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Original Article

Medium-term follow-up of renal function in hypoxaemic congenital heart disease patients

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Abstract *Introduction:* Hypoxaemic congenital heart disease (CHD) patients are at higher risk of complications. The aim of this study was to compare and follow-up blood and 24-hour urine analytical data in hypoxaemic and non-hypoxaemic CHD patients. *Methods:* The inclusion criteria for this study were as follows: patients older than 14 years of age with a structural CHD with or without associated hypoxaemia. *Results:* In total, 27 hypoxaemic and 48 non-hypoxaemic CHD patients were included in order to compare blood and 24-hour urine analytical data. Among hypoxaemic patients, 13 (48.1%) were male, two (7.4%) had diabetes mellitus, one of whom was a smoker, one (3.7%) had systemic arterial hypertension, and 11 (40.7%) showed pulmonary arterial hypertension. The mean follow-up time was 3.1 ± 1.9 years. Hypoxaemic CHD patients showed higher proteinuria concentrations (g/24 hours) (0.09 (0.07; 0.46) versus 0.08 (0.07; 0.1), $p = 0.054$) and 24-hour albumin excretion rate (μg/min) (16.5 (11.2; 143.5) versus 4.4 (0.0; 7.6), $p < 0.001$) compared with non-hypoxaemic CHD patients; however, no significant differences were found in the proteinuria levels and in the 24-hour albumin excretion rate in CHD patients with associated hypoxaemia, both at baseline and at follow-up. When divided into groups, hypoxaemic patients with palliative shunts showed significantly higher proteinuria concentrations compared with hypoxaemic patients not operated on or with Fontan procedures ($p = 0.01$). No significant differences were seen in 24-hour proteinuria and 24-hour albumin excretion rate during the follow-up of patients with palliative shunts. *Conclusions:* Hypoxaemic CHD patients have significant higher 24-hour proteinuria concentration and 24-hour albumin excretion rate compared with non-hypoxaemic CHD patients. Among hypoxaemic CHD patients, those with palliative shunts showed the highest 24-hour proteinuria concentrations.

Keywords: CHD; hypoxaemia; proteinuria; impaired renal function; follow-up

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ALTHOUGH A FEW DECADES AGO ONLY A MINORITY OF congenital heart disease (CHD) patients could reach adulthood, at present, thanks to the improvement in the treatment of congenital heart abnormalities, many of these patients are reaching adulthood. In fact, adults with CHD are an increasing population, which will continue to grow in the future.

The spectrum of adult CHDs is extremely varied, from septal defects and valvular obstructions to complex hypoxaemic single-ventricle lesions with pulmonary outflow obstruction, which may require palliation with staged surgical repairs. Similarly, uncorrected high-flow and/or high-pressure congenital heart anomalies may lead to the development of chronic pulmonary arterial hypertension, shunt reversal, and secondary hypoxaemia (Eisenmenger syndrome). As hypoxaemia entails a higher risk of long-term complications such as renal insufficiency[1–3] and as proteinuria identifies patients with an increased risk of cardiovascular problems, we understand the considerable growing interest of hypoxaemia in CHD patients.[4,5]

The aims of this study were to compare proteinuria concentration and the 24-hour albumin excretion

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rate between hypoxaemic and non-hypoxaemic CHD patients and to evaluate whether hypoxaemic CHD patients have new, persistent, or worsening proteinuria at medium-term follow-up.

Methods

In total, 27 hypoxaemic CHD patients (cases) and 48 non-hypoxaemic CHD patients (controls) were studied and compared in order to observe the differences between demographic data, blood samples, and 24-hour urine tests. Hypoxaemic CHD patients were also followed-up to assess the renal function at medium term.

Cases and controls for the study were recruited from the Adolescent and Adult Congenital Heart Disease Unit of the Complejo Hospitalario Universitario Insular-Materno Infantil of Gran Canaria. Controls were selected at random from asymptomatic non-hypoxaemic CHD patients, above 14 years of age, with an atrial septal defect or a ductus – both of them had to be small defects not operated on or operated on during infancy – or a restrictive ventricular septal defect. Patients with ventricular dilatation or dysfunction were not included. Meanwhile, the inclusion criteria for the case group were as follows: aged above 14 years and having a structural CHD with associated hypoxaemia. Hypoxaemic patients were excluded from the follow-up based on the following criteria: death, lived outside the island, or inability or refusal to participate in the study. Hypoxaemic and non-hypoxaemic CHD patients were matched for diabetes mellitus and systemic arterial hypertension.

Hypoxaemic CHD patients were divided into the following categories: non-operated, repaired with palliative surgery such as Blalock–Taussig's and Glenn's shunts, or operated on with a Fontan procedure. Patients with more than one defect were classified according to the prevalent lesion from a clinical or haemodynamic point of view. Patients were identified as hypoxaemic if their haemoglobin oxygen saturation, measured using a digital oximeter (Model 512 Handheld Pulse Oximeter; Novametrix Medical Systems Inc., Wallingford, CT, United States of America), was 93% or less.

All the patients were Caucasians, and all of them or their parents gave their informed consent for participation in the study. The protocol of the study was approved by the hospital's Ethics Committee.

CHD patients were examined in an outpatient setting. After an overnight fasting period of at least 10 hours, blood samples were collected to measure serum levels of creatinine, albumine, total proteins, and N-terminal pro B-type natriuretic peptide. In addition, a 24-hour urine test was carried out with the patients on their usual diet, except that they had to avoid alcohol intake and strenuous exercise. Measurement of serum creatinine, albumine and total protein levels as well as the 24-hour urine test were carried out by spectrophotometry usingan Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany). Determination of the N-terminal pro B-type natriuretic peptide concentration was carried out by immunoassay using the Siemens Stratus CS Acute Care Diagnostic System (Siemens Healthcare Diagnostics, Inc., Newark, DE, United States of America).

Body weight and height were measured with the patients wearing light clothes and barefoot, and body mass index was determined as weight (kg)/[height (m) × height (m)]. Glomerular filtration rate was estimated in all the patients with Modification of Diet in Renal Disease formulae ($186 \times [\text{creatinine (mg/dl)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.724 \text{ if female}]$).[6,7] The diagnosis of pulmonary arterial hypertension was performed if there was a resting mean pulmonary artery pressure of $\geqslant$25 mmHg. Pulmonary artery pressure was calculated invasively by means of cardiac catheterisation or non-invasively using Doppler echocardiography;[8] 24-hour proteinuria was established if the urine protein concentration was higher than 0.15 g, which was considered our upper normal reference range. Meanwhile, the normal value for 24-hour albumin excretion rate was between 0 and 20 μg/min.

The values are expressed as mean ± standard deviation or as median and quartile values (25, 75). Qualitative variables were expressed as counts (percentages). A related samples Student t-test or the Mann–Whitney U-test was used to compare two dependent samples as the assumption of normality or homogeneity of variance was met or not met, respectively. The non-parametric Kruskal–Wallis H-test was used for comparing two or more independent samples. Meanwhile, the Wilcoxon non-parametric test was used to compare two paired samples. Binary logistic regression multivariate analysis was performed to compare the 24-hour proteinuria (concentrations $\leqslant$0.15 or >0.14 g/24 hours) and the 24-hour albumin excretion rate (concentrations $\leqslant$20 or >20 μg/min) dichotomous variables with those independent variables that had a p-value below 0.10 in the univariate analysis. The results are expressed as odds ratio and its 95% confidence interval. The data analyses were performed using SPSS 20.0 (SPSS Institute, Chicago, IL, United States of America); p values below 0.05 were considered to be significant.

Results

Between September, 2008 and January, 2013, 27 out of 560 CHD patients met the inclusion criteria described for hypoxaemic patients in the methodology section; 13 (48.1%) patients were male, two (7.4%) patients had

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diabetes mellitus, one of whom was a smoker, one (3.7%) patient had systemic arterial hypertension, and 11 (40.7%) patients showed pulmonary arterial hypertension. Body mass index was 23.9 ± 6.6, and the mean follow-up time was 3.1 ± 1.9 years.

Table 1 shows the distribution of hypoxaemic CHD patients, according to the type of cardiac abnormality, the surgery performed, and the existence of pulmonary arterial hypertension; nine patients were under oral anticoagulation therapy, one patient was under aspirin treatment, eight patients used furosemide, three patients used spironolactone, three patients used β-blockers, three patients used digoxin, three patients used amiodarone, two patients used allopurinol, one patient used calcium antagonists, one patient used angiotensin-converting enzyme, and one patient used angiotensin II receptor blockers. Of the 11 patients with pulmonary arterial hypertension, seven patients were under bosentan treatment and one patient was under sildenafil therapy.

In the non-hypoxaemic group (48 patients), 27 patients had restrictive ventricular septal defects, 16 patients had atrial septal defects – nine patients were not operated on due to its small size and seven patients were operated on during infancy – and four patients had ductus arteriosus – three patients showed a small ductus and one patient had a ductus arteriosus operated on during infancy. None of them were under medical treatment.

Table 2 shows the demographic data and laboratory test results of hypoxaemic (cases) and non-hypoxaemic (control) CHD patients at baseline. Hypoxaemic CHD patients showed almost significantly higher 24-hour urine protein levels and significantly higher 24-hour albumin excretion rates compared with non-hypoxaemic CHD patients. Meanwhile, binary logistic regression multivariate analysis, including as independent predictors age, sex, being or not being hypoxaemic, haemoglobin concentration, and haematocrit level, showed that being acyanotic was the only protective factor from developing 24-hour proteinuria [odds ratio 0.163; 95% CI 0.038–0.698; p = 0.015] and 24-hour albumin excretion [odds ratio 0.092; 95% CI 0.016–0.52; p = 0.007].

Table 3 shows the demographics and analytical data of hypoxaemic CHD patients at baseline and at follow-up. No significant differences were seen in the 24-hour urine parameter during the follow-up, except for 24-hour urine glucose excretion. In relation to blood parameters, hypoxaemic CHD patients showed significantly higher haematocrit levels at follow-up, despite having similar basal oxygen saturations and haemoglobin concentrations. Out of 27 patients, nine of them (33.3%) at baseline and 10 of them (37%) at the end of the study showed 24-hour proteinuria. Of the nine patients with 24-hour proteinuria at baseline, seven (77.8%) patients had persistent proteinuria at the follow-up, including two patients who were on angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers therapy, respectively.

Table 4 shows the demographic data and laboratory test results from different subgroups of hypoxaemic CHD patients – none operated on, with palliative surgery, or with a Fontan procedure, – at baseline. This table evidences significantly higher urine protein (g/24 hours) concentrations in those CHD patients with a palliative surgery; however, at medium-term follow-up, non-significant differences were found in urine protein levels (g/24 hours) and 24-hour albumin excretion rates (μg/min) among the three subgroups of hypoxaemic CHD patients. Similarly, no significant differences were observed between baseline and follow-up 24-hour proteinuria or 24-hour albumin excretion rate among patients with palliative shunts. Meanwhile, binary logistic regression multivariate analysis of hypoxaemic CHD patients at follow-up, including as independent

Table 1. Types of hypoxaemic CHDs, type of surgical repair, and number of patients with pulmonary arterial hypertension (PAH).

Type of hypoxaemic CHD (n)	Non-operated	Palliative fistulae	Fontan	Mustard	Patch repair	Total	PAH
Atrial septal defect	0	0	0	0	2	2	2
Ventricular septal defect	4	0	0	0	1	5	5
Complete AVSD	1	0	0	0	0	1	1
D-TGA	0	0	1	2	0	3	0
Tetralogy of Fallot	1	0	0	0	0	1	0
Triscuspide atresia	0	1	2	0	0	3	0
Pulmonary atresia	0	3	1	0	0	4	1
Single ventricle	2	1	1	0	0	4	2
DORV	1	2	0	0	0	3	0
AV pulmonary fistulae	1	0	0	0	0	1	0
Total	10	7	5	2	3	27	11

AV = arteriovenous; AVSD = atrioventricular septal defect; DORV = double-outlet right ventricle; D-TGA = dextro-transposition of the great arteries; n = number of patients

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Table 2. Demographic data and laboratory test results from hypoxaemic and non-hypoxaemic CHD patients at baseline.

	Hypoxaemic (27)	Non-hypoxaemic (48)	p
Age (years)	30.9 ± 11.8	25.4 ± 12.4	0.037
Sex (male)	12 (44.4)	27 (56.2)	0.616
Body mass index	23.6 ± 5.9	24.8 ± 5.2	0.850
Basal oxygen saturation (%)	83.9 ± 6.8	98.2 ± 1.1	<0.001
Haemoglobin (g/dl)	17.4 ± 3.7	14.5 ± 1.3	<0.001
Haematocrit (%)	51.9 ± 11.0	41.2 ± 6.7	<0.001
Serum glucose (mg/dl)	92.5 ± 12.7	95.0 ± 8.4	0.396
Serum creatinine (mg/dl)	1.02 ± 0.2	1.0 ± 0.15	0.113
Serum total proteins (g/dl)	7.3 ± 0.4	7.6 ± 0.45	0.060
Serum albumine (g/dl)	4.3 (4.0; 4.5)	4.5 (4.2; 4.7)	0.019
Glomerular filtration rate (ml/min/1.73 m^2)	98.8 ± 29.8	99.7 ± 14.2	0.249
Urine creatinine (g/24 hours)	0.97 ± 0.4	1.45 ± 0.5	0.001
Urine proteins (g/24 hours)	0.09 (0.07; 0.46)	0.08 (0.07; 0.1)	0.054
24-hour albumin excretion rate (μg/min)	16.5 (11.2; 143.5)	4.4 (0.0; 7.6)	<0.001
Urine glucose (mg/24 hours)	25.6 (1.9; 59.5)	37.9 (8.2; 58.4)	0.106
Urine sodium (mM/24 hours)	129.9 ± 62.6	129.5 ± 51.9	0.985
Urine potassium (mM/24 hours)	53.2 ± 23.1	57.4 ± 26.4	0.581
Urine chlorine (mM/24 hours)	136.8 ± 60.4	133.8 ± 56.2	0.876
Urine calcium (mg/24 hours)	86.5 ± 69.2	144.8 ± 85.6	0.002
Urine phosphorus (mg/24 hours)	547.8 ± 230.5	706.3 ± 313.4	0.052
Tubular phosphate re-absorption (%)	82.8 ± 8.8	85.4 ± 6.2	0.050
N-terminal-pro-B-type natriuretic peptide (pg/ml)	557.4 ± 615.5	105.3 ± 239.9	0.001

Quantitative variables are expressed as mean ± standard deviation or as median and 25th and 75th percentile. Glomerular filtration rate estimated with Modification of Diet in Renal Disease formulae

Table 3. Demographic data and laboratory test results from the 27 hypoxaemic CHD patients at baseline and at follow-up.

	Baseline	At follow-up	p
Age (years)	30.9 ± 11.8	34.0 ± 11.4	<0.001
Basal oxygen saturation (%)	83.9 ± 6.8	85.0 ± 7.9	0.574
Haemoglobin (g/dl)	17.4 ± 3.7	17.5 ± 4.4	0.550
Haematocrit (%)	51.9 ± 11.0	54.4 ± 12.3	0.020
Serum creatinine (mg/dl)	1.02 ± 0.2	1.0 ± 0.2	0.675
Serum total proteins (g/dl)	7.3 ± 0.4	7.2 ± 0.2	0.062
Serum albumin (g/dl)	4.3 (4.0; 4.5)	4.3 (3.8; 4.7)	0.895
Glomerular filtration rate (ml/min/1.73 m^2)	98.8 ± 29.8	95.9 ± 22.2	0.400
Urine creatinine (g/24 hours)	0.97 ± 0.4	0.93 ± 0.4	0.531
Urine proteins (g/24 hours)	0.09 (0.07; 0.46)	0.12 (0.09; 0.35)	0.120
24-hour albumin excretion rate (μg/min)	16.5 (11.2; 143.5)	11.9 (6.9; 27.3)	0.695
Urine glucose (mg/24 hours)	25.6 (1.9; 59.5)	28.5 (0.0; 57.7)	0.041
Urine sodium (mM/24 hours)	129.9 ± 62.6	126.6 ± 45.0	0.987
Urine potassium (mM/24 hours)	53.2 ± 23.1	49.7 ± 16.9	0.758
Urine chlorine (mM/24 hours)	136.8 ± 60.4	125.1 ± 45.6	0.531
Urine calcium (mg/24 hours)	86.5 ± 69.2	78.7 ± 58.9	0.911
Urine phosphorus (mg/24 hours)	547.8 ± 230.5	582.4 ± 320.7	0.808
Tubular phosphate re-absorption (%)	82.8 ± 8.8	85.1 ± 7.1	0.270
N-terminal-pro-B-type natriuretic peptide (pg/ml)	557.4 ± 615.5	707.1 ± 851.6	0.079

Quantitative variables are expressed as mean ± standard deviation or as median and 25th and 75th percentile. Glomerular filtration rate estimated with Modification of Diet in Renal Disease formulae

factors age, sex, haemoglobin concentration, haematocrit level, basal oxygen saturation, pulmonary arterial hypertension, and the different types of hypoxaemic CHD, including non-operated, palliative, and Fontan procedure, determined that none of these parameters favoured, by themselves, the development of 24-hour proteinuria. Similar findings were observed for 24-hour albumin excretion rate in hypoxaemic CHD patients.

Discussion

Healthy kidneys excrete <150 mg of protein/day, of which ~20 mg is albumin. Meanwhile,

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Table 4. Demographic data and laboratory test results from different types of hypoxaemic CHD patients at baseline.

	Non-operated (10)	Palliative (7)	Fontan (5)	p
Age (years)	35.6 ± 10.9	31.2 ± 12.4	23.8 ± 11.7	0.128
Basal oxygen saturation (%)	83.2 ± 5.4	80.8 ± 4.9	91.0 ± 1.0	0.003
Haemoglobin (g/dl)	18.9 ± 3.8	18.8 ± 3.5	14.7 ± 1.1	0.057
Haematocrit (%)	57.6 ± 10.7	56.0 ± 10.1	43.1 ± 2.9	0.031
Serum creatinine (mg/dl)	1.1 ± 0.3	1.0 ± 0.2	0.9 ± 0.1	0.480
Serum total proteins (g/dl)	7.4 ± 0.5	7.3 ± 0.6	7.5 ± 0.3	0.894
Serum albumin (g/dl)	4.1 (3.9; 4.5)	4.3 (4.0; 4.3)	4.4 (1.4; 5.0)	0.703
Glomerular filtration rate (ml/min/1.73 m^2)	91.1 ± 30.1	93.1 ± 24.9	116.7 ± 22.8	0.257
Urine creatinine (g/24 hours)	13.0 ± 6.2	17.1 ± 5.8	18.2 ± 2.9	0.370
Urine proteins (g/24 hours)	0.08 (0.06; 0.14)	0.59 (0.43; 2.69)	0.08 (0.07; 0.08)	0.010
24-hour albumin excretion rate (μg/min)	16.0 (7.7; 101.1)	117.9 (4.4; 560.9)	6.8 (6.7; 11.2)	0.384
Urine glucose (mg/24 hours)	25.1 (0.0; 359.1)	8.1 (3.5; 31.2)	40.0 (8.8; 63.7)	0.685
Urine sodium (mM/24 hours)	104.2 ± 41.0	130.3 ± 61.9	182.0 ± 59.3	0.076
Urine potassium (mM/24 hours)	53.2 ± 20.8	40.1 ± 12.0	59.5 ± 22.3	0.343
Urine chlorine (mM/24 hours)	107.1 ± 37.9	132.8 ± 65.6	179.0 ± 50.2	0.092
Urine calcium (mg/24 hours)	71.0 ± 78.7	58.9 ± 35.8	104.6 ± 42.6	0.436
Urine phosphorus (mg/24 hours)	504.4 ± 277.8	625.0 ± 128.6	609.5 ± 187.2	0.516
Tubular phosphate re-absorption (%)	79.2 ± 12.7	79.0 ± 5.3	89.6 ± 3.5	0.132
N-terminal-pro-B-type natriuretic peptide (pg/ml)	230.1 (64; 486.6)	383 (221; 1166)	680 (88; 697)	0.572

Quantitative variables are expressed as mean ± standard deviation or as median and 25th and 75th percentile. Glomerular filtration rate estimated with Modification of Diet in Renal Disease formulae

microalbuminuria is defined as daily excretion of 30–300 mg of albumin/day and is an early and sensitive marker of nephropathy. Microalbuminuria is associated with an increased risk of cardiovascular disease in patients with and without diabetes and/or hypertension, and proteinuria has been shown to be an independent risk factor for the progression of kidney disease rather than simply being a marker for glomerular dysfunction;[4,9] however, little is known about proteinuria and its progression over time in hypoxaemic CHD patients.[10–12]

Hypoxia, by itself, may damage glomeruli and increase permeability, which ultimately leads to endothelial swelling and sclerosis. On the other hand, secondary erythrocytosis may promote shear stress and intraglomerular release of nitric oxide and angiogenic factors,[13–15] which may favour glomerular damage.

Moreover, shunted systemic venous megakaryocytes in the systemic arterial circulation with faulty pulmonary clearance, as seen in hypoxaemic CHD patients with right-to-left shunt, may carry cytoplasmic platelet-derived growth factor and transforming growth factor-β to the glomerular capillary beds, stimulating mesenchymally derived cells, enhancing connective tissue formation, and promoting protein synthesis, extracellular matrix formation, fibrosis, and cell proliferation.[14] This may explain, besides hypoxaemia, the emergence of proteinuria in patients with palliative corrections as it occurred in our series. Patients with palliative surgeries have a single-ventricle or double-ventricle morphology, and therefore a near-complete mixing of their systemic and pulmonary venous blood. On the contrary, non-operated CHD patients with pulmonary arterial hypertension (Eisenmenger syndrome) have lower shunts because the pressures in both the ventricles are equalised. Meanwhile, in the Fontan procedure, all the blood returning to the heart first passes through the pulmonary bed, which is the reason why there are no shunted systemic venous megakaryocytes in the systemic arterial circulation.

In addition, a low cardiac output may favour renal hypoperfusion,[16] renal damage, and secondary proteinuria. Volume overload, frequently seen in patients with palliative shunts, may impair over time the systemic ventricular function leading to renal hypoperfusion. On the contrary, advantages of a Fontan circuit include near normalisation of the arterial saturation and the abolishment of the chronic volume overload. To this is added the fact that myocardial hypoxaemia, by itself, may induce ventricular dysfunction. Finally, diuretics – most commonly used in complex heart abnormalities – may increase the risk of volume depletion. Similarly, the administration of radiographic contrast agents may lead to direct toxic effects on kidney cells.

Moreover, age and obesity may increase the risk of renal insufficiency. Elderly patients have less renal reserve capacity, and therefore greater susceptibility to the development of chronic renal disease with any given insult. Meanwhile, obesity has become not only a risk factor for the development of proteinuria[17,18] but also a factor for rapid progression to renal failure.[19] Nevertheless, none of these two factors – age and overweight – seem to have an important influence

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on the analytical parameters of our series, because our patients were young and their body mass index was within the normal limits. Despite this fact, other authors have determined that proteinuria is a significant and independent predictor of end-stage renal disease, even after adjustment for body mass index.[20]

In relation to hypertension and diabetes, the two biggest risk factors for proteinuria, none of them seems to justify the proteinuria observed in our hypoxaemic CHD series after matching both the CHD groups, with and without hypoxaemia, for classic cardiovascular risk factors; however, we should take into account that proteinuria in the general population is generally the consequence of manifest glomerular damage, whereas microalbuminuria is in most cases related to underlying diabetes or hypertension, which are frequently not diagnosed.[9]

Regarding urine creatinine levels, daily excretion varies by 4–8%, irrespective of diet and physical activity. Moreover, not only the type of diet but the way it is prepared can influence creatinine excretion. In addition, different drugs may affect creatinine concentration and its excretion or interfere with its assays; however, we think that a low muscle mass,[21] a finding frequently seen in hypoxaemic CHD patients,[22] may be the key factor that explains the significant lower daily creatinine excretion observed in our series. This is especially important as some authors, in the general population, have shown that baseline daily urinary excretion of creatinine is inversely associated with mortality and with major cardiovascular events.[23]

Regarding the resolution of proteinuria during follow-up, in two out of nine patients with baseline proteinuria it could have been in the context of transient and orthostatic proteinuria, up to 5% of adolescents may have orthostatic or postural proteinuria. As a rule, patients with orthostatic proteinuria excrete <1 g of protein over 24 hours, as it occurred in both our patients, is uncommon over the age of 30, and the long-term prognosis for adolescents with orthostatic proteinuria is excellent;[9] however, highly concentrated urine may also show an abnormal result even when the absolute daily protein excretion is normal. For this reason, insisting on proper urine collection and carrying out an appropriate follow-up of such patients are important to know whether proteinuria persists after repeat testing.

Despite our awareness of the study's limitations because of the small number and the young age of our hypoxaemic CHD patients, we think that routine testing for microalbuminuria and proteinuria should be recommended for CHD patients with associated hypoxaemia and/or heart failure,[24] especially if they have been corrected with palliative surgeries; however, there is currently insufficient evidence to determine the effectiveness of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists in patients with stage 1–3 chronic kidney disease who do not have diabetes mellitus, despite reducing proteinuria levels.[25–27] Nonetheless, longer-term follow-up studies with a greater number of patients should be performed to determine the renal outcome and the response of proteinuria to potential treatments.

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Conflicts of Interest

None.

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