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ORIGINAL ARTICLE

Optimizing risk stratification in heart failure and the selection of candidates for heart transplantation

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KEYWORDS
Cardiopulmonary exercise testing;
Heart failure;
Heart transplantation;
Peak oxygen consumption;
Risk stratification;
Ventilatory efficiency slope

Abstract
Introduction and Aims: Selecting patients for heart transplantation is challenging. We aimed to identify the most important risk predictors in heart failure and an approach to optimize the selection of candidates for heart transplantation.
Methods: Ambulatory patients followed in our center with symptomatic heart failure and left ventricular ejection fraction ≤40% prospectively underwent a comprehensive baseline assessment including clinical, laboratory, electrocardiographic, echocardiographic, and cardiopulmonary exercise testing parameters. All patients were followed for 60 months. The combined endpoint was cardiac death, urgent heart transplantation or need for mechanical circulatory support, up to 36 months.
Results: In the 263 enrolled patients (75% male, age 54±12 years), 54 events occurred. The independent predictors of adverse outcome were ventilatory efficiency (VE/VCO_2) slope (HR 1.14, 95% CI 1.11-1.18), creatinine level (HR 2.23, 95% CI 1.14-4.36), and left ventricular ejection fraction (HR 0.96, 95% CI 0.93-0.99). VE/VCO_2 slope was the most accurate risk predictor at any follow-up time analyzed (up to 60 months). The threshold of 39.0 yielded high specificity (97%), discriminated a worse or better prognosis than that reported for post-heart transplantation, and outperformed peak oxygen consumption thresholds of 10.0 or 12.0 ml/kg/min. For low-risk patients (VE/VCO_2 slope <39.0), sodium and creatinine levels and variations in end-tidal carbon dioxide partial pressure on exercise identified those with excellent prognosis.
Conclusions: VE/VCO_2 slope was the most accurate parameter for risk stratification in patients with heart failure and reduced ejection fraction. Those with VE/VCO_2 slope ≥39.0 may benefit from heart transplantation.
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PALAVRAS-CHAVE
Prova de esforço cardiorrespiratória;
Insuficiência cardíaca;
Transplantação cardíaca;
Consumo de oxigénio de pico;
Estratificação de risco;
Declive da eficiência ventilatória

Aprimoramento da estratificação de risco na insuficiência cardíaca e da seleção de candidatos a transplantação cardíaca

Resumo
Introdução e objetivos: A seleção de doentes para transplantação cardíaca é difícil. Procurámos identificar os preditores de risco mais relevantes na insuficiência cardíaca e uma abordagem para aprimorar a seleção de candidatos a transplantação.
Métodos: Doentes sintomáticos com insuficiência cardíaca e fração de ejeção ventricular esquerda $\leq$ 40%, ambulatórios, seguidos no nosso centro, completaram prospetivamente uma avaliação basal abrangente, inclusive parâmetros clínicos, laboratoriais, eletrocardiográficos, ecocardiográficos e prova de esforço cardiorrespiratória; foram seguidos por 60 meses. *Endpoint* combinado: morte de causa cardíaca, transplantação urgente ou necessidade de assistência mecânica, até aos 36 meses.
Resultados: Nos 263 doentes incluídos (75% homens, 54 $\pm$12 anos) ocorreram 54 eventos. O declive da eficiência ventilatória (declive VE/VCO2) (HR 1,14, IC 95% 1,11-1,18), a creatinina (HR 2,23, IC 95% 1,14-4,36) e a fração de ejeção ventricular esquerda (HR 0,96, IC 95% 0,93-0,99) foram preditores independentes de eventos. O declive VE/VCO2 foi o melhor preditor em qualquer período analisado (até aos 60 meses). O limiar 39,0 apresentou elevada especificidade (97%), discriminou um prognóstico melhor ou pior do que o reportado no pós-transplante cardíaco e superou os limiares 10,0 ou 12,0 mL/kg/min de consumo de oxigénio de pico. Em doentes de baixo risco (declive VE/VCO2 <39,0) o sódio, a creatinina e a variação no exercício da pressão parcial de dióxido de carbono expirado identificaram aqueles com excelente pronóstico.
Conclusões: O declive VE/VCO2 foi o melhor preditor de risco em doentes com insuficiência cardíaca e fração de ejeção reduzida. Doentes com declive VE/VCO2 $\geq$39,0 poderão beneficiar de transplantação cardíaca.
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List of abbreviations

Δ $PetCO_2$	variation of end-tidal carbon dioxide partial pressure
CI	confidence interval
CPET	cardiopulmonary exercise testing
HF	heart failure
HTX	heart transplantation
IDI	integrated discrimination improvement
ISHLT	International Society for Heart and Lung Transplantation
LVEF	left ventricular ejection fraction
NRI	net reclassification improvement
VO_2 max	peak oxygen consumption
VE/VCO_2 slope	ventilatory efficiency slope

Introduction

A wide variety of predictors of adverse outcome in heart failure (HF) have been described and it can be difficult to choose the most appropriate tools in clinical practice.[1,2] Risk stratification should be as accurate as possible, particularly when selecting patients for heart transplantation (HTX), as procedure-related morbidity and mortality are non-negligible and it cannot be offered to all candidates due to the shortage of donors.[3] For ambulatory patients, both the American Heart Association and the International Society for Heart and Lung Transplantation (ISHLT) recommend the use of peak oxygen consumption (VO_2 max) achieved in cardiopulmonary exercise testing (CPET), with optional use of risk scores in gray zones; VO_2 max <10-12 ml/kg/min is considered a listing criterion for HTX.[4,5] We believe that risk stratification and referral criteria for HTX can be improved using simple parameters. Additional CPET variables have shown to be accurate for risk stratification, particularly the ventilatory efficiency (VE/VCO_2) slope.[6–8] However, most studies that highlight the value of ergospirometric parameters have focused mainly on clinical and CPET data, without comprehensive assessment of other parameters, and few had long-term follow-up.[6–9] Identifying robust criteria for selecting patients for HTX should be based on a comprehensive prospective clinical and complementary assessment.

Our aims were to identify the most accurate predictors of adverse events in non-transplanted patients with HF and an approach to optimize the selection of patients for HTX.

Methods

The investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the study protocol.

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