Rev. Inst. Med. trop. S. Paulo
40 (5): 301-307, September-October, 1998.

HEART ANEURYSM IN CHAGAS' DISEASE

José Alberto MELLO DE OLIVEIRA (1)

SUMMARY

This prospective study on 41 autopsy collected human hearts concerns the "apical" lesion in Chagas' disease. Previous report did not show a correlation between lesion frequency and heart weight then discarding a vascular factor in its pathogenesis. The present paper involves other variables besides the heart weight to evaluate the relative coronary insufficiency. Distinct colored gel (green and red) injected through the capillary beds of both coronary arteries defined the extent of both vessels before separating the atria and removing the sub-epicardium fat. The Right Ventricle (RV) and Left Ventricle (LV) free walls furnished the RV/LV mass ratio. The myocardium mass colored green (right coronary artery — RC) and the whole Ventricular Weight (VW) determined the RC/VW mass ratio. The heart weight plus these mass ratios, graded and added, composed a score inversely proportional to the myocardium irrigation condition. It intended to be a more sensitive morphologic evaluation of the relative ischaemia to correlate to the apical lesion. This study showed a right deviation for the relative accumulated frequency of lesions plotted as a score function and a significant difference for higher scores in hearts with aneurysm. It suggests a ischaemic factor intervening in the apical lesion pathogenesis in Chagas' cardiopathy.

KEYWORDS: Chagas'disease; Coronary arteries; Heart hypertrophy; Myocardial ischaemia.

INTRODUCTION

The "apical aneurysm" is a very special heart lesion occurring in Chagas' disease whose identification helps in the macroscopic diagnosis of the cardiopathy[33]. Its location is the left heart apex, less frequently the right side[20,21]. There are also reports on thinning in the right ventricle wall adjoining the septum[37] and the left ventricle posterior wall[37,44]. Research improved the disease knowledge since the Chagas' discovery[10], especially after the fifties[6,8,11,18,19,23,24,40,41,44,45] but fails until now to explain many unsolved pathogenic aspects including the heart "apical aneurysm".

Heart lesions in Chagas' disease should be catecholaminogenic[36]. A similar apical lesion experimentally induced in rats through isoproterenol injection suggests a pathway involving the myocardium cell membrane ß-receptors[30,31]. These papers support the Köberle's neurogenic theory[20-22]. That theory supposes Chagas' cardiopathy as a result of the sympathetic dominance after the parasympathetic denervation occurring in the acute phase. There would be a neurocardiopathy with relative coronary insufficiency and hypoxic intervening lesions due to the heart sympathetic dominance. The coronary arteries trunks dilated in Chagas' heart disease as compared to other cardiopathies[38] support the concept of a vascular phase in the neurogenic theory. Post mortem coronary arteriography in Chagas' disease showed scarce vascularization in the left apex[16]. Investigation on the coronary circulation in Chagas' cardiopathy showed apical ventricular regional hypoperfusion[28]. Most of the hypoxic lesions are mainly microscopic and of scattered distribution. The apical "aneurysm" would be the more conspicuous hypoxic manifestation of such evolution though it is not present in all cases. Heart hypertrophy as a sign of relative coronary insufficiency[7,14,25,46] could directly correlate with a higher frequency of the apical lesion. Previous study failed to find such a correlation to support the coronary insufficiency hypothesis in Chagas' heart disease[2,37]. However heart weight alone is not sufficient to identify heart hypertrophy. It is better discriminated using combined values of heart weight and ventricle mass ratios[12,15]. Furthermore the anatomic pattern of coronary distribution[32,42] may play a role in the coronary artery reserve[5]. Recent review of Chagas' heart disease implicates a microangiopathy in the pathogenesis of the myocardial lesions[41] giving new support to the vascular phase. These reports[8,16,28,41] then justify to resume the question of the relative ischaemia since they point out to a vascular factor in the pathogenesis of the Chagas' heart disease.

(1) Professor of Pathology, Department of Pathology, School of Medicine of Ribeirão Preto, University of São Paulo, São Paulo, Brazil.
Correspondence to: José Alberto Mello de Oliveira, Department of Pathology, School of Medicine of Ribeirão Preto. Av. Bandeirantes 3900. 14049-900 Ribeirão Preto, SP, Brazil. Phone/fax: 55 16 633 1068. E-mail: jamdoliv@fmrp.usp.br

MATERIAL AND METHODS

This protocol conducted on 41 hearts from autopsies of the Department of Pathology of the School of Medicine of Ribeirão Preto (São Paulo State - Brazil), studied cases that had Chagas' disease as the first or associated cause of death. Positive complement fixation test (Machado-Guerreiro reaction) in autopsy collected blood and pericardium liquid and/or the heart macroscopic aspect[33] gave the criteria to accept the diagnosis. They were 28 men (age varying between 19 and 73 years) and 13 women (age varying between 32 and 80 years). In every case the heart was carefully washed, weighed and examined to identify and register the most characteristic lesion, the wall thinning and bulging in the ventricles, especially in the left side apex.

The preparation of the 41 hearts followed the protocol described in a previous report[32]. They were part of a wider sample gathered for the study of the anatomic pattern of coronary arteries in human hearts with and without hypertrophy. In that protocol the simultaneous perfusion of the capillary beds of both coronary arteries with a gelatin-salt mixture allowed to color the myocardium green for right side and red for left side. Then the ventricle myocardium was divided into three parts — the right ventricle (RV) and left ventricle (LV) free walls and the interventricular septum (IVS) — after separating the atria and carefully removing the sub-epicardium fat [12, 17, 32]. The weights of the RV and LV free walls allowed to obtain the "Right Ventricle/ Left Ventricle" mass ratio (RV/LV). The extent of the right coronary (RC) artery territory was also identified in each heart, either restricts to the RV free wall or reaching the posterior half of the IVS and/or the LV free wall. These parts separated again for muscle masses colored green and red determined the distinctly colored myocardium weights. These data furnished the RC fraction in the whole ventricular mass, i.e. the "Right Coronary/ Ventricular Weight" mass ratio (RC/VW). The present report deals only with the left and right ventricular weights and the ventricular RC and the left coronary (LC) arteries dependent territories.

The heart weight, the RV/LV and RC/VW mass ratios graded or graded and added composed scores related to the presence or absence of the left apical lesion in the examined hearts. The criterion for hearts without weight hypertrophy was the heart weight limited of 350g and 300g for men and women, respectively. The standard values for the RV/LV and RC/VW mass ratios in hearts without weight hypertrophy were those previously reported [32], respectively RV/LV = 0.56 ± 0.07 and RC/VW = 0.38 ± 0.11. That study showed no differences between sexes for both ratios.

The grades for heart weight were "I" for cases up to 350g for men and 300g for woman; "II" for hearts weights more than 350 and 300g and up to 450g and 400g, respectively; and "III" for cases over these limits. The grades for RV/LV mass ratio were "I" for hearts within one standard deviation around the mean value referred above for cases without weight hypertrophy; "II" for hearts with greater values and up to two standard deviation and "III" for cases exceeding two standard deviation around that mean. The grades for RC/VW mass ratio were "I" for hearts within one standard deviation around that referred mean value for cases without hypertrophy; "II" for hearts with greater values and up to two standard deviation around the mean and "III" for hearts exceeding two standard deviation around that mean. The scores to be obtained could vary between 1 and 3 minimum for one variable and 3 to 9 maximum for combined variables, being further correlated to hearts with and without the apical lesion. The two-tailed Fisher Exact Test[43] gave the probability at a 5% level to accept the H_0 hypothesis that scores did not directly correlate to the lesion frequency.

RESULTS

Table 1 lists the studied cases including sex, age, heart weight, RV/LV and RC/VW mass ratios, the grades for each variable, the maximum heart scores and the presence or absence of the left ventricle apical lesion on each heart. They are 41 cases of Chagas' disease but 29 with apical aneurysm. Minimal and maximal values were respectively 180 and 740g for heart weights; 0.32 and 0.81 for the RV/LV mass ratio; 0.29 and 0.63 for the RC/VW mass ratio.

Table 2 summarizes these data. There was 3 aneurysms in 8 cases grade I for the variable "Heart Weight", 16 aneurysms in 20 cases grade II and 10 aneurysms in 13 cases grade III. There was 9 aneurysms in 16 cases grade I for "RV/LV", 10 aneurysms in 15 cases grade II and 10 aneurysms in 10 cases grade III. There was 21 aneurysms in 33 cases grade I for "RC/VW", 7 aneurysms in 7 cases grade II and 1 aneurysm in the only case grade III. The two-tailed Fisher Exact Test showed a $p<0.05$ concerning the RV/ LV mass ratio and no significant differences for the other variables.

Table 3 shows the distribution of the 41 hearts for the presence of the apical lesion related to scores obtained by adding pairs of variables. The two-tailed Fisher Exact Test for the paired variables showed a $p=0.047$ for "Heart Weight + RV/LV". Furthermore it showed a $p=0.012$ for "Heart Weight + RC/VW" and $p=0.039$ for "RV/LV + RC/VW". The "p" value in every case, lower than the 5% limit allowed to reject H_0 for all the combinations of variables.

Table 4 shows the frequency distribution of cases as related to the heart scores calculated by adding the "Heart Weight + RV/ LV + RC/VW" grades. The table also shows the accumulated frequencies (AF) equalized through the Relative Accumulated Frequency (RAF) logarithm. RAF is calculated throughout the formula $[(N+1)/(N-AF+1)]$ where N is the total number of cases in each group; AF is the absolute accumulated frequency. The Fisher Exact Test applied to the contingence table 2x5 (score versus lesion present or absent) showed a two-tailed probability $p=0.033$ associated with its occurrence under H_0. The values for the *logRAF* in both groups are graphically displayed in the Figure 1 as a score function showing a right deviation for the greater scores from cases with the apical aneurysm.

TABLE 1

Sex, age, grades on Heart Weight, "Right Ventricle/Left Ventricle" (RV/LV) and "Right Coronary/ Ventricular Weight" (RC/VW) mass ratios, heart scores and absence (A) or presence (P) of the apical lesion in the left ventricle of human hearts in 41 cases of Chagas' disease.

Case N°	Sex	Age	Heart Weight		RV/LV		RC/VW		Heart Score	Apical Lesion	
			(g)	Grade	Ratio	Grade	Ratio	Grade			
1	Male	57	320	I	0.63	I	0.49	I	3	A	
2		34	340	I	0.49	I	0.39	I	3	A	
3		68	350	I	0.55	I	0.41	I	3	A	
4		41	180	I	0.69	II	0.46	I	4	A	
5		29	250	I	0.69	II	0.43	I	4	A	
6		52	400	II	0.59	I	0.41	I	4	A	
7		38	400	II	0.63	I	0.45	I	4		P
8		73	410	II	0.50	I	0.41	I	4		P
9		19	420	II	0.52	I	0.39	I	4		P
10		65	450	II	0.49	I	0.37	I	4		P
11		62	420	II	0.50	I	0.53	II	5		P
12		40	410	II	0.44	II	0.33	I	5	A	
13		66	430	II	0.42	II	0.42	I	5	A	
14		29	450	II	0.47	II	0.35	I	5		P
15		73	370	II	0.67	II	0.55	II	6		P
16		48	410	II	0.37	III	0.33	I	6		P
17		25	400	II	0.36	III	0.58	II	7		P
18		27	450	II	0.72	III	0.51	II	7		P
19		40	560	III	0.55	I	0.45	I	5	A	
20		61	660	III	0.55	I	0.41	I	5		P
21		47	700	III	0.50	I	0.43	I	5		P
22		58	740	III	0.62	I	0.42	I	5	A	
23		40	560	III	0.45	II	0.32	I	6	A	
24		71	580	III	0.44	II	0.30	I	6		P
25		56	620	III	0.46	II	0.33	I	6		P
26		57	490	III	0.41	III	0.44	I	7		P
27		57	530	III	0.32	III	0.42	I	7		P
28		29	550	III	0.79	III	0.41	I	7		P
29	Female	45	300	I	0.42	II	0.35	I	4		P
30		40	250	I	0.69	II	0.56	II	5		P
31		44	260	I	0.68	II	0.63	III	6		P
32		51	320	II	0.54	I	0.33	I	4		P
33		48	330	II	0.52	I	0.34	I	4	A	
34		47	310	II	0.64	II	0.37	I	5		P
35		46	330	II	0.42	II	0.29	I	5		P
36		80	380	II	0.48	II	0.38	I	5		P
37		33	320	II	0.76	III	0.44	I	6		P
38		62	390	II	0.40	III	0.21	II	7		P
39		32	500	III	0.53	I	0.38	I	5		P
40		65	560	III	0.38	III	0.41	I	7		P
41		38	630	III	0.81	III	0.50	II	8		P

TABLE 2

Chagas' heart disease: frequency of cases with the apical lesion distributed according to grades assigned to the Heart Weight, the "Right Ventricle/Left Ventricle" (RV/LV) and "Right Coronary/ Ventricular Weight" (RC/VW) mass ratios (see text).

Grade	Heart weight*		RV/LV**		RC/VW*	
	n	lesion	n	lesion	n	lesion
I	08	03	16	9	33	21
II	20	16	15	10	07	07
III	13	10	10	10	01	01
Total	41	29	41	29	41	29

Two-tailed Fisher Exact test: (*) not significant; (**) P<0.05

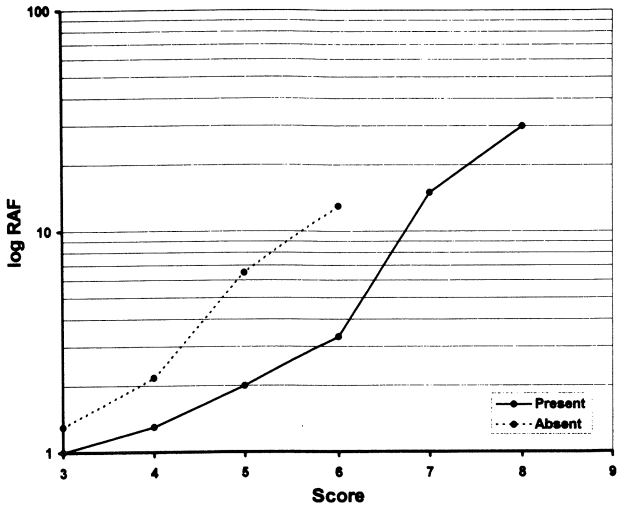

Figure 1 - Chagas' disease: *LogRAF* (Relative Accumulated Frequency) of the apical aneurysm in the left ventricle for 12 hearts without and 29 with the lesion plotted as a function of heart scores in 41 human cases.

TABLE 3

Chagas' heart disease: distribution of cases without (An Abs) and with (An Pres) aneurysm in the left ventricle apex of 41 human hearts as related to scores based on the paired variales: Heart Weight (HW), "Right Ventricle/Left Ventricle" (RV/LV) and "Right Coronary/ Ventricular Weight" (RC/VW). Probability (p) obtained through a two-tailed Fisher Exact test.

Score	HW + RV/LV		HW + RC/VW		RV/LV + RC/VW	
	An Abs	An Pres	An Abs	An Pres	An Abs	An Pres
2	3		5	1	7	
3	4	9	4	12	5	8
4	4	8	3	15		8
5	1	7		1		8
6		5				5
Total	12	29	12	29	12	29
p	0.047		0.012		0.039	

COMMENTS

Chagas' heart disease is a complex and still now poorly understood cardiopathy. The main facts well established are the identification of the etiologic agent (*Trypanosoma cruzi*, Chagas 1909), scattered focal myocytolysis[27] and fibrosis, disturbances of the electric stimulus generation and conduction[4,13], the post-ganglionic autonomic nervous cells wasting[22], the presence of mural "aneurysms" either in the left and/or right apex[20-22] or more infrequently elsewhere[37,44], the inflammatory infiltration by immunologically competent[45] and phagocytic cells, congestive

TABLE 4

Chagas' heart disease: frequency of the apical lesion in the left ventricle of 41 human cases as correlated to the score based on the heart weight, RV/LV and RC/VW mass ratios. **n** = number of cases in each score; **AF** = Accumulated Frequency; **RAF** = Relative Accumulated Frequency obtained through the formula [(N+1)/(N-AF+1)].

Score	Aneurysm absent (N=12)				Aneurysm present (N=29)			
	n*	AF	RAF	log RAF	n*	AF	RAF	log RAF
3	3	3	1.30	0.11			1.00	0.00
4	4	7	2.17	0.34	7	7	1.30	0.12
5	4	11	6.50	0.81	8	15	2.00	0.30
6	1	12	13.00	1.11	6	21	3.33	0.52
7					7	28	15.00	1.18
8					1	29	30.00	1.48
9								

(*) Two-tailed Fisher Exact Test: P<0.05 comparing score and lesion frequency in both groups.

cardiac insufficiency[13] and sudden death[22]. How to gather all these facts in an unitary concept is still now debatable and far from being reached. The heart macroscopic aspect at autopsy may show a global cardiac hypertrophy and dilation (cardiomegaly) suggesting a functional congestive cardiopathy. However ventricle hypertrophy without dilation or even a small heart are not infrequent. Bulging of the conus arteriosus, the presence of tiny delicate granules linearly disposed along the coronary vessels (fibrous pericarditis "in rosary") or a lymphnode between the aorta and pulmonary artery trunks are also macroscopic findings. In every situation the diagnosis is easier if the characteristic apical "aneurysm" is present with or without mural thrombi. The apical aneurysm of the Chagas' cardiopathy differs from the post-infarct aneurysm. It does not display the typical thick collagen infiltration of the healed infarct though some people designated it "apical infarct"[35]. Usually the wall becomes so thin as to be translucent suggesting that the myocells are lost through a mechanism scarcely eliciting the repair process. It seems as to the epicardium and endocardium become face to face without myocardium interposed. The collagen quality in the apical lesion reparative process in Chagas' heart disease is different as compared to that from the myocardium infarct[9]. The healing aspect changes when mural thrombosis intervene and the collagen may be found as part of the thrombus organization. Previous reports dealing with this lesion considered inflammatory[8,34], mechanical[1,39], neurogenic[20,21], vascular[3,20,21,26,27,29] and ß-receptor stimulating[30,31] factors implicated in its pathogenesis. Recently, other observations[41] showed lesions at the microvasculature level corroborating the presence of vascular factors in its pathogenesis. An *in vivo* study of the coronary circulation[28] using specific markers of myocardial flow showed regional ventricular hypoperfusion especially in the apex and lateral view of the left ventricle free wall. KÖBERLE[20-22] considered Chagas' heart disease as a neurocardiopathy beginning in the acute period of the *T.cruzi* infection, when mural autonomic neurocytes are destroyed. Later follow the vascular and myogenic phases. The autonomic control lost by parasympathetic denervation causes hypertrophy because of the sympathetic dominance. In this theory the vascular phase is consequence of a relative coronary insufficiency to attend the myocardial metabolic needs in the denervated heart. In this phase there should be scattered focal necrosis from hypoxic origin. Finally follows the myogenic phase with continuing focal myocardial necrosis, inflammation and fibrosis.

There is a consensus about the efficiency of the coronary arterial system for a good irrigation of the normal heart but there is also a bulk and broad clue about its limitations face to heart hypertrophy[7,14,25,46]. Coronary artery dilation demonstrated in Chagas' heart disease may reflect the sustained coronary insufficiency[38]. Many reports refer a relative coronary insufficiency[7,14,25,46] when heart hypertrophy induces a loss of adequate proportion between myocardium mass and irrigation then causing a relative ischaemia. This mechanism has been supposed to be involved in this cardiopathy[24]. However previous report studying the heart weight and the frequency of the apical lesion[2,37] in Chagas' heart disease failed to demonstrate a direct correlation between them. This study on 41 hearts in autopsies that had Chagas' disease as the first or associated cause of death shows the apical lesion distributed along with all the heart weight range (Table 1) confirming previous reports[2,37]. Table 1 displays a case weighing 740g without the apical lesion. Scores taken from the variable "Heart Weight" alone (Table 2) did not show significant difference between the heart groups with and without aneurysm.

The present paper considered that other variables (RV/LV and RC/VW mass ratios) rather than the heart weight alone could help in evaluating the coronary insufficiency intervening in the apical lesion pathogenesis in Chagas' heart disease. The heart weight as unique criterium for heart hypertrophy masks some aspects that become evident when one takes into account an isolated ventricular hypertrophy even in hearts with small weight[12,15]. Otherwise the anatomic pattern of coronary distribution[32,42] may play a role in the coronary artery reserve[5] then justifying the RC/VW mass ratio inclusion in this study. The values of these mass ratios have a normal distribution around the mean. It justifies to assign grades I to III to individuals as they deviate from the most frequent mean values. In the case of the RV/LV mass ratio these deviations correspond to right or left ventricle hypertrophy. In the case of the RC/VW mass ratio it corresponds to right or left coronary artery dominance. The grades of the isolated RV/LV mass ratio here analyzed showed a significant difference in the lesion frequency related to the heart groups (Table 2). However there was no difference between the same groups when considered the isolated RC/VW mass ratio. This sample is probably too small to show a significant difference concerning this variable alone, since the great majority of hearts (33 cases) are RC/VW grade I (Table 2). The concentration of cases in grade I hearts reflects the narrow variation range of the RC fraction irrigating the ventricles as shown in a previous paper[32]. It is to be noticed that all the other 8 cases had the apical lesion (7 cases graded II and 1 graded III). Furthermore scores obtained by adding pairs of variables showed for all their combinations a significant difference for the lesion frequency in both groups (Table 3).

These 41 cases were furthest separated using a score calculated by adding all the variables grades. This score intended to be more sensitive in evaluating through a morphological criterion the proportion between myocardial mass and the irrigation condition. It means that greater the score worse the irrigation condition. Table 4 shows no cases with apical lesion in hearts with the smaller score 3. Otherwise the frequency of hearts with the apical lesion is greater in the higher scores with a significant statistical difference. The *logRAF* for both groups put in a graphical form shows a right deviation for the hearts with the apical lesion and indicate that it has a higher incidence as far as worse is the heart irrigation. Nevertheless the overlap among cases with and without aneurysm in the intermediate scores (4 to 6) deserves further investigation as well as the capricious locations of the ventricular wall thinning in the apex and elsewhere. The heart apex is usually irrigated by the LC artery in its frontiers with the RC territory. Even the other locations of ventricular wall thinning referred in previous reports[37,44] are in the frontiers between both territories. The nature of this histotoxic anoxy still remains to be investigated. There is no obstruction of the main trunks and branches of the coronary arteries[1,2]. Arteritis referred in Chagas' patients for intramural

vessels in oesophagus biopsies[6] are not conspicuous in the Chagas' heart disease[44]. Microangiopathy with microthrombus in the capillary vessels[41] could explain the hypoxidosis, myocell necrosis and fibrosis.

In summary this macroscopic study suggests that all the variables combinations here used were more effective than the heart weight alone for the morphologic evaluation of the relative coronary insufficiency. It corroborates the vascular phase[20] in the evolution of Chagas' heart disease pointed out by other reports[28,41] suggesting hypoxic factors intervening in the pathogenesis of the apical lesion.

RESUMO

Aneurisma cardíaco na doença de Chagas

Trata-se de estudo prospectivo referente à lesão apical da cardiopatia chagásica em 41 corações humanos. A relatada falta de correlação entre freqüência da lesão e peso do coração, descartou o fator patogênico vascular. Neste trabalho avalia-se a insuficiência coronária relativa incluindo outras variáveis além do peso do coração. A perfusão do leito capilar com gel de cores diferentes para cada coronária (verde e vermelho) permitiu delimitar seus territórios antes de separar os átrios e a gordura sub-epicárdica. As paredes livres dos ventrículos direito (RV) e esquerdo (LV) definiram o índice RV/LV. O peso do miocárdio ventricular corado em verde (artéria coronária direita-RC) e o peso ventricular total (VW) definiram o índice RC/VW. O peso do coração e esses dois índices, graduados e somados, compuseram um "score" de valor inversamente proporcional à condição de irrigação do miocárdio. Tencionou-se, com este "score", obter uma avaliação morfológica da isquemia relativa, a ser relacionada com a frequência do aneurisma da ponta. A frequência acumulada relativa das lesões obtida para dois grupos de corações (sem e com aneurisma) revelou valores maiores dos "scores" para os chagásicos com a lesão, corroborando a existência de uma fase vascular interveniente na patogênese da lesão apical.

ACKNOWLEDGEMENTS

Grant support by the *Comissão de Aperfeiçoamento de Pessoal de Nível Superior - CAPES - (Bolsa de Dedicação Acadêmica) and the Fundação de Apoio ao Ensino, Pesquisa e Assistência (Hospital das Clínicas - FMRPUSP)*.

REFERENCES

1. ALMEIDA, H.O. - A "lesão vorticilar" na cardiopatia chagásica crônica. Aspectos morfológicos. **Rev. goiana Med.**, 28: 23-31, 1982.

2. ALMEIDA, H.O. - Hipóxia como fator patogenético da lesão apical em chagásicos crônicos. **Rev. goiana Med., 32**: 129-139, 1986.

3. ANDRADE, Z.A. - A lesão apical do coração na miocardite crônica chagásica. **Hospital (Rio de J.), 50**: 803-812, 1956.

4. BRASIL, A. - A mutabilidade eletrocardiográfica na cardiopatia chagásica crônica. **Rev. Ass. méd. Minas Gerais, 4**: 149-152, 1953.

5. BLOOR, C.M. - **Cardiac pathology**. Philadelphia, J.B. Lippincott, 1978. p. 51-53.

6. BRITO, T. & VASCONCELOS, E. - Necrotizing arteritis in megaesophagus. Histopathology of ninety-one biopsies taken from the cardia. **Rev. Inst. Med. trop. S. Paulo**, 1:195-206, 1959.

7. BÜCHNER, F. - Patologia general de la circulación. In: BÜCHNER, F. **Patologia general**. Madrid, Revista de Occidente, 1964. p. 194-264.

8. CARVALHAL, S.; PORTUGAL, O.; PALADINO, N. et al. - Alterações do complexo QRS nas derivações precordiais e seu substrato anatômico em pacientes portadores de miocardite chagásica crônica. **Rev. paul. Med., 45**: 161-168, 1954.

9. CASTAGNINO, H.E. & TORANZOS, F.A. - Histologic correlation of ischemic and chagasic ventricular aneurysms. Relation to physiopathology. **Arch. Inst. Cardiol. Méx., 58**: 425-432, 1988.

10. CHAGAS, C. - Nova espécie mórbida do homem, produzida por um *Trypanosoma* (*Trypanosoma cruzi*). Nota prévia. **Brasil-méd., 23**(16): 161; 1909.

11. CHIALE, P.A.; ROSENBAUM, M.B.; ELIZARI, M.V. et al. - High prevalence of antibodies against beta 1- and beta 2-adrenoceptors in patients with primary electrical abnormalities. **J. Amer. Coll. Cardiol., 26**: 864-869, 1995.

12. DAVIES, M.J.; POMERANCE, A. & LAMB, D. - Techniques in examination and anatomy of the heart. In: POMERANCE, A. & DAVIES, M.J., ed. **The pathology of the heart**. London, Blackwell Scientific Publications, 1975. p. 1-48.

13. DIAS, E.; LARANJA, F.S. & NÓBREGA, G. - Doença de Chagas. **Mem. Inst. Oswaldo Cruz, 43**: 495-581, 1945.

14. DODGE, J.T.; BROWN, G.; BOLSON, E.L. & DODGE, H. - Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. **Circulation, 86**: 232-246, 1992.

15. DULL, M. - Gewichtsbestimmungen der reinen Muskelmasse beider Herzkammern bei normaler und pathologischer Herzbelastung. **Beitr. path. Anat., 105**: 337-365, 1941.

16. FERREIRA, C.S.; LOPES, E.R.; CHAPADEIRO, E. et al.. - Coronariografia post-mortem na cardite chagásica crônica. Correlação anátomo-radiológica. **Arq. bras. Cardiol., 34**: 81-86, 1980.

17. FULTON, R.M.; HUTCHINSON, E.C. & JONES, A.M. - Ventricular weight in cardiac hypertrophy. **Brit. Heart J., 14**: 413-420, 1952.

18. JÖRG, M.E. - Tripanosomiasis cruzi: anarquia angiotopografica por descapilarización mesenquimorreactiva, cofactor patogénico de la miocardiopatia crónica. **Pren. méd. argent., 61**: 94-106, 1974.

19. KÖBERLE, F. & NADOR, E. - Etiologia e patogenia do megaesôfago no Brasil. **Rev. paul. Med., 47**: 643-661, 1955.

20. KÖBERLE, F. - Cardiopatia chagásica. **Hospital (Rio de J.), 53**(3): 9-50, 1958.

21. KÖBERLE, F. - Patologia y anatomia patologica de la enfermedad de Chagas. **Bol. Ofic. sanit. Panamer., 51**: 404-428, 1961.

22. KÖBERLE, F. - Chagas' disease and Chagas' syndromes: the pathology of American trypanosomiasis. **Advanc. Parasit., 6**: 63-116, 1968.

23. KÖBERLE, F. - Chagas-Krankheit und Chagas-Leiden. In: GSELL, O.; ST. GALLEN & MOHR, W., ed. - **Infektionskrankheiten. Band IV. Rickettsiosen und Protozoenkrankheiten**. Berlin, Springer-Verlag, 1972. p 290-324.

24. LARANJA, F.S.; DIAS, E.; NÓBREGA, G. & MIRANDA, A. - Chagas' disease. **Circulation, 14**: 1035-1060, 1956.

25. LINZBACH, A.J. - Heart failure from the point of view of quantitative anatomy. **Amer. J. Cardiol., 5**: 370-382, 1960.

26. MAGARINOS-TORRES, C. - Arteriolosclerose das finas ramificações arteriais do miocárdio (coronarite chagásica) e miocitólise focal do miocárdio na cardiopatia chagásica crônica. **Hospital (Rio de J.), 54**: 597-610, 1958.

27. MAGARINOS-TORRES, C. - Miocitólise e fibrose focal do miocárdio na doença de Chagas. **Mem. Inst. Oswaldo Cruz, 58**: 161-182, 1960.

28. MARIN-NETO J.A.; SIMÕES, M.V.; AIRES-NETO E.M. et al. - Studies of the coronary circulation in Chagas' heart disease. **Rev. paul. Med., 113**: 826-834, 1995.

29. MELLO DE OLIVEIRA, J.A. - **Contribuição ao estudo da patogenia do "aneurisma" da ponta na cardiopatia chagásica**. Ribeirão Preto, 1967. (Tese – Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo).

30. MELLO DE OLIVEIRA, J.A. - Observações sobre a histoquímica de algumas enzimas do miocárdio na fase crônica da infecção experimental pelo *Trypanosoma cruzi*, Chagas, 1909, em ratos Wistar. **Rev. goiana Med., 22**: 1-65, 1976.

31. MELLO DE OLIVEIRA, J.A. - Adrenergic receptors: is Chagas' heart disease a model to their study in a human pathologic condition?. In: WEGMANN, R.J. & WEGMANN, M.A., ed. **Recent advances in cellular and molecular biology. V.3. Neurobiochemical transmitter pathways, adrenoceptors and muscarinic receptors**. Leuven, Peeters Press Belgium, 1992. p. 213-216.

32. MELLO DE OLIVEIRA, J.A. - Myocardial ventricular mass related to coronary artery distribution in human hearts. **Int. J. Cardiol., 62**: 23-29, 1997.

33. MENEZES, H. & KÖBERLE, F. - Do valor do exame macroscópico no diagnóstico da cardiopatia chagásica. **Hospital (Rio de J.), 68**: 139-144, 1965.

34. MIGNONE, C. - **Alguns aspectos da anatomia patológica da cardite chagásica crônica**. São Paulo 1958. (Tese de Cátedra – Faculdade de Medicina da Universidade de São Paulo)

35. MONTES PEREJA, J.; AMARGOS, A.; ESTABLE, J.J. & FERREIRA BEIRUTTI, P. - Forma cardiaca de la trypanosomiasis cruzi. **Arch. urug. Cardiol., 2**: 119-132, 1938.

36. OLIVEIRA, J.S.M. - Cardiopatia "chagásica" experimental. **Rev. goiana Med., 15**: 77-133, 1969.

37. OLIVEIRA J.S.; MELLO DE OLIVEIRA, J.A.; FREDERIGUE JR., U. & LIMA-FILHO, E.C. - Apical aneurysm of Chagas' heart disease. **Brit. Heart J., 46**: 432-437, 1981.

38. OLIVEIRA, J.S.M.; SANTOS, J.C.M.; MUCILLO, G. & FERREIRA, A.L. - Increased capacity of the coronary arteries in chronic Chagas' heart disease: further support for the neurogenic pathogenesis concept. **Amer. Heart J., 109**: 304-308, 1985.

39. RASO, P. - **Contribuição ao estudo da lesão vorticilar (especialmente do vortex esquerdo) na cardite chagásica crônica**. Belo Horizonte, 1964. (Tese – Faculdade de Medicina da Universidade Federal de Minas Gerais).

40. RIBEIRO DOS SANTOS, R.; RASSI, A. & KÖBERLE, F. - Chagas' disease. **Antibiot. and Chemother., 3**: 115-134, 1981.

41. ROSSI, M.A. - Microvascular changes as a cause of chronic cardiomyopathy in Chagas' disease. **Amer. Heart J., 120**: 233-236, 1990.

42. SCHLESINGER, M. J. - Relation of the anatomic pattern to pathologic conditions of the coronary arteries. **Arch. Path., 30**: 403-415, 1940.

43. SPIEGEL, S. - **Nonparametric statistics for the behavioral sciences**. New York, McGraw-Hill, 1956. p. 95-158

44. SUAREZ, J.A.; PUIGO, J.J.; NAVA-RHODE, J.R. et al. - Estudio anatomopatológico de 210 casos de miocardiopatias en Venezuela. **Acta méd. venez., 15**: 320-330, 1968.

45. TEIXEIRA, A.R.L. - The immunology of experimental Chagas' disease. IV. The production of lesions in rabbits similar of those of Chagas' disease in man. **Amer. J. Path., 80**:163-177, 1975.

46. WOODS, J.D. - Relative ischæmia in the hypertrophied heart. **Lancet, 1**: 696-698, 1961.

Received: 7 April 1998
Accepted: 4 September 1998