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# Cardiovascular findings in classic homocystinuria

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ABSTRACT

*Objective:* describe cardiovascular findings from echocardiograms and electrocardiograms in patients with Classic Homocystinuria
*Methods:* this retrospective exploratory study evaluated fourteen subjects with Classic Homocystinuria (median age = 27.3 years; male $n = 8$, B6-non-responsive $n = 9$ patients), recruited by convenience sampling from patients seen Hospital de Clínicas de Porto Alegre (Brazil), between January 1997 and July 2020. Data on clinical findings, echocardiogram and electrocardiogram were retrieved from medical records.
*Results:* Eight patients presented some abnormalities on echocardiogram ($n = 6$) or electrocardiogram ($n = 5$). The most frequent finding was mild tricuspid regurgitation ($n = 3$), followed by mitral valve prolapse, mild mitral regurgitation, enlarged left atrium and aortic valve sclerosis ($n = 2$ patients each). Aortic root ectasia was found in one patient. Venous thrombosis was reported in six patients: deep vein thrombosis of lower limbs (n = 3), ischaemic stroke ($n = 1$), cerebral venous sinus thrombosis (n = 1) and pulmonary vein thrombosis (n = 1).
*Conclusion:* mild valvulopathies seen to be common in patients with Classic Homocystinuria, but more studies regarding echocardiogram and electrocardiogram in this population are needed to draw absolute conclusions.

## 1. Introduction

Classic Homocystinuria (HCU) or Cystathionine β-Synthase Deficiency (CBS) is a rare autosomal recessive inborn error of metabolism (OMIM 236200), characterized by markedly increased concentrations of plasma total homocysteine (tHcy) and methionine [1]. The incidence of HCU is estimated to be at least 0.38:100,000, varying from ~0.72:100,000 in non-Finnish Europeans, ~0.45:100,000 to the lower rates reported among Africans (~0.20:100,000) and Asians (~0.02:100,000) [2]. HCU can be classified according to responsiveness to pyridoxine (vitamin B6), as responsive and non-responsive, but it is also known that some patients will have an intermediate metabolism [1]. Treatment with pyridoxine is prescribed for all patients; a combination of methionine-restricted diet, methionine-free metabolic formula, vitamin B12, betaine and folate is used in pyridoxine non-responsive individuals [1].

Clinical manifestations observed in responsive patients usually are milder and develop later in life [3]. Thromboembolic events are common, due to the well-known association between elevated plasma homocysteine and intraluminal venous thrombi formation [4]. Besides cardiovascular events, systemic manifestations are also seen, such as ectopia lentis, marfanoid habitus, osteoporosis, intellectual disability and psychiatric illness [3,5].

There is a paucity of information regarding heart disease in HCU patients. Although not fully understood, it is known that damage to connective tissue can happen [6] and chronically elevated plasma tHcy could reduce in fibrillin-1 disulfide bonds, leading to changes in both cardiac structure and function [7]. Mainly findings were described in

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**Table 1**
– Clinical summary of the Classic Homocystinuria patients included in the study ($n = 14$).

| Patient | Gender | Pyridoxine Responsiveness | tHcy at Diagnosis (μmol/L) (Ref 5–15) | tHcy Mean (SD) (μmol/L) (Ref 5–15) | Age at Diagnosis (years) | Arterial Hypertension | Genotype* | Thromboembolic Events (age) | HCU Treatment |
|---|---|---|---|---|---|---|---|---|---|
| 1a | F | No | 273.0 | – | 7 | No | c.[253G > A]; c.[253G > A] p.[Gly85Arg]; p.[Gly85Arg] | Ischaemic stroke (22 years) | Restricteded protein diet |
| 1b | F | No | – | 266.5 (±79.6) | 5 | Yes | c.[253G > A]; c.[253G > A] p.[Gly85Arg]; p.[Gly85Arg] | Cerebral venous sinus thrombosis (30 years) | Pyridoxine, folic acid, irregular restricteded protein diet, betaine |
| 1c | M | No | – | 156.7 (±62.2) | 14 | No | c.[253G > A]; c.[253G > A] p.[Gly85Arg]; p.[Gly85Arg] | No | Pyridoxine, folic acid, irregular restricteded protein diet, irregular methionine-free metabolic formula, betaine |
| 2 | M | No | 348.0 | 141.7 (±40.6) | 13 | No | c.[828 + 1G > A; c.[209 + 1delG p.[828ins104,737del92]; p? | No | Pyridoxine, folic acid, irregular restricteded protein diet, methionine-free metabolic formula, betaine |
| 3a | F | No | 228.0 | 205.2 (±61.7) | 20 | No | c.[828 + 1G > A]; c.[828 + 1G > A] p.[828ins104,737del92] | Left leg and pulmonary venous thrombosis (15 years) | Pyridoxine, folic acid, irregular restricteded protein diet, |
| 3b | F | No | 189.4 | 205.3 (±97.6) | 32 | No | c.[828 + 1G > A]; c.[828 + 1G > A] p.[828ins104,737del92] | Right leg venous thrombosis (19 years) | Pyridoxine, folic acid, irregular restricteded protein diet, |
| 4 | F | No | – | 88.9 (±15.1) | 8 | No | c.[828 + 1G > A]; c.[1126G > A] p.[828ins104,737del92]; p.[Asp376Asn] | No | Pyridoxine, folic acid, irregular restricteded protein diet |
| 5 | F | No | 89.4 | 123.4 (±29.8) | 18 | No | c.[572C > T]; c.[572C > T] p.[Thr191Met]; p.[Thr191Met] | No | Pyridoxine, folic acid, betaine |
| 6 | M | Yes | 431.2 | 17.1 (±3.6) | 34 | Yes | c.[833 T > C]; c.[833 T > C] p.[Ile278Thr]; p.[Ile278Thr] | No | Pyridoxine, folic acid |
| 7 | M | Yes | – | 12.4 (±2.7) | 4 | Yes | c.[146C > T]; c.[1058C > T] p.[Pro49Leu]; p.[Thr353Met] | No | Pyridoxine, folic acid |
| 8 | M | Partial | – | 63.4 (±33.1) | 2 | No | c.[284 T > C]; c.[284 T > C] p.[Ile95Thr]; p.[Ile95Thr] | Ischaemic stroke (8 months) | Pyridoxine, folic acid, restricteded protein diet, methionine-free metabolic formula, betaine |
| 9 | M | No | – | 116.2 (±41.3) | 6 | No | c.[444delG]; c.[444delG] p.[Asn149fs]; p.[Asn149fs] | Right leg venous thrombosis (16 years) | Pyridoxine, folic acid, restricteded protein diet, betaine |
| 10 | M | Partial | 184.6 | 98.4 (±74.0.1) | 4 | No | c.[526G > A]; c.[1598 T > G] p. [Glu176Lys]/p.[Val533Gly] | No | Pyridoxine, folic acid, restricteded protein diet, methionine-free metabolic formula |
| 11 | M | Yes | 150.3 | 189.8 (±55.9) | 55 | Yes | c.[833 T > C]; c.[833 T > C] p.[Ile278Thr]; p.[Ile278Thr] | No | No treatment |

F/M: female/male; tHcy: total homocysteine. *See reference 19 to genotype of patients 1–9.

case reports, like orthostatic postural tachycardia [8] or calcified atrial mass [9], the later a result from endothelial dysfunction - already documented in HCU. In addition to that, patients with classic phenotype also have higher incidence of aortic root ectasia, seen by echocardiography [10].

## 2. Materials and methods

We performed a retrospective, exploratory study in a reference center for metabolic diseases at Hospital de Clínicas de Porto Alegre, Brazil. All procedures and data collection were in accordance with the

**Table 2**
– Electrocardiogram Findings in HCU patients ($n = 11$).

| Patient | ECG 1 (age) | ECG 2 (age) | ECG 3 (age) | ECG 4 (age) | ECG 5 (age) | ECG 6 (age) |
|---|---|---|---|---|---|---|
| 1a | Normal (24.0 yo) | Normal (27.4 yo) | NP | NP | NP | NP |
| 1b | Left atrial overload (16.7 yo) | Normal (19.4 yo) | Normal (22.8 yo) | Normal (27.0 yo) | Normal (32.7 yo) | NP |
| 1c | Early ventricular repolarization (25.2 yo) | Normal (27.9 yo) | Left ventricular overload Early ventricular repolarization (30.1 yo) | Left ventricular overload (39.5 yo) | Left ventricular overload Early ventricular repolarization (40.3 yo) | Left ventricular overload (41.8 yo) |
| 2 | Normal (16.6 yo) | Normal (19.0 yo) | Normal (20.8 yo) | Normal (22 yo) | NP | NP |
| 3a | Normal (21.5 yo) | NP | NP | NP | NP | NP |
| 3b | Incomplete right bundle branch block (32.5 yo) | Normal (34.0 yo) | NP | NP | NP | NP |
| 6 | Normal (39.0 yo) | Normal (40.0 yo) | Normal (41.0 yo) | NP | NP | NP |
| 8 | Normal (8.6 yo) | Left ventricular overload (17.8 yo) | Left ventricular overload (21.2 yo) | Normal (22.4 yo) | Left ventricular overload (23.6 yo) | NP |
| 9 | Left bundle branch block (25.3 yo) | Left bundle branch block (26.9 yo) | NP | NP | NP | NP |
| 10 | Normal (4.3 yo) | Normal (5.3 yo) | NP | NP | NP | NP |
| 11 | Normal (55.3 yo) | Normal (55.4 yo) | NP | NP | NP | NP |

NP = Not performed.

ethical standards of the local research committee and Helsinki Declaration. A convenience sample of 14 patients were included, whose information (electrocardiogram, echocardiogram and clinical data), from January 1997 to July 2020, was retrieved from medical records.

Pyridoxine responsiveness was defined as tHcy reduction in plasma to less than 50 μmol/L after treatment with pyridoxine; partial responsiveness was considered when more than 20% decrease in tHcy levels happened, but remained above 50 μmol/L and non-responsive when tHcy fell less than 20% after pyridoxine [1]. Arterial hypertension was defined according to AHA/ACC guidelines [11]. Aortic root measurement in the echocardiogram, was from leading edge to leading edge and a standardized z score was determined using the method of Devereaux for adults (>18 years old) and the method of Gautier for children and adolescents [12,13]. A z score < 2.0 was considered normal. The minimal regurgitation was not considered in the analysis, because usually it represents a physiological finding [14].

Statistical analyses were carried out in IBM SPSS Statistics, Version 21.0 (SPSS Inc., Chicago, IL) and the level of significance was considered 5%. Binary regression model was used to verify the effect of tHcy and pyridoxine responsiveness in hypertension, left ventricular overload, mild mitral regurgitation, mild tricuspid regurgitation, aortic valve sclerosis, mitral valve prolapse and enlarged left atrium.

## 3. Results

Fourteen patients from 11 families, 4.3 to 55.42 years old (median age = 27.3; IQ = 22.5–33.8) were included. Other main characteristics are summarized in Table 1. Patients 1a, 1b and 1c are siblings, same as 3a and 3b. Thirteen patients were receiving specific HCU treatment at the time of the study. Arterial hypertension was diagnosed in four patients, all of them taking at least one antihypertensive medication and all, except one, pyridoxine-responsive. Episodes of thrombosis were reported in six patients: two suffered ischaemic stroke, three had deep vein thrombosis in lower limbs and one patient presented cerebral venous sinus thrombosis.

A total of 34 electrocardiograms results were available for 11 patients and 46 complete echocardiograms for all patients. Eight patients presented at least one abnormality on echocardiogram ($n = 6$) or electrocardiogram ($n = 5$). Detailed electrocardiogram results and the age they were performed, are shown in Table 2; most patients had at least one, to a maximum of six different exams, however only incomplete reports were available for patients 4, 5 and 7. Regarding echocardiographic heart studies, all echocardiograms were transthoracic, being an exception patient 1a's second test, that was transesophageal. All patients left ventricular ejection fraction were greater than 50%, $n = 4/14$ patients (28.6%) had at least a valvar change at some point, all of them mild and not related to clinical manifestations. The most frequent finding on echocardiogram was mild tricuspid regurgitation ($n = 3$), followed by mitral valve prolapse, left atrial enlargement, aortic valve sclerosis and mild mitral regurgitation, described in two patients each (Table 3). Aortic root ectasia was found in one patient. No correlation was found between tHcy and hypertension, left ventricular overload, mild mitral regurgitation, mild tricuspid regurgitation, aortic valve sclerosis, mitral valve prolapse and enlarged left atrium; likewise, these variables did not have any statistically significant correlation with pyridoxine responsiveness.

## 4. Discussion

There is a lack of knowledge regarding heart disease in HCU patients, only some case series describe findings on electro and echocardiogram exams. Valve changes in HCU patients such as mitral prolapse, mitral and tricuspid regurgitation are rarely described [15,16]. Among the study subjects, we found a high prevalence of those, such as mitral prolapse, mitral and tricuspid regurgitation and aortic valve sclerosis. These results might be seen as exploratory, since such findings were not extensively described in HCU and our cohort was not matched with healthy subjects. We hypothesize that this correlation can be valid, as connective tissue - the main heart valve component - can be impaired in HCU patients [6,7]. The prevalence of findings, such as tricuspid regurgitation and mitral regurgitation, in pyridoxine-responsive ($n = 3$) and partially responsive ($n = 2$) patients seem to be lower than in non-responsive patients ($n = 9$). On the other hand, aortic valve abnormalities were more common in pyridoxine-responsive patients, possibly

**Table 3**
– Echocardiogram Findings in 14 HCU patients.

| Patient | Echo 1 | Echo 2 | Echo 3 | Echo 4 | Echo 5 | Echo 6 | Echo 7 | Aortic Root |
|---|---|---|---|---|---|---|---|---|
| 1a | Normal (22.0 yo) | Normal (22.0 yo) | Normal (27.4 yo) | NP | NP | NP | NP | Normal (Z < 2) |
| 1b | Mild mitral regurgitation (22.7 yo) | Mild Diastolic deficit (27.0 yo) | Mild mitral and tricuspid regurgitation (30.7 yo) | Mild mitral and tricuspid regurgitation (32.4) | Normal (Minimal mitral and tricuspid regurgitation) (32.7 yo) | Normal (Minimal mitral and tricuspid regurgitation) (33.3 yo) | Normal (Minimal mitral and tricuspid regurgitation) (34.0 yo) | Normal (Z < 2) |
| 1c | Normal (30.0 yo) | Normal (31.2 yo) | Mild mitral regurgitation. (38.3 yo) | Normal (40.3 yo) | Mild mitral regurgitation (40.9 yo) | Mitral valve prolapse and mild regurgitation. Mild tricuspid regurgitation (41.8 yo) | Mitral valve prolapse and mild regurgitation. (42.0 yo) | Normal (Z < 2) |
| 2 | Normal (17.5 yo) | Normal (19.0 yo) | Normal (20.0 yo) | Normal (22.0 yo) | NP | NP | NP | Normal (Z < 2) |
| 3a | Normal (21.5 yo) | NP | NP | NP | NP | NP | NP | Normal (Z < 2) |
| 3b | Normal (32.5 yo) | Normal (34.0 yo) | NP | NP | NP | NP | NP | Normal (Z < 2) |
| 4 | Mild tricuspid regurgitation Mild left atrial enlargement (25.8 yo) | NP | NP | NP | NP | NP | NP | Normal (Z < 2) |
| 5 | Normal (17.3 yo) | NP | NP | NP | NP | NP | NP | Normal (Z < 2) |
| 6 | Aortic valve sclerosis and mild regurgitation (37.1 yo) | Mild aortic regurgitation (39.0 yo) | Mild aortic regurgitation (40.0 yo) | Aortic valve sclerosis and mild regurgitation (41.0 yo) | NP | NP | NP | Normal (Z < 2) |
| 7 | Normal (21.3 yo) | Normal (23.8 yo) | NP | NP | NP | NP | NP | Normal (Z < 2) |
| 8 | Small interventricular communication (6.9 yo) | Small interventricular communication (8.6 yo) | Small interventricular communication (11.6 yo) | Mitral valve prolapse. (17.8 yo) | Mitral valve prolapse. (21.2 yo) | Mitral valve prolapse. (22.4 yo) | Mitral valve prolapse. (23.6 yo) | Normal (Z < 2) |
| 9 | Normal (19.0 yo) | Normal (26.1 yo) | Normal (27.1 yo) | | | | | Normal (Z < 2) |
| 10 | Normal (4.3 yo) | Normal (5.33 yo) | Normal (6.0 yo) | NP | NP | NP | NP | Normal (Z < 2) |
| 11 | Aortic valve sclerosis Aortic root ectasia. Mild diastolic dysfunction. Slight enlargement of left atrium (55.4 yo) | NP | NP | NP | NP | NP | NP | Aortic root ectasia (Z ≥ 2) |

NP = Not performed.

because this group was older.

Regarding electrocardiogram features, the main alteration was left ventricular overload, likely due to mitral regurgitation and mitral prolapse present in these patients. One female, 32 years old, normal blood pressure, had an incomplete right bundle branch block (RBBB), a common encounter at all ages, more prevalent in male and associated with hypertension, but not to other cardiovascular risk factors [17]. Moreover, partial RBBB is not associated with cardiovascular mortality, but some patients can evolve later with complete RBBB [17]. Another male from our cohort, 25 years old, normotensive, presented a left bundle branch block (LBBB) in one electrocardiogram, but his echocardiograms were all normal from age 19 to 27 years. Interestingly, LBBB is associated with arterial hypertension, age, coronary artery disease, left ventricular hypertrophy, ST-T abnormalities and an increased cardiothoracic ratio, none of them present in this subject [18]. Early ventricular repolarization was detected in one patient, who also had left ventricular overload. The former can be found in up to 13% of healthy individuals, although it is identified as a potential cause of sudden death [18]. It is possible that these combined findings are correlated.

We found a prevalence of 30% of arterial hypertension, similar to described in the literature for HCU [10]. Aortic root ectasia was present in one patient of our cohort, also described previously among HCU individuals [10]. He was known to suffer from arterial hypertension, but his blood pressure was controlled by pharmacological therapy. The relationship between arterial hypertension and aortic root ectasia is controversial, despite the large number of studies that tried to establish correlation [10]. Furthermore, no patients presented myocardial infarction (acute or previous), what is dissonant from 4% prevalence, described in the literature [1]. Ultimately, no familial pattern was observed for either echocardiograms or electrocardiograms findings.

## 5. Conclusion

This study described 10-year cardiological follow-up in a cohort of fourteen patients with HCU, showing high prevalence of mild valvulopathies. Our main limitations were the lack of a control group and its

retrospective and exploratory design. According to our results, we suggest considering an echocardiogram and electrocardiogram for each patient, at least in their first visit and monitor periodically their arterial blood pressure. That is justified by the fact that previous studies suggest an increased risk of ischaemic heart disease in HCU patients. Additionally, we believe that our report is not the definitive answer regarding echocardiogram and electrocardiogram in this population, but the opening for more discussion and new questions.

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*Authors' roles*

1- Conception and design of study: A. Conception, B. Organization, C. Execution;
2- Acquisition and analysis of data: A. Acquisition; B. Analysis of data.
3- Manuscript: A.Writing of the first draft; B. Review and Critique.
1- Marco Antônio Baptista Kalil: 1A, 1B, 1C, 2A, 2B, 3A (Nothing to disclose).
2- Karina Carvalho Donis: 1A, 1B, 1C, 2A, 2B, 3B (Nothing to disclose).
3- Fabiano de Oliveira Poswar: 2A, 2B, 3B (Nothing to disclose).
4- Bruna Bento dos Santos: 1C, 2A, 2B, 3B (Nothing to disclose).
5- Ângela Barreto Santiago Santos: 2B, 3B (Nothing to disclose).
6- Ida Vanessa Doederlein Schwartz: 1A, 1B, 1C, 2B, 3B (Nothing to disclose).

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