



Clinical, electrocardiographic and echocardiographic evolution of chronic Chagas disease treated with nifurtimox on prolonged follow-up in Chile: observational study

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ABSTRACT

Objectives: This study aimed to describe the electrocardiographic and echocardiographic status of chronic Chagas disease (cChD) patients treated with nifurtimox.

Methods: An observational study was performed in 146 cChD patients followed over a mean of 7.9 years. **Results:** Of the 146 patients, 41 (28.1%) with normal electrocardiogram (ECG) at baseline maintained this condition, 34 (23.3%) with altered ECG at baseline normalised the alterations, and 46 (31.5%) with ECG abnormalities at baseline maintained this condition [23 (15.8%) with small alterations]. Finally, 25 cases (17.1%) in indeterminate phase altered the ECG. Differences before and after follow-up ($P < 0.001$) were found. The percentage of beneficial treatment was different than expected by chance ($Z = 4.8$; $P < 0.001$) and the annual percentage of cases that developed ECG alterations was lower than that of a historical cohort of untreated patients ($P < 0.001$). An echocardiogram was performed in 68 patients with baseline ECG alterations. The ejection fraction (EF) was normal in 57 (83.8%) and abnormal in 11 (16.2%). In 38 patients with ECG abnormalities that did not progress after treatment, EF and segmental motility (SM) were normal in 31 (81.6%) and 26 (68.4%), respectively. In 17 patients with ECG abnormalities, EF and SM were normal in 15 (88.2%) and 14 (82.4%) cases, respectively.

Conclusion: Less progression to cardiomyopathy compared with a historical untreated cohort as well as the EF/SM results in patients with abnormal ECG that did not progress and in indeterminate cChD that altered the ECG suggests a beneficial effect of nifurtimox.

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Introduction

Chagas disease (ChD) is an anthroponosis caused by the protozoan parasite *Trypanosoma cruzi*. It is considered endemic in 21 countries. The World Health Organization (WHO) estimates that 6–7 million people are infected with *T. cruzi* in endemic regions of Latin America. Currently more than 25 million people live at risk in these areas [1]. Originally confined to the American continent,

ChD is currently becoming a global health problem [2]. It affects poor populations with little political voice and causes stigma and discrimination [3]. The WHO included ChD among the neglected tropical diseases [4]. Currently, <1% of patients with ChD have access to care and treatment, although the disease caused the loss annually of ~752 000 working days because of premature deaths and US\$1.2 billion in productivity in the seven southernmost American countries [5].

The natural history of ChD includes two successive phases, acute and chronic; the latter phase can be indeterminate or determinate. Almost 50–60% of chronic cases develop the indeterminate phase, an asymptomatic period, and 30–40% belong to the

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determinate phase with cardiac and/or digestive involvement [6]. Chronic Chagas cardiomyopathy (CCC) is the worst form of the disease owing to its high morbidity and mortality [7]. CCC patients with heart failure have a worse prognosis than other cardiomyopathies with heart insufficiency and present a higher frequency of strokes compared with a non-ChD cohort [8,9].

In cardiomyopathy due to *T. cruzi* there is cell damage, microangiopathy, inflammation and fibrosis that compromise the myocardial and electroconductive systems: this causes systolic and/or diastolic dysfunction, electrical conduction disorders and ventricular arrhythmias that are the basis of its clinical consequences of heart failure, complete atrioventricular (AV) block and sudden death [10,11]. Persistence of parasitaemia is the most important factor in the progression of cardiac damage. Other factors contribute less to the pathogenesis such as autoimmunity and others not completely known [12–16].

According to the WHO, ChD treatment is based on two drugs, nifurtimox (NFX) and benznidazole, both of which produce secondary effects in 30–85% of cases [17,18]. In acute acquired cases cure of 70–75% can be obtained, in congenital cases 100%, and in chronic cases 30–35% cure can be achieved with these drugs [19]. To date, it is believed that <1% of patients with ChD have been treated owing to lack of awareness of doctors and other professionals about the importance of therapy as well as shortage of medications, economic limitations, etc. [20,21].

The aim of this observational study was to describe the electrocardiographic and echocardiographic status of patients with chronic ChD (cChD) treated with NFX after a mean of 7.9 years of follow-up in Chile.

Materials and methods

A total of 146 seropositive untreated adults were confirmed as cChD in 2005–2007 by two conventional serological tests, namely enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence for IgG (IIF-IgG), as previously described [22]. Most of them were women who participated in a congenital ChD study treated after their breastfeeding period [23]. All of the patients came from two hyperendemic zones of Chile, the provinces of Choapa and Limarí, Coquimbo Region, located between 29° 02' and 32° 16' south latitude. All patients were submitted to anamnesis, physical examination and 12-lead electrocardiogram (ECG) and were divided into two groups according to whether or not they presented ECG alterations. At the end of the study, an echocardiogram (ECHO) was performed in the field on patients with altered ECG (outpatients clinic Los Cóndores, Quilimarí, Coquimbo, Region Province of Choapa, Chile) using an ultrasound scanner GE VIVIT S₆ (GE). The ejection fraction (EF) was determined by automatic calculation of FEx speckle tracking; alteration of the segmental motility (SM) of the left ventricle was corroborated by the technique of global longitudinal strain (GLS). Final interpretation of these tests was performed by specialist cardiologists following the double-blind protocol recommended by the WHO; the investigator analysing ECG traces and ECHOs was unaware of the state of the patient [24]. In baseline conditions, 80 (54.8%) and 66 (45.2%) individuals had altered and normal ECGs, respectively.

According to current ministerial regulations [25] and under informed consent, the 146 patients were treated between January 2007 and December 2012 in healthcare centres according to place of origin with NFX 8 mg/kg/day for 60 days without exceeding 700 mg/day. All patients concluded their treatment according to the study protocol. Electrocardiographic tests were classified by cardiologists as normal (N), with small (S) (sinus bradycardia, prolonged QTc period, first-degree AV blockage, repolarisation alteration, nodal rhythm, ischaemia image, short PR and left axis) or important (I) alterations [complete right bundle branch block

(CRBBB), incomplete right bundle branch block (IRBBB), left anterior hemiblock (LAHB), left ventricular hypertrophy and ventricular extrasystoles] at the beginning of the treatment and at the end of the follow-up period.

The effect of NFX on the electrocardiographic tests before and after treatment was compared using the Stuart–Maxwell test (an extension of the McNemar test to 3 × 3 contingency tables) [26]. The annual percentage of patients with cChD in indeterminate phase who developed electrocardiographic alterations in this study was compared with that of a historical cohort of 67 untreated patients with indeterminate phase followed for 4 years (1981–1984) [27] with similar ages, sex and place of origin as the current study with a Z-test. We defined treatment with NFX as beneficial if, at the end of the prolonged follow-up period, the ECG was normal (N–N, S–N or I–N). The treatment was considered unsuccessful when important (I) alterations of tracing ECG remained (I–I) or progressed (N–I). We compared the percentage of beneficial results with that expected by chance (50%) with the Z-test. A *P*-value of <0.05 was considered statistically significant.

The following parameters of the ECHO were considered: EF, normal (>55%) or low; motility, normal or with akinesia, dyskinesia, hypokinesia or asynchrony; and SM, normal or abnormal.

Co-morbidities were determined from the existing official information in the clinical records of the hospitals or local independent health clinics. These data were confirmed in the interviews of the investigators with each of the patients under study.

Results

Of the 146 cChD patients in the study, 120 (82.2%) were female and 26 (17.8%) male, with an age range of 7.4–74.2 years [mean ± standard deviation (S.D.) 41.6 ± 12.07 years] and 10.1–72.3 (mean ± S.D. 51 ± 15.02 years), respectively. There was an age difference between females and males (Student's *t*-test = 3.45; *P* < 0.0007). The age ranges of the groups with and without altered ECG were 22.0–68.8 years (mean 44.0 years) and 7.4–74.2 years (mean 42.4 years), respectively (Student's *t*-test = 0.72; *P* = 0.47).

Most of the patients were from Salamanca (*n* = 56; 38.4%), followed by Illapel (*n* = 37; 25.3%), Combarbalá (*n* = 22; 15.1%), Canela (*n* = 19; 13.0%) and Los Vilos (*n* = 12; 8.2%). After treatment, all the patients were examined twice a year in outpatient clinics (rural patients) and hospitals (urban patients) by our research group. A total of 18 and 128 patients had their last post-therapy control in 2017 and 2018, respectively. The endpoint of follow-up was performed a mean of 7.9 years post-therapy (Supplementary Table S1). At baseline, 66 patients (45.2%) had normal ECG (without cardiomyopathy) and 80 (54.8%) presented alterations of the ECG (with cardiomyopathy). After treatment, the ECG was normal in 75 (51.4%) individuals and altered in 71 (48.6%).

Table 1 describes the evolution of the ECG tracings observed 7.9 years after therapy with NFX, according to the place of origin of the 146 patients and the criteria previously established for the interpretation of the ECG by the cardiologists, i.e. normal (N) and small (S) or important (I) alterations. The final electrocardiographic condition was established as follows: normal ECG before and after treatment (N–N), 41 cases (28.1%); normal ECG that evolved to small alterations after treatment (N–S), 18 cases (12.3%); normal ECG that presented important alterations after treatment (N–I), 7 cases (4.8%); small alterations that normalised after treatment (S–N), 27 cases (18.5%); small alterations that remained after treatment (S–S), 21 cases (14.4%); small alterations that evolved to important abnormalities after treatment (S–I), 2 cases (1.4%); important ECG abnormalities that normalised after treatment (I–N), 7 cases (4.8%); important ECG abnormalities that changed to small alterations after treatment (I–S), 1 case (0.7%); and important alterations that remained after treatment (I–I), 22 cases (15.1%).

Table 1

Electrocardiogram (ECG) results of 146 patients with chronic Chagas disease treated with nifurtimox and evaluated pre- and post-therapy after 7.9 years of follow-up, according to place origin.

Locality	N-N		S-N		I-N		N-S		N-I		S-S		S-I		I-S		I-I		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Canela	1	2.4	10	37.0	2	28.6	2	11.1	0	0	2	9.5	0	0	0	0	2	9.1	19	13.0
Combarbalá	9	22.0	3	11.1	0	0	2	11.1	2	28.6	2	9.5	0	0	0	0	4	18.2	22	15.1
Illapel	10	24.4	7	25.9	4	57.1	7	38.9	2	28.6	4	19.0	1	50.0	0	0	2	9.1	37	25.3
Los Vilos	3	7.3	3	11.1	0	0	1	5.6	0	0	3	14.3	0	0	0	0	2	9.1	12	8.2
Salamanca	18	43.9	4	14.8	1	14.3	6	33.3	3	42.9	10	47.6	1	50.0	1	100	12	54.5	56	38.4
Total	41	28.1	27	18.5	7	4.8	18	12.3	7	4.8	21	14.4	2	1.4	1	0.7	22	15.1	146	100

N-N, normal ECG before and after treatment; S-N, small alterations that normalised after treatment; I-N, important alterations that normalised after treatment; N-S, normal ECG that evolved to small alterations after treatment; N-I, normal ECG that evolved to important alterations after treatment; S-S, small alterations that remained after treatment; S-I, small alterations that evolved to important alterations after treatment; I-S, important alterations that changed to small alterations after treatment; I-I, important alterations that remained after treatment.

Table 2

Electrocardiogram (ECG) alterations before treatment in 34 chronic Chagas disease patients who normalised the ECG tracing after treatment with nifurtimox.

ECG alteration before treatment	N	%
pQTc	17	50.0
pQTc+RA	1	2.9
SB	3	8.8
RA	4	11.8
CRBBB+AVB-1°G	1	2.9
LAHB	2	5.9
VE	2	5.9
NR	1	2.9
LVH	1	2.9
sPR	1	2.9
IRBBB	1	2.9
Total	34	100

pQTc, prolonged QTc interval; RA, repolarisation alteration; SB, sinus bradycardia; CRBBB, complete right bundle branch block; AVB-1°G, first-degree atrioventricular block; LAHB, left anterior hemiblock; VE, ventricular extrasystoles; NR, nodal rhythm; LVH, left ventricular hypertrophy; sPR, short PR interval; IRBBB, incomplete right bundle branch block.

Table 2 shows in detail the baseline alterations that normalised in 34 patients (23.3%) after treatment. Table 3 describes the ECG abnormalities at baseline in 46 patients (31.5%) that maintained this condition post-treatment, 23 of them (50.0%) with small alterations at baseline and Table 4 shows that 25 patients (17.1%) with normal ECG at baseline altered the ECG, 18 (72.0%) with small alterations. These results (Tables 2–4) were observed after a mean follow-up of 7.9 years, with a median and interquartile range of 7.82 years and 7.23–8.17 years, respectively.

We found differences before and after the follow-up period (Stuart–Maxwell test, $\chi^2 = 23.57$, $P < 0.01$). The percentage of favourable treatments (51.4%) (i.e. normal ECG at the final point of the prolonged follow-up period) was different than expected by chance ($Z = 4.8$; $P < 0.001$), and the annual percentage of patients with cChD in indeterminate phase that developed ECG alterations in this study was lower than that of a historical cohort of untreated patients ($Z = 67.9$; $P < 0.001$) (Tables 4 and 5).

Of the 80 patients with cChD and ECG abnormalities at baseline, an ECHO was performed in 68 (85.0%). The EF was normal in 57 (83.8%) and abnormal in 11 (16.2%). An ECHO was performed in 38 (82.6%) of 46 patients with cardiomyopathy and ECG abnormalities that did not progress after treatment with NFX. The EF was normal in 31 (81.6%) of them, and in 26 (68.4%) the SM was also normal (Table 6).

An association was found between motility ($\chi^2_5 = 12.4$; $P = 0.03$) and SM ($\chi^2_5 = 12.4$; $P = 0.03$) alteration with ECG abnormalities, specifically with repolarisation and left axis alteration. In 17 patients (68%) in indeterminate phase who presented ECG abnormalities after treatment, an ECHO could be performed. The

Table 3

Electrocardiogram (ECG) alterations (small and/or important) of 46 patients with chronic Chagas disease that were maintained after treatment with nifurtimox.

ECG alterations		N	%
Before treatment	After treatment		
pQTc	SB	6	13.0
CRBBB	CRBBB	5	10.9
CRBBB	CRBBB+LAHB	1	2.2
ISIM	ISIM	1	2.2
ISIM	SB	1	2.2
ISIM	SB+RA	1	2.2
LAHB	LAHB	3	6.5
LAHB+CRBBB	LAHB+CRBBB	2	4.3
LAHB	CRBBB	1	2.2
LAHB+pQTc	LAHB	1	2.2
LAHB	SB+LAHB	1	2.2
LVH	LVH	1	2.2
pQTc+LAHB	SB+LAHB	1	2.2
pQTc+CRBBB	CRBBB+LAHB	1	2.2
pQTc+LAHB	SB+LAHB	1	2.2
pQTc+IRBBB	SB	1	2.2
SB	SB	7	15.2
SB	SB+IRBBB	1	2.2
SB	pQTc	1	2.2
SB+AVB1°G	SB+AVB1°G	1	2.2
SB+LAHB	SB+LAHB	1	2.2
SB+CRBBB+pQTc	NR+CRBBB+VE	1	2.2
SB+pQTc	SB	1	2.2
SB+IRBBB	SB+IRBBB	1	2.2
RA	SB	2	4.3
SB+RA	SB+RA	1	2.2
SB	LVH	1	2.2
Total		46	100

pQTc, prolonged QTc interval; SB, sinus bradycardia; CRBBB, complete right bundle branch block; LAHB, left anterior hemiblock; ISIM, ischaemia image; RA, repolarisation alteration; LVH, left ventricular hypertrophy; IRBBB, incomplete right bundle branch block; AVB-1°G, first-degree atrioventricular block; NR, nodal rhythm; VE, ventricular extrasystoles.

Table 4

Electrocardiogram (ECG) tracing of 25 patients with chronic Chagas disease that were altered after treatment with nifurtimox.

ECG alteration after treatment	N	%
SB	12	48.0
SB+IRBBB	1	4.0
IRBBB	3	12.0
NR	1	4.0
LA	3	12.0
SB+AVB-1°G	1	4.0
LVH	1	4.0
RA	2	8.0
VE	1	4.0
Total	25	100

SB, sinus bradycardia; IRBBB, incomplete right bundle branch block; NR, nodal rhythm; LA, left axis; AVB-1°G, first-degree atrioventricular block; LVH, left ventricular hypertrophy; RA, repolarisation alteration; VE, ventricular extrasystoles.

Table 5

Electrocardiogram (ECG) abnormalities indicated on the final ECGs of 67 subjects with Chagas infection whose initial ECGs had shown no abnormalities: 1981–1984 (historical control group, Arribada et al., 1986 [27]).

ECG findings	N	%
AA	1	3.6
Unifascicular block (CRBBB, LAHB)	5	17.9
Bifascicular block (CRBBB+LAHB)	1	3.6
ISIM	2	7.1
RA	3	10.7
pQTc	16	57.1
Total no. of abnormalities	28	100
Total no. of ECGs with abnormalities	26 (6.5) ^a	38.8 (9.7) ^a
Total	67	

AA, auricular arrhythmia; CRBBB, complete right bundle branch block; LAHB, left anterior hemiblock; ISIM, ischaemia image; RA, repolarisation alteration; pQTc, prolonged QTc interval.

^a Number and percentage of patients who altered their ECG per year.

EF was normal in 15 cases (88.2%) and the SM in 14 cases (82.4%) (Table 7).

No differences were found between co-morbidities in the group with ECG abnormalities and the group of cChD patients in indeterminate phase (Table 8).

Discussion

The ECG is the gold standard for the diagnosis of heart involvement in patients with cChD in the field where this study was performed. It could be argued that there are patients with ChD cardiomyopathy with normal ECG and altered ECHO, but these cases are very few. A specialist cardiologist could point out that cardiac magnetic resonance imaging (MRI) is a procedure that allows cardiac involvement to be determined even in patients with ChD

in indeterminate phase [28–30]. Although these two statements are true, the possibility of performing both procedures is not easy since they can only be performed in high-complexity hospitals far from the reach of patients with ChD.

Most of the patients studied were women, since men were usually working when the study was performed, as we have observed in other studies on cChD [22]. The mean age of men was significantly greater than that of women (51 years vs. 41.6 years). It is worth nothing that of the 146 patients with cChD, 80 (54.8%) had ECG alterations suggestive of chronic Chagas cardiomyopathy (CCC) and only 66 cases (45.2%) had normal ECG before treatment. Although CCC requires several years to develop [7], in this study no difference between the mean age of the groups with and without cardiomyopathy (44.0 years and 42.4 years, respectively) was found (Student's *t*-test, 0.72; *P* = 0.47). The percentage of ECG abnormalities in patients with cChD before treatment (54.8%) was similar to the 51% described in 2013 by Ribeiro et al. [31] but higher than the 32% [32] and 40.1% [33] observed in other studies. At a mean of 7.9 years post-treatment with NFX, 75 (51.4%) of the 146 patients had a normal ECG and 71 (48.6%) were altered.

Of the 75 cases with normal ECG at the end of follow-up post-therapy, 41 (28.1%) and 34 (23.3%) had a normal (N-N) or altered ECG at baseline (S-N or I-N), respectively (Table 1). The overall result of these three groups (51.4%) can be considered as beneficial according to the established criteria.

The ECG alterations that reversed were minor alterations that may be reversible, such as prolonged QTc period in 18 cases (52.9%), repolarisation alterations in 4 patients (11.8%) and isolated sinus bradycardia in 3 individuals (8.8%). Only one case associated with CRBBB and first-degree AV block returned to normal (Table 2).

Table 6

Electrocardiogram (ECG) abnormalities and echocardiogram (ECHO) results of 38 chronic Chagas disease patients with cardiomyopathy that did not progress after treatment with nifurtimox at 7.9 years of follow-up.

ECG abnormalities				ECHO					
Pre-therapy	N	Post-therapy	N	EF	N	Motility	N	SM	N
SB	6	SB	6	Normal	6	Normal	6	Normal	6
SB	1	LVH	1	Normal	1	Asynchrony	1	Abnormal	1
SB	1	SB, IRBBB	1	Normal	1	Normal	1	Normal	1
SB, QTc↑	1	SB	1	Normal	1	Normal	1	Normal	1
SB, QTc↑, CRBBB	1	NR, CRBBB, VE	1	Low	1	Septal dyskinesia	1	Abnormal	1
SB, AVB-1°G	1	AVB-1°G	1	Normal	1	Normal	1	Normal	1
SB, LAHB	1	SB, LAHB	1	Normal	1	Normal	1	Normal	1
SB, IRBBB	1	SB, IRBBB	1	Normal	1	Normal	1	Normal	1
SB, RA	1	SB, RA	1	Normal	1	Apical hypokinesia	1	Abnormal	1
CRBBB	2	CRBBB	2	Normal	2	Normal	2	Normal	2
CRBBB	1	CRBBB	1	Normal	1	Septal dyskinesia	1	Abnormal	1
CRBBB	1	CRBBB	1	Low	1	Anterolateral dyskinesia	1	Abnormal	1
CRBBB	1	CRBBB	1	Low	1	Inferior dyskinesia	1	Abnormal	1
CRBBB	1	CRBBB, LAHB	1	Low	1	Lateral inferior dyskinesia	1	Abnormal	1
QTc↑	4	SB	4	Normal	4	Normal	4	Normal	4
QTc↑	1	SB	1	Low	1	Normal	1	Normal	1
QTc↑, LAHB	2	SB, LAHB	2	Normal	2	Normal	2	Normal	2
QTc↑, IRBBB	1	SB	1	Normal	1	Antero-apical hypokinesia	1	Abnormal	1
QTc↑, CRBBB	1	CRBBB, LAHB	1	Low	1	Diffuse hypokinesia	1	Abnormal	1
LAHB	1	LAHB	1	Normal	1	Normal	1	Normal	1
LAHB	1	CRBBB	1	Normal	1	Normal	1	Normal	1
LAHB	1	LAHB	1	Normal	1	Septal dyskinesia	1	Abnormal	1
LAHB	1	SB, LAHB	1	Normal	1	Normal	1	Normal	1
LAHB, CRBBB	1	LAHB, CRBBB, RA	1	Low	1	Inferior akinesia	1	Abnormal	1
ISIM	1	RA	1	Normal	1	Normal	1	Normal	1
ISIM	1	ISIM	1	Normal	1	Normal	1	Normal	1
RA	1	SB	1	Normal	1	Normal	1	Normal	1
LVH	1	LVH	1	Normal	1	Antero-apical hypokinesia	1	Abnormal	1
Total	38		38		38		38		38

EF, ejection fraction; SM, segmental motility; LVH, left ventricular hypertrophy; IRBBB, incomplete right bundle branch block; QTc↑, QTc interval increased; CRBBB, complete right bundle branch block; NR, nodal rhythm; VE, ventricular extrasystoles; AVB-1°G, first-degree atrioventricular blockage; LAHB, left anterior hemiblock; RA, repolarisation alteration; ISIM, ischaemia image

Table 7

Electrocardiogram (ECG) abnormalities and echocardiogram (ECHO) results after treatment with nifurtimox of 17 chronic Chagas disease patients with indeterminate period after 7.9 years of follow-up.

ECG abnormalities	N	ECHO					
		EF ^a	N	Motility	N	Segmental Motility	N
SB	8	Normal	8	Normal	8	Normal	8
IRBBB	2	Normal	2	Normal	2	Normal	2
RA	2	Normal	1	Septal dyskinesia	1	Abnormal	1
		Low	1	Anterolateral hypokinesia	1	Abnormal	1
LA	3	Low	1	Inferior hypokinesia	1	Abnormal	1
		Normal	2	Normal	2	Normal	2
VE	1	Normal	1	Normal	1	Normal	1
LVH	1	Normal	1	Normal	1	Normal	1
Total	17		17		17		17

EF, ejection fraction (^a normal value, >55%); SB, sinus bradycardia; IRBBB, incomplete right bundle branch block; RA, repolarisation alteration; LA, left axis; VE, ventricular extrasystoles; LVH, left ventricular hypertrophy

Table 8

Co-morbidities of 118 patients with chronic Chagas disease, including 64 with Chagas cardiomyopathy (CC) and 54 without heart involvement (NC).

Pathology	CC		NC		χ^2_1	P-value
	n	%	n	%		
Arterial hypertension	3	4.7	4	7.4	0.72	0.39
Arterial hypertension plus other pathologies	13	20.3	6	11.1		
Total	16	25.0	10	18.5		
Hypercholesterolaemia	3	4.7	5	9.3	0.67	0.41
Hypercholesterolaemia plus other pathologies	18	28.1	9	16.7		
Total	21	32.8	14	25.9		
Hypothyroidism	3	4.7	4	7.4	0.15	0.7
Hypothyroidism plus other pathologies	6	9.4	5	9.3		
Total	9	14.1	9	16.7		
Diabetes mellitus	1	1.6	2	3.7	0.88	0.35
Diabetes mellitus plus other pathologies	10	15.6	4	7.4		
Total	11	17.2	6	11.1		
Obesity	8	12.5	4	7.4	0.83	0.36
Overweight	12	18.8	14	25.9	0.88	0.35
Smoker	13	20.3	5	9.3	2.77	0.1
Total	33	51.6	23	42.6	0.95	0.33

Of the 71 cases with altered ECG at the end of the follow-up post-therapy, 46 (31.5%) maintained the ECG alterations after treatment. Of these, 23 (50.0%) corresponded to small alterations, of which the most frequent were: 21 (45.7%) sinus bradycardia, which includes 3 combined cases, 1 (2.2 %) prolonged QTc and 1 ischaemia image (2.2%). Of the 23 (50.0%) other patients with significant alterations of the ECG tracing, 12 (26.1%) were LAHB, with 8 combined cases. Four of these were CRBBB. The other 11 cases (23.9%) correspond to 6 isolated cases and 1 combined CRBBB, 2 combined IRBBB and 2 left ventricular hypertrophy (Table 3). Twenty-five cases (17.1%) were patients who evolved from normal to abnormal ECG, and at least 19 of them (76.0%) were small alterations (Table 4). It is important to emphasise that 23/46 cases (50.0%) maintained small alterations for almost 8 years in the ECG tracing without progression. Treatment prevented the progression to CCC in this group of patients.

In this study it is not possible to infer about the causes of post-therapy ECG alterations in 25/146 (17.1%) cases with normal ECG pre-therapy. In the strict sense, they should be considered cases of treatment failure, although almost 76% have only minor alterations that can be controlled annually according to the current protocols of consideration of cChD patients (Table 4). The rate of annual progression to CCC in this study was 2.3%, which is lower than the 9.7% reported in Chile ($Z = 4.8$; $P < 0.001$) and also than the 11% in Latin American immigrants in the USA [34,35].

It is important to point out that the magnitude of cardiac damage that causes a reversible compromise in cardiomyopathy is not known. Unlike the BENEFIT project [36] where no clinical changes were observed between CCC cases treated with benznidazole and

untreated over a period of 5.4 years, in this study a lower progression towards cardiomyopathy was observed after 7.9 years of follow-up. In BENEFIT, the baseline electrocardiographic alterations were more severe (CRBBB 50%, LAHB 34% and pacemaker 14%) and more frequent than in this study. The lower progression of patients with cChD in indeterminate phase of heart disease in this study could be due to earlier therapy and a more benign evolution of ChD in Chile [37]. We found differences between patients with cChD with normal ECG at baseline that were altered after therapy compared with individuals with altered ECG that normalised. In CCC, reversing the ECG to normal or with minimal changes is very beneficial; comparing these patients with those expected by chance, an improvement was evident (69.7%; $P < 0.001$). There was less annual progression towards heart disease than that reported in other studies.

Forty patients (27.4%) had small ECG alterations at end of the follow-up period, including 21 S-S cases (14.4%), 1 I-S case (0.7%) and 18 N-S cases (12.3%) (Table 1). If we had incorporated the S-S cases (small ECG alterations that did not progress in the follow-up) as a beneficial NFX effect, the percentage of beneficial treatment would be greater than the 51.4% obtained according to the established criteria.

Considering the ECG as the gold-standard indicator of CCC, although without pathognomonic or exclusive alterations [38,39], treatment with NFX had good results in this study. Similar results have been obtained recently in the USA for Latin-American immigrants with ChD treated with NFX and followed for 3.9 years [33].

An association between repolarisation and left axis ECG alteration with motility and SM on the ECHO was found. Normality of

the EF and SM of the CCC cases that maintained the ECG alterations after therapy (81.6% and 68.4%, respectively) is an indicator of a low cardiac involvement possibility influenced by treatment.

Limitations of this study are that there are variables that could not be compared since some were not measured in the historical cohort. In 1986, echocardiography was just in development (M-mode).

Conclusions

In our observational longitudinal cohort, those individuals treated with NFX showed less progression to CCC than a historical untreated cohort. ECG abnormalities that presented or appeared at the end of the study were very benign, confirmed by ECHO.

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Ethical approval

This study was approved by the Ethics Committee of Human Research of the Medicine Faculty of the University of Chile. All individuals evaluated in this study agreed to participate with written informed consent [Protocols 049/2009 and 012/2016 Fondecyt Regular Projects].

Competing interests

None declared.

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Supplementary materials

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