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Clinical Research

Cerebral Hemodynamics During Exercise and Recovery in Heart Transplant Recipients

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ABSTRACT

Background: The aims of this work were (1) to compare cerebral oxygenation-perfusion (COP), central hemodynamics, and peak oxygen uptake ($\dot{V}O_2$peak) in heart transplant recipients (HTRs) vs age-matched healthy controls (AMHCs) during exercise and recovery and (2) to study the relationships between COP, central hemodynamics, and $\dot{V}O_2$peak in HTRs and AMHCs.

Methods: Twenty-six HTRs (3 women) and 27 AMHCs (5 women) were recruited. Maximal cardiopulmonary function (gas exchange analysis), cardiac hemodynamics (impedance cardiography), and left frontal COP (near-infrared spectroscopy) were measured continuously during and after a maximal ergocycle (Ergoline 800S, Bitz, Germany) test.

Results: Compared with AMHCs, HTRs had lower $\dot{V}O_2$peak, maximal cardiac index (CImax), and maximal ventilatory variables ($P < 0.05$).

RÉSUMÉ

Introduction : Les objectifs du présent travail étaient de : 1) comparer la perfusion et l'oxygénation cérébrale (POC), l'hémodynamie centrale et le prélèvement d'oxygène au pic (VO_2 pic) chez les receveurs de transplantation cardiaque (RTC) *vs* les témoins en santé appariés selon l'âge (TSAA) durant l'effort et à la récupération; 2) étudier les relations entre la POC, l'hémodynamie centrale et la VO_2 pic chez les RTC et les TSAA.

Méthodes : Vingt-six RTC (dont 3 femmes) et 27 TSAA (dont 5 femmes) étaient recrutés. La capacité cardiorespiratoire maximale (analyse des échanges gazeux), l'hémodynamie cardiaque (bioimpédance cardiaque) et la POC frontale gauche (spectroscopie proche de l'infrarouge) étaient continuellement mesurées pendant et après une épreuve d'effort maximal sur ergocycle (Ergoline 800-S, Bitz, Allemagne).

Heart transplantation is an accepted therapeutic intervention for select patients with advanced heart failure. This intervention improves their survival,[1] quality of life, and ability to return to work.[2] However, peak oxygen uptake ($\dot{V}O_2$peak) remains 40%-60% lower in heart transplant recipients (HTRs) compared with healthy age-matched controls.[3-5] In HTRs, central factors for this limitation during exercise include chronotropic incompetence resulting from cardiac denervation, diastolic dysfunction,[3-6] and a 30%-40% reduction of maximal cardiac output.[7] In addition, peripheral vascular factors also limit $\dot{V}O_2$peak in HTRs,[4,5,7] with negative vascular effects from immunosuppressive agents or corticosteroids, or both.[7] Previous studies in patients with valvular disease demonstrated lower cerebral oxygenation (assessed by near-infrared spectroscopy [NIRS]), compared with healthy controls, during maximal incremental exercise, cerebral oxygenation being related to $\dot{V}O_2$peak and ventilatory threshold.[8] Similarly, patients with chronic heart failure showed lower cerebral oxygenation-perfusion

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COP was lower during exercise (oxyhemoglobin [ΔO_2Hb], 50% and 75% of $\dot{V}O_2$peak, total hemoglobin [ΔtHb], 100% of $\dot{V}O_2$peak; $P < 0.05$), and recovery in HTRs (ΔO_2Hb, minutes 2-5; ΔtHb, minutes 1-5; $P < 0.05$) compared with AMHCs. End-tidal pressure of CO_2 was lower during exercise compared with that in AMHCs ($P < 0.0001$). In HTRs, CImax was positively correlated with exercise cerebral hemodynamics ($R = 0.54$-0.60; $P < 0.01$).

Conclusions: In HTRs, COP was reduced during exercise and recovery compared with that in AMHCs, potentially because of a combination of blunted cerebral vasodilation by CO_2, cerebrovascular dysfunction, reduced cardiac function, and medication. The impaired $\dot{V}O_2$peak observed in HTRs was mainly caused by reduced maximal ventilation and CI. In HTRs, COP is impaired and is correlated with cardiac function, potentially impacting cognitive function. Therefore, we need to study which interventions (eg, exercise training) are most effective for improving or normalizing (or both) COP during and after exercise in HTRs.

Résultats : Comparativement aux TSAA, les RTC avaient un $\dot{V}o_2$ pic, un index cardiaque maximal (ICmax) et des variables ventilatoires maximales ($P < 0,05$) plus faibles. La POC était plus basse au cours de l'effort (oxyhémoglobine [ΔO_2Hb], 50 % et 75 % de la $\dot{V}o_2$ maximale, hémoglobine totale [ΔtHb], 100 % de la $\dot{V}o_2$ pic; $P < 0,05$) et de la récupération chez les RTC (ΔO_2Hb, minutes 2-5; ΔtHb, minutes 1-5; $P < 0,05$) comparativement aux TSAA. La pression télé-expiratoire en CO_2 était plus faible au cours de l'effort comparativement à celle des TSAA ($P < 0,0001$). Chez les RTC, l'ICmax était positivement corrélé avec l'hémodynamie cérébrale à l'effort ($R = 0,54$-$0,60$; $P < 0,01$).

Conclusions : Chez les RTC, la POC était plus basse que celle des TSAA au cours de l'effort et de la récupération, possiblement en raison de la combinaison de la vasodilatation cérébrale par le CO_2 réduite, du dysfonctionnement cérébrovasculaire, de la diminution du fonctionnement cardiaque et de la médication. La détérioration de la $\dot{V}o_2$ pic observée chez les RTC était principalement causée par la diminution de la ventilation et de l'IC maximaux. Chez les RTC, la POC est détériorée et corrélée avec le fonctionnement cardiaque, et pourrait avoir des répercussions sur la fonction cognitive. Par conséquent, nous avons besoin d'étudier quelles interventions (p. ex. l'entraînement à l'effort) sont plus efficaces pour améliorer ou normaliser (ou les deux) la POC pendant et après l'effort chez les RTC.

(COP) (by NIRS) during exercise and recovery compared with healthy controls,[9,10] with cerebral oxygenation being related to $\dot{V}O_2$peak and resting cardiac function (left ventricular ejection fraction percentage).[9,10] Finally, in patients with coronary heart disease, decreased cerebral oxygenation was shown to be an independent predictor of future cardiovascular death and to be related in part to cerebral arteriosclerosis.[11,12] In addition, studies with small sample sizes have demonstrated restored cerebral blood flow (at rest, measured by echography) after transplantation.[13-15] Cognitive function is also improved after transplantation but may not be fully restored in the long term compared with that in AMHCs,[16] potentially affecting daily activities and quality of life. At present, it is unknown if HTRs have impaired COP during and after exercise (vs AMHCs) and if exercise (including daily activities) would chronically expose them to reduced cerebral oxygenation. Additionally, it is unclear if a higher fitness level ($\dot{V}O_2$peak) and preserved central hemodynamic function are protective factors that are associated with better COP during and after exercise.

Therefore, the aims of this work were (1) to compare COP, central hemodynamics, and $\dot{V}O_2$peak in HTRs vs age-matched healthy controls (AMHCs) during exercise and recovery and (2) to study the relationships between COP, central hemodynamic, and $\dot{V}O_2$peak in HTRs and AMHCs.

Methods

Patients

A total of 53 adults were recruited from the Cardiovascular Prevention and Rehabilitation Centre of the Montreal Heart Institute, including 26 HTRs (age, 27-76 years) and 27 AMHCs (age, 26-85 years). For AMHCs, inclusion criteria were age > 18 years, no evidence of coronary heart disease, ability to perform a maximal incremental exercise test, and at most 1 of the following cardiovascular risk factors: dyslipidemias, hypertension, overweight, and treatment medications.[17-19] The exclusion criteria for AMHCs were recent acute coronary syndrome (<3 months), significant resting electrocardiographic abnormality, history of ventricular arrhythmias or congestive heart failure, stroke, uncontrolled hypertension, recent coronary bypass surgery (<3 months), recent percutaneous transluminal coronary angioplasty (<6 months), left ventricular ejection fraction < 45%, pacemaker or implantable cardioverter defibrillator, recent modification of medication (<2 weeks), and musculoskeletal conditions making exercise on an ergocycle difficult or contraindicated. In AMHCs, 1 participant was treated for dyslipidemia with a statin drug and 1 participant was treated for hypertension with a calcium channel blocker (Supplemental Table S1). In HTRs, inclusion criteria were age > 18 years, heart transplantation, stable clinical condition including optimal medication and with no cardiac allograft rejection, and ability to perform a maximal incremental exercise test.[17-19] All participants provided written informed consent, and the protocol was approved by the local ethics committee. All participants underwent a baseline evaluation that included a medical history and a physical examination, with measurement of height and weight, body composition (body composition analyzer functioning with bioimpedance principle, model BC418; Tanita, Tokyo, Japan) and fasting blood sample (glucose and lipid profile).[18,19] All participants performed a maximal cardiopulmonary exercise test (CPET) with gas exchange analysis on an ergocycle.[18] During CPET, COP (near-infra red spectroscopy) and central hemodynamics (impedance cardiography) were measured continuously.[17,20]

Maximal cardiopulmonary exercise testing

This test was performed on an ergocycle (Ergoline 800S, Bitz, Germany), with an individualized protocol that included a 3-minute warm up at 20 W, followed by a power increase of 10 to 20 W/min until exhaustion at a pedaling speed > 60 rpm.[17,18] Gas exchange was measured continuously at rest,