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Original Article

Pathological assessment of end-stage heart failure in explanted hearts in correlation with hemodynamics in patients undergoing orthotopic heart transplantation

Giulia Ottaviani [a,b,*], Rajko Radovancevic [c], Biswajit Kar [c], Igor Gregoric [c], L. Maximilian Buja [a]

[a] Department of Pathology and Laboratory Medicine, The University of Texas Health Science Center at Houston, Houston, TX, USA
[b] "Lino Rossi" Research Center for the study and prevention of unexpected perinatal death and sudden infant death syndrome (SIDS); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[c] Center for Advanced Heart Failure, Memorial Hermann Heart and Vascular Institute, The University of Texas Health Science Center at Houston, Houston, TX, USA

ABSTRACT

Background: To date, there has been little research, if any, on the pathological correlates of end-stage heart failure in the explanted hearts of orthotopic heart transplant (OHT) recipients in correlation with the patients' hemodynamics. We sought to compare the gross and histopathological parameters in hearts explanted—native or previously transplanted—from patients with end-stage heart failure with the clinical hemodynamics parameters at the time of OHT.
Methods: Forty patients undergoing OHT were enrolled in this study and divided into two groups according to whether they suffered from ischemic (ICMP) or nonischemic cardiomyopathy (NICMP). All study patients were treated with OHT for end-stage heart failure at The University of Texas Health Science Center at Houston. The pathological investigations of the hearts were focused on the study of the underlying cause of heart failure leading the patient to OHT; on the quantification of the extent and severity of fibrosis, hypertrophy, and myocytolysis; and on validating a semiquantitative grading scale. Analyses of multiple sections of the explanted hearts were carried out. The heart weights were recorded and compared with the grades of fibrosis, hypertrophy of cardiomyocytes, and myocytolysis. The grades of fibrosis, hypertrophy, and myocytolysis were evaluated in right and left ventricles and atria (with areas of confluent infarction excluded). The pathological parameters were correlated with the patients' clinical parameters.
Results: Twenty-two patients (20 men, 2 women, mean age±S.E.M., 62.3±2.2 years) suffered from ICMP and 18 patients (9 men, 9 women, mean age±S.E.M., 56.3±2.8 years) from NICMP. All the clinical and pathological measured variables were comparable between the two groups, except for pulmonary vascular resistance, which was higher in the NICMP group of patients, and the grade of myocytolysis, which was significantly higher in the ICMP vs. NICMP group. Most of the clinical and pathological variables were overall linearly correlated.
Conclusions: Both ICMP and NICMP groups of end-stage heart failure requiring OHT presented high grades of fibrosis, hypertrophy, and myocytolysis. Heart failure is the final common pathway of a variety of primary cardiovascular diseases regardless of the ischemic or nonischemic nature of the cardiomyopathy.

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1. Introduction

Heart failure (HF) is defined as a complex clinical syndrome of symptoms and signs that suggest impairment of the heart as a pump supporting physiological circulation caused by structural or functional abnormalities of the heart [1]. According to the most recent report from the American Heart Association [2], at the age of 40, in both men and women free of disease at baseline, the remaining lifetime risk of developing HF is 20%, and HF accounts for 36% of cardiovascular disease deaths. It has been projected that, in the United States, the prevalence of HF will increase 46% from 2012 to 2030. Although survival after HF diagnosis has improved over time, the death rate remains high, and about 50% of the patients suffering from HF die within 5 years of diagnosis [2].

Treatment of patients suffering from severe HF by orthotopic heart transplantation (OHT) has been proven to significantly improve their survival rate and quality of life. The heart transplant recipients have a 5-year survival after heart transplantation of 77.5% if males and 75.6% if females [2].

According to the International Society for Heart and Lung Transplantation Registry Quarterly Reports for Heart in North America [3], in 2015, the two most common etiologies of HF that have led patients to

heart transplantation are cardiomyopathy and coronary artery disease, which account respectively for 54.2% and 28.1% of cases. Less common causes treated with heart transplantation include congenital heart disease (7%), retransplant/graft failure (2.8%), and valvular heart disease (2.3%). Pathological examination of the explanted hearts has a role in confirming the clinical diagnosis of the type of cardiomyopathy and, in some cases, yielding a more accurate diagnosis [4].

Recently, to quantify the extent and severity of fibrosis and hypertrophy in HF, a semiquantitative grading scale was developed in order to identify pathological features useful in predicting clinical outcome [5]. However, to date, there has been little research, if any, on the pathological parameters of end-stage HF in the explanted hearts of the OHT recipients in correlation with the patient's hemodynamics. In particular, no clinicopathological guidelines are currently available to evaluate the deterioration of myocardial function in HF as a marker of the clinical hemodynamic status.

The purpose of this study was to evaluate clinical and pathological parameters in hearts explanted from patients with end-stage HF—either native or previously transplanted hearts—at the time of OHT, comparing the HF from ischemic cardiomyopathy (ICMP) versus nonischemic cardiomyopathy (NICMP). We also sought to validate a semiquantitative grading scale in order to quantify the extent and severity of fibrosis, hypertrophy, and myocytolysis in HF hearts.

2. Patients and methods

2.1. Study population and data collection

The institutional review board at The University of Texas Health Science Center at Houston, in agreement with Memorial Hermann Healthcare System, Texas Medical Center, reviewed and approved the research protocol.

All study patients were treated with OHT for end-stage HF at the Advanced Heart Failure Center at the Memorial Hermann–Texas Medical Center Hospital and The University of Texas Health Science Center at Houston from October 2012 through December 2013. Patients were eligible for this study if they met the following criteria: a diagnosis of end-stage HF, recipients of OHT, age older than 18 years, younger than 80 years, and diagnosis and treatment at our institution. OHT recipients who previously underwent SynCardia procedure, a prior heart transplantation, or any other procedures prior to the OHT were also included in this study.

A total of 40 patients undergoing OHT were retrospectively enrolled to the study. The participants were divided into two groups based on clinical and pathological criteria [6–8], as follows:

1. Ischemic cardiomyopathy OHT recipients: 22 patients
2. NICMP OHT recipients: 18 patients.

Electronic and hard-copy medical records were reviewed to obtain pertinent information about patients' history, treatments, and outcomes. Heart failure etiology and underlying comorbidities were documented for all patients. The collected information included the following: demographic data, i.e., age, age at diagnosis, race, gender, socio-occupational status, marital status; medical history including family history, review of systems, height, weight, body mass index (BMI), body surface area (BSA), smoke habit, electrolytes, and lipid profile; hemodynamic data including blood pressure, ejection fraction, pulmonary capillary wedge pressure (PCWP), right atrial pressure/central venous pressure, systolic pulmonary arterial pressure (PAP), diastolic PAP, mean PAP, systolic right ventricular pressure (RVP), diastolic RVP, mean RVP, cardiac index (CI), cardiac output (CO), and pulmonary vascular resistance (PVR); description of all treatments including surgical data and detailed OHT procedure description; echocardiographic reports; and pathology reports of the explanted heart from the 40 patients with end-stage HF—either native or previously transplanted hearts—at the time of OHT.

2.2. Pathological assessment

A total of 40 explanted hearts—either native or previously transplanted hearts—were obtained from patients undergoing OHT. The gross and histopathological analyses, including, in particular, the severity and extent of fibrosis, hypertrophy, and myocytolysis, were examined in blinded fashion without initial knowledge of the cause of HF, age, or other clinicopathological information of the patients undergoing OHT. Only after the histopathological assessment of each explanted heart had been completed were the pathological findings matched with the corresponding patients' medical records.

Each heart was systematically weighted, inspected, measured, and examined for pathological changes in the left ventricle (LV), right ventricle (RV), ventricular septum (VS), atria (A) pericardium, endocardium, and coronary arteries. Multiple samples of the myocardium and coronary arteries were fixed in formaldehyde, embedded in paraffin, and stained with hematoxylin and eosin (H&E) and Masson's trichromic stains.

The histopathological investigations included the study of the underlying cause of HF leading the patient to the OHT, and the quantification of the extent and severity of fibrosis and hypertrophy, validating a semiquantitative grading scale reported by Segura et al. [5].

Briefly, each myocardial sample was scored histopathologically with a grade of 0=negative; 1=mild (occasional foci/scars); 2=moderate (multiple foci/scars); or 3=severe (extensive) to evaluate the extent of reactive (interstitial/perivascular) fibrosis and replacement fibrosis, hypertrophy, and myocytolysis.

The fibrosis combined score was the sum of the grades of reactive and replacement fibrosis, ranging from 0 (absent) to 6 (severe) fibrosis.

Hypertrophy was identified as an increase in diameter of cardiomyocytes (CMCs) as well as increase in size and hyperchromasia of the CMC nuclei. Degree of CMC hypertrophy was graded as 0=negative, 1=mild (occasional foci). 2=moderate (multiple foci), or 3=severe (extensive, diffuse).

In addition to the previously reported grading system for pathological assessment of HF [5,9,10], colliquative myocytolysis was identified as CMC showing varying stages of vacuolization and loss of myofibrils; its extent and/or severity was graded as 0=negative, 1=mild, 2=moderate, or 3=severe. The myocardium being analyzed excluded areas of confluent infarction. The LV, RV, VS, and A of each heart were given a total score for fibrosis, CMC hypertrophy, and myocytolysis.

The histopathological analyses of the explanted hearts were carried out on multiple sections, representative for each hearts' segments, to identify and quantify the grade of fibrosis—reactive (interstitial/perivascular) and replacement—CMC hypertrophy, and myocytolysis. The average number of specimens and inherent histological sections examined from LV, RV, VS, and A was, respectively, 2.1, 1.1, 1.15, and 0.6, for an average total of five specimens/sections analyzed for each heart.

The extension of fibrosis—interstitial/perivascular and replacement—hypertrophy, and myocytolysis were compared in LV, RV, VS, and A. The pathological parameters were correlated with the patients' clinical features and hemodynamics in order to identify the clinicopathological correlations for the two groups of OHT recipients: those suffering from ICMP versus NICMP.

2.3. Statistical analysis

Quantitative data were expressed as means±S.E.M. The significance of differences between group parameters was evaluated by Student's t test, χ^2 test, or Fisher's test. In case of skewed distribution, a nonparametric Whitney rank sum test was used. One-way analysis of variance was used for quantifying and partitioning variance between groups. The relationship between variables was analyzed by Pearson correlation. Statistics were compiled and plotted using SigmaPlot (version 13; Systat Software Inc., Chicago, IL, USA). The selected level of significance was $P<.05$, two-tailed.