus one third of the difference between systolic and diastolic pressure. Echocardiography was performed using an ATL UltraMark 4 machine (Advanced Technology Laboratories, Bothel, Washington, USA), with 3- to 5-MHz Doppler transducers. Left ventricular (LV) dimensions and mass were assessed from 2D guided M-mode tracings, according to the recommendations of the American Society of Echocardiography[16]. M-mode measurements were averaged from 5 cycles. LV end-systolic, end-diastolic, and stroke volumes were calculated with the use of Simpson's method. Echocardiograms were acquired and results were recorded and revised by 2 qualified and independent echocardiographers, blinded to patient condition. The inter-observer correlation coefficient for echocardiographic measurements was 0.84.

Results

Median age, baseline values of Hb, Ht, F Hb and MBP were similar in treated and untreated patients (table 1 and 2).

The average values of echocardiographic measurements were similar in both groups and within the range of clinically normal values, at the beginning of the observational period (table 2). At 36 months of follow-up, MBP was lower than the baseline value (table 2) only in the treated group ($P = 0.02$). Significant increases in left ventricular mass (LVM), left ventricular mass index (LVMI), posterior left ventricular wall thickness in end-diastole (PWT), interventricular septal wall thickness in end-diastole (SWT), and aortic root diameter (AD) values were seen in untreated, but not in enalapril-treated patients. No major changes were seen in left ventricular systolic diameter (LVSD), diastolic dimension (LVDD) and ejection fraction (LVEF), and left atrial diameter (LAD), in both groups, along the observation period.

No significant correlation was detected between the data obtained by echocardiography and levels of Hb, Ht, F Hb, MBP, microalbuminuria and GFR using the Spearman coefficient (data not shown). Comparison of the two groups, taking the changes detected before and after 36 months into account, showed no significant differences.

In January 2006, no symptoms or signals related to renal or cardiac failure were found in any of the enrolled patients. Later on, enalapril was discontinued in 2 treated patients, who presented a decrease in GFR (lower than 60 mL/min). On the other hand, 2 previously untreated patients switched to enalapril treatment due to significant reductions in GFR (40% and 50%) and increases in albuminuria (50% and 60%), indicating renal glomerular damage. In addition, one patient from the untreated group evolved to chronic renal failure and another patient did not continue the follow-up. In January 2008, one untreated patient presented cardiac failure that required chronic red blood cell transfusion, however, no symptoms or signals related to cardiac failure were seen in patients from the treated group.

Discussion

Although ACEi successfully decreases remodelling in patients with cardiac dysfunction after acute myocardial infarction[11] there is, as far as we know, no experience with these agents on the cardiac function of SCD patients. In this study, the effects of 36 months of enalapril treatment on the cardiovascular structure and function of 9 patients with SCD and microalbuminuria and 9 patients without microalbuminuria were investigated.

The study showed that enalapril causes a reduction in the MBP of patients, even in those with normal systemic BP. Reduction in MBP due to the effect of enalapril has been previously reported in SCD patients[8,9]. Echocardiography is a useful non-invasive technique to assess changes in cardiac structure and function[6]. In this study, significant increases in LVM,

Table 1. – *Clinical and laboratory characteristics of sickle cell disease patients*

Enalapril Status	Diag	Sex	Age (years)	Haemoglobin (g/dL)	Haematocrit (%)	MCV (fL)	F Hb (%)	α-globin genotype	Haplotype	HU	Microalb (μg/min)	GFR (mL/min)
Treated												
1	SS	M	27	11.5	35.4	103.3	8.1	αα/αα	Benin/Benin	Yes	163	142
2	SS	F	23	8.0	23.0	124.1	4.4	αα/αα	Benin/Benin	Yes	156	155
3	Sβ°	F	38	8.7	26.7	74.1	2.3	αα/αα	NP	No	94	98
4	SS	F	55	8.5	25.8	97.3	1.4	-α/αα	Bantu/Bantu	No	64	96
5	SS	F	24	10.2	28.4	99.7	7.1	αα/αα	Bantu/Bantu	Yes	92.1	123
6	SS	F	36	7.5	22.5	96.2	2.7	αα/αα	Bantu/Bantu	No	83.4	109
7	SS	M	29	8.0	24.3	83.1	4.7	αα/αα	Benin/Benin	No	77	137
8	SS	F	37	7.8	22.3	94.4	3.5	αα/αα	Benin/Bantu	No	173	183
9	SS	M	20	9.4	27.0	109.3	4.5	-α/αα	Bantu/Bantu	Yes	177	149
Median (range)			29 (20-55)	8.5 (7.5-11.5)	25.8 (22.3-35.4)	97.3 (74.1-124.1)	4.4 (1.4-8.1)				94 (64-177)	137 (96-183)
Untreated												
1	Sβ°	M	25	8.9	26.4	72.0	5.0	-α/αα	NP	No	18.2	160
2	SS	F	37	7.6	19.8	106.8	11.0	αα/αα	Benin/Bantu	Yes	5.8	114
3	SS	F	22	8.9	26.4	90.4	1.7	αα/αα	Bantu/Bantu	No	16.8	137
4	SS	F	34	9.3	23.5	85.3	6.4	-α/-α	Sengal/Benin	No	7.2	124
5	SS	F	30	7.2	21.6	94.4	4.0	αα/αα	Benin/Bantu	No	6.4	158
6	SS	F	39	9.7	29.6	83.7	4.1	αα/αα	Benin/Benin	No	8.6	116
7	SS	M	25	7.7	22.3	92.3	7.0	αα/αα	Bantu/Bantu	No	17.1	119
8	SS	F	28	7.6	19.8	111.2	9.3	αα/αα	Benin/Bantu	Yes	3.94	168
9	SS	M	50	8.4	23.4	86.2	2.5	αα/αα	Benin/Bantu	No	8.3	112
Median (range)			30 (22-50)	8.4 (7.2-9.7)	23.4 (19.8-29.6)	90.4 (72-111.2)	5.0 (1.7-11.0)				8.3 (3.9-18.2)	124 (112-168)
P value *			0.82	0.48	0.17	0.27	0.44				0	0.78

* Wilcoxon rank sum test was used to compare patients and control subjects. Diag: diagnosis, MCV: mean corpuscular volume, F Hb: foetal haemoglobin, HU: hydroxyurea, Microalb: microalbuminuria, GFR: glomerular filtration rate, SS: sickle cell anaemia, Sβ: sickle cell anaemia plus beta thalassaemia, NP: not performed.

Table 2. – *Cardiovascular parameters in enalapril-treated and untreated sickle cell disease patients before the study entry and after 36 months of follow-up*

Variables (reference interval)	Untreated group Baseline values	Untreated group Values after 36 months	*P* value	Enalapril-treated group Baseline values	Enalapril-treated group Values after 36 months	*P* value
MBP (70-100 mm Hg)	80 (73-102)	83 (67-103)	0.67	90 (79-110)	83 (70-97)	**0.02**
LVM (94-276 g)	176.8 (96.3-255.3)	240 (164.0-326.0)	**0.01**	171.9 (107.4-217.9)	221.0 (87.8-383.0)	0.08
LVMI (g/m^2)	122.0 (64.3-154.5)	137.3 (109.0-205.0)	**0.04**	122.6 (86.4-163.2)	155.5 (63.2-229.5)	0.31
LVSD (25-40 mm)	33.0 (25.0-38.0)	30.0 (28.0-38.0)	0.99	33.0 (28.0-39.0)	32.0 (24.0-35.0)	0.15
LVDD (35-56 mm)	49.0 (40.0-60.0)	52.0 (46.0-56.0)	0.51	53.0 (45.0-58.0)	49.0 (41.0-61.0)	0.55
LVEF (> 58%)	65.6 (58-78.2)	69.1 (58.0-77.0)	0.50	69.0 (64.0-75.0)	69.0 (64.0-74.0)	0.72
PWT (7-11 mm)	8.0 (7.0-10.0)	10.0 (9.0-12.0)	**0.01**	8.0 (7.0-11.0)	10.0 (7.0-12.0)	0.12
SWT (7-11 mm)	9.0 (7.0-10.0)	10.0 (9.0-12.0)	**0.01**	8.0 (6.0-11.0)	10.0 (7.0-13.0)	0.10
LAD (20-40 mm)	35.0 (29.0-48.0)	39.0 (31.0-45.0)	0.31	36.0 (27.0-42.0)	36.0 (29.0-46.0)	0.47
AD (20-37 mm)	28.0 (27.0-31.0)	33.0 (27.0-35.0)	**0.01**	27.0 (24.0-38.0)	29.0 (23.0-42.0)	0.26

Values expressed as median values (range). MBP: mean blood pressure, LVM: left ventricular mass, LVMI: left ventricular mass index, LVSD: left ventricular systolic diameter, LVDD: left ventricular diastolic dimension, LVEF: left ventricular ejection fraction, PWT: posterior left ventricular wall thickness in end-diastole, SWT: interventricular septal wall thickness in end-diastole, LAD: left atrial diameter, AD: aortic root diameter. The Wilcoxon-signed rank test was used to compare the values

LVMI, PWT, SWT and AD were seen in the untreated group but not in the enalapril-treated patients, and no major changes were seen in the LVSD, LVDD, LVEF and LAD in either group along the observation period. These data indicate a trend toward cardiac and aortic root remodelling in untreated SCD patients during the study interval. The lack of success to detect significant differences in the comparison of the two groups, taking into account the changes detected before and after 36 months of treatment, may be attributed to the small number of cases enrolled in this study.

The abnormal haemodynamic loading associated with anaemia has been shown to cause the remodelling of the LV in SCD patients[17] and LV and aortic root remodelling have emerged as strong independent predictors of cardiovascular events in patients with specific cardiovascular diseases[18]. However, whether cardiovascular remodelling would in fact, represent an additional risk for the patients with SCD remains unclear. It is worth noting that with the improvement of medical care, patients with SCD are living longer and might be exposed to the most prevalent cardiovascular

diseases such as hypertension and atherosclerosis. In this context, it has been suggested that BP at levels below the usual clinical cut-off values may represent relative hypertension for SCD patients, with an impact on target end-organs damage[19]. Thus, the reduction in BP might explain our findings indicating that prolonged treatment with enalapril may prevent cardiovascular remodelling in SCD patients, and suggests that this benefit may be extended to changes in other target organs. Indeed, in spite of microalbuminuria having previously been described as a risk factor for cardiac remodelling[20], at the end of our study, patients with microalbuminuria treated with ACEi, presented superior cardiac performance compared to those in the untreated group.

In conclusion, the results shown herein suggest that long-term treatment with enalapril could have beneficial effects on cardiac remodelling of SCD patients. However, a large and longer trial concerning the response to enalapril in these patients, with and without microalbuminuria, should be carried out to clarify this issue.

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