NHETS – Necropsy Heart Transplantation Study

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Abstract

Background: Discrepancies between pre and post-mortem diagnoses are reported in the literature, ranging from 4.1 to 49.8 % in cases referred for necropsy, with important impact on patient treatment.

Objective: To analyze patients who died after cardiac transplantation and to compare the pre- and post-mortem diagnoses.

Methods: Perform a review of medical records and analyze clinical data, comorbidities, immunosuppression regimen, laboratory tests, clinical cause of death and cause of death at the necropsy. Then, the clinical and necroscopic causes of death of each patient were compared.

Results: 48 deaths undergoing necropsy were analyzed during 2000-2010; 29 (60.4 %) had concordant clinical and necroscopic diagnoses, 16 (33.3%) had discordant diagnoses and three (6.3%) had unclear diagnoses. Among the discordant ones, 15 (31.3%) had possible impact on survival and one (2.1%) had no impact on survival. The main clinical misdiagnosis was infection, with five cases (26.7 % of discordant), followed by hyperacute rejection, with four cases (20 % of the discordant ones), and pulmonary thromboembolism, with three cases (13.3% of discordant ones).

Conclusion: Discrepancies between clinical diagnosis and necroscopic findings are commonly found in cardiac transplantation. New strategies to improve clinical diagnosis should be made, considering the results of the necropsy, to improve the treatment of heart failure by heart transplantation. (Arq Bras Cardiol. 2014; 102(5):505-509)

Keywords: Heart Transplantation; Autopsy.

Introduction

The necroscopic examination has contributed to the evolution of medical knowledge. However, the frequency at which medical centers perform necropsies has been declining in recent decades, in different series. The assumed reasons for this phenomenon are diverse and include cultural aspects, lack of authorization by families, lack of financial resources for the procedure, an aging population and less interest in necropsy findings in the elderly, a decrease in the scientific interest in the necroscopic findings and hesitation facing the possibility of medical error detection. Considering this historical trend, discrepancies between pre and post-mortem diagnoses continue to be reported, ranging from 4.1 to 49.8% of cases referred for necroscopic examination[1]. A recent study did not evaluate the diagnoses obtained through pre-mortem clinical data with the necroscopic diagnoses of patients undergoing cardiac transplantation.

This study aimed to assess patients who died after cardiac transplantation and were submitted to necropsy, analyzing the causes of death and comparing the pre- and post-mortem diagnoses.

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Methods

Retrospective study was carried out by analysis of medical records of deaths from heart transplantation that were submitted necropsy in the period 2000-2010. Clinical data for analysis of comorbidities, immunosuppression regimen, laboratory test results, clinical cause of death and cause of death at the necropsy were collected.

The pre-mortem death diagnosis was compared with the post-mortem one and then the discrepancies between the two diagnoses were classified according to Goldman et al[2] criteria adapted by Battle et al[3], while some cases were not classified[4]. The classification was as follows:

• Major discrepancies:

- class I: discrepancies in major diagnosis, with impact on survival;

- class II: discrepancies in major diagnosis, with no impact on survival;

• Minor discrepancies:

- class III: discrepancies in minor diagnoses not directly related to cause of death;

- class IV: discrepancies in minor occult diagnoses (non-

diagnosable), but with possible epidemiological or genetic importance;

• Non-discrepancy:

- class V: non-discrepant diagnoses;

• Non-classifiable cases:

- class VI: patients whose clinical or necroscopic diagnoses cannot be performed adequately.

Deaths were also differentiated as early or late, with early being those that occurred up to 1 year after transplantation and late the ones that occurred after 12 months. Discrepancies were evaluated in these two groups, verifying the causes of death.

This study was approved by the Research Ethics Committee. It was not necessary to obtain the signed free and informed consent, as this was a retrospective study based on the analysis of medical records.

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Results

From 2000 to 2010, 124 patients submitted to cardiac transplantation died. Cardiac transplantation of the 124 patients occurred from February 1987 to March 2010. Of these 124 patients, 48 were submitted to necropsy, which comprise the study sample. Figure 1 shows the case selection flowchart of the study.

The mean age was 41 years and 67% were men. The mean post-transplantation follow-up duration was 991 ± 1,728 days. The most frequent etiology of the disease (before transplantation) was chagasic heart disease. Regarding comorbidities, 44% of the patients had hypertension, 31% dyslipidemia, and 18% diabetes mellitus. Table 1 shows the general characteristics of the patients.

Table 1 - Clinical characteristics of studied patients

Characteristics	n = 48
Age (years)	41 ± 16
Male gender (%)	67
Follow-up after transplantation (days)	991 ± 1,728
Etiology (%)	
Ischemic	14.6
Idiopathic	29.2
Hypertensive	2.1
Chagas disease	31.3
Others	13
Systemic Arterial Hypertension (%)	44
Diabetes mellitus (%)	18
Dyslipidemia (%)	31
Leukocytes	8,590 ± 4,972
Sodium (mEq/L)	136 ± 4
Creatinine (mg/dL)	1.9 ± 0.6
Urea (mg/dL)	79 ± 56
Potassium (mEq/L)	4.5 ± 0.6
Hemoglobin (g/dL)	12.5 ± 2.17
Medications (%)	
Cyclosporine	50
Tacrolimus	14.6
Mycophenolate mofetil	54
Corticosteroids	77
Azathioprine	29.2
Sirolimus	14.6

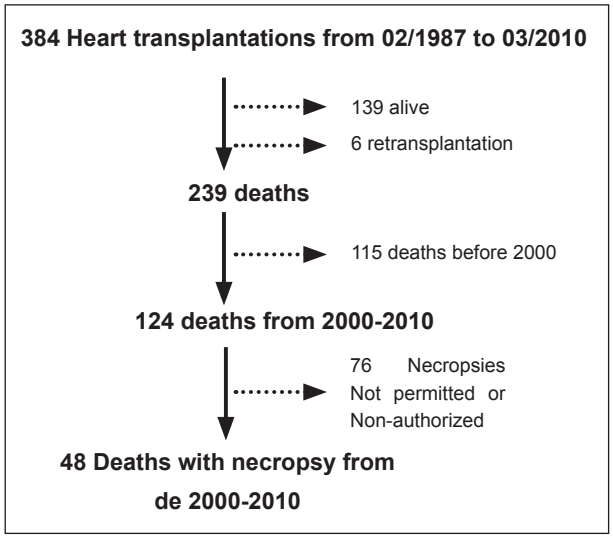

Figure 1 - *Flowchart of case selection.*

Of the 48 analyzed cases, 29 (60.4 %) had concordant clinical and necroscopic diagnoses (class V), 16 (33.3 %) had discordant diagnoses and three (6.3%) had an unclear diagnosis (class VI). Among the discordant ones, 15 (31.3%) had possible impact on survival (class I) and one (2.1%) had no impact on survival (class II). The main clinical misdiagnosis was infection, with five cases (26.7% of discordant ones), followed by hyperacute rejection, with four cases (20% of discordant ones) and pulmonary thromboembolism with three cases (13.3% of discordant ones). Figure 2 shows the chart distribution of necropsies, based on the classification of discrepancies. Figure 3 and Table 2 compare the clinical and necroscopic diagnoses of class I discordant cases.

A total of 62.5 % (30 cases) were classified as early deaths and 37.5 % as late ones (18 cases). Among the early cases, 56% were concordant with impact on survival (class V), 33% discordant with impact on survival (class I),

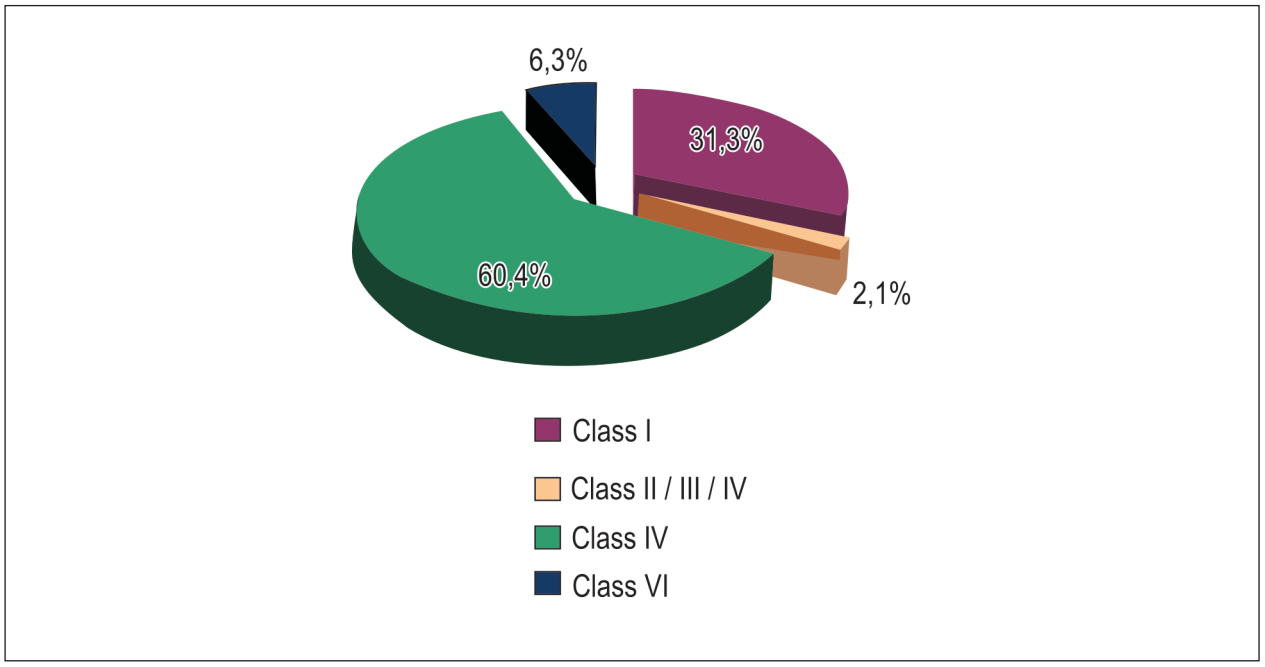

Figure 2 - *Distribution of discrepancies between clinical and necroscopic diagnoses.*

3% discordant with no impact on survival (class II) and 6 % had unclear diagnoses (Class VI). Among the late, 67% were concordant with impact on survival (class V), 28% discordant with impact on survival (class I) and 5.6% had unclear diagnoses (Class VI).

The causes of death verified at the necropsies were acute graft dysfunction (22.9%), acute rejection (20.8 %), infection (18.8%), Graft Vascular Disease (GVD-16.7%), other causes (14.6%) and unknown causes (6.3%).

In the group classified as early death, 37 % of deaths were due to acute graft dysfunction, 20% acute humoral rejection, 16.7% septic shock, 16.7% from other causes, and 6% of unknown causes.

In the late group, 45% of deaths were due to GVD, 17% to acute cellular rejection, 11% to septic shock, 22% from other causes and 5% of unknown causes.

Discussion

Our study showed a significant frequency of discrepancies between clinical and necroscopic diagnoses of the cause of death, most often with a possible impact on survival.

In the literature, no recent studies were found comparing the clinical and necroscopic causes of death in patients undergoing cardiac transplantation, making this work a current tool for information analysis.

On the other hand, the rate of discordance in the present sample, on average, was higher than that observed in other series of patients unrelated to heart transplantation. Discrepancies values of 7.5 to 23 %, classified as major, were found in patients admitted to the intensive care unit, with 11-13% for minor discrepancies[5,6]. For patients admitted to general hospitals, there were 6-37 % of major discrepancies and 25-28 % of minor ones[7-9].

The most difficult necroscopic diagnosis to be clinically hypothesized was acute graft dysfunction. In this series, it was misdiagnosed as hyperacute rejection, hemorrhagic shock and septic shock. These data show the difficulty to confirm this diagnosis in clinical practice, as it depends on situations related to the perioperative period (the donor's conditions, time of ischemia, myocardial protection and the recipient's prior pulmonary hypertension) and the degree of suspicion of the attending physician, as there is no specific marker for the diagnosis.

Another premortem unsuspected necroscopic diagnosis was GVD. This was confused with other conditions that lead to ventricular dysfunction with cellular rejection and pulmonary thromboembolism. Although GVD is one of the main late causes of post-transplantation death[10] a dose of clinical suspicion is also needed to initiate the appropriate diagnostic method.

Finally, another common diagnostic error was acute humoral rejection, which is known by its diagnostic difficulties, requiring advanced immunohistological methods, such as immunofluorescence and immunoperoxidase, in addition to the fact that the patient needs to be capable of being submitted to endomyocardial biopsy procedure.

Taking into account only the necroscopic cause of death, the data from this study are similar to those in the literature[11,12], with emphasis on acute graft dysfunction, infection, rejection and GVD. Separating the deaths in early and late cases, acute graft dysfunction and GVD stood out, respectively.

Regarding the cause of cardiomyopathy that led to transplantation, this sample differs from that found in the

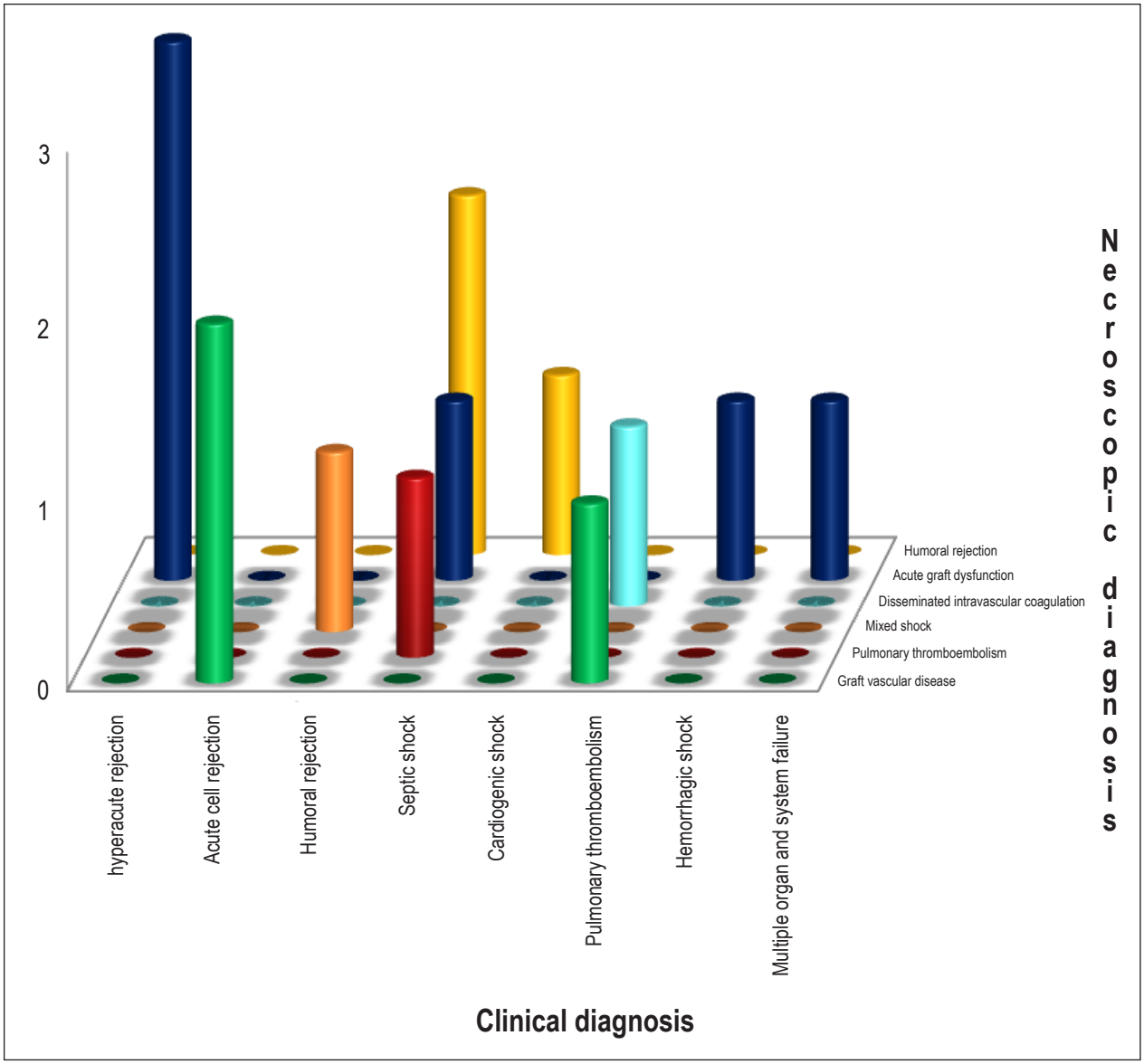

Figure 3 - *Comparison between clinical and necroscopic diagnoses of class I discordant cases.*

Table 2 - Comparison between clinical and necroscopic diagnoses of class I discordant cases

		Clinical Diagnosis							
		HR	ACR	AHR	SS	CS	PTE	HS	MOSF
Necroscopic Diagnosis	GVD		2				1		
	PTE				1				
	MS			1					
	DIC						1		
	AGD	3			1			1	1
	AHR				2	1			

HR: hyperacute rejection; ACR: acute cellular rejection; AHR: acute humoral rejection, SS: septic shock, CS: cardiogenic shock; PTE: pulmonary thromboembolism, HS: Hemorrhagic shock; MOSF: multiple organ and system failure; GVD: graft vascular disease, MS: mixed shock, DIC: disseminated intravascular coagulation; AGD: acute graft dysfunction.

International Society of Heart and Lung Transplantation Annual Report, 2012. While the most prevalent etiology in this study was Chagas' disease, followed by idiopathic dilated cardiomyopathy, the global data showed the most prevalent etiology was idiopathic dilated cardiomyopathy (54 %), followed by ischemic heart disease (37 %)[10]. This difference is due to the prevalence of Chagas disease in our country, unlike what occurs in Europe and North America.

Among the limitations of this study is sample size, which reflects the decrease in the number of necropsies in recent decades, as mentioned before. Consequently, only 38.7 % of deaths between 2000 and 2010 were submitted to necropsy and were included in the study, which may interfere with the results.

Moreover, the analysis of records may not accurately reveal the clinical cause of death, as factors such as incomplete filling out of medical records and difficulties in understanding older records, which were not yet electronic, can interfere with the impression of the presumed clinical cause of death.

Conclusion

Discrepancies between clinical diagnosis and necroscopic findings are commonly found in cardiac transplantation. New strategies to improve clinical diagnosis should be made, considering necroscopic results to improve the treatment of heart failure by heart transplantation.

Author contributions

Conception and design of the research: Ayub-Ferreira SM, Bocchi EA; Acquisition of data: Valette TN, Ayub-Ferreira SM, Benvenuti LA, Issa VS, Bacal F, Chizzola PR, Souza GEC, Fiorelli AI, Santos RHB; Analysis and interpretation of the data: Valette TN, Ayub-Ferreira SM, Benvenuti LA, Issa VS, Bacal F, Chizzola PR, Souza GEC, Fiorelli AI, Santos RHB; Statistical analysis: Ayub-Ferreira SM; Writing of the manuscript: Valette TN; Critical revision of the manuscript for intellectual content: Ayub-Ferreira SM, Benvenuti LA, Bocchi EA; Supervision / as principal investigator: Bocchi EA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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