Désadaptations cardiovasculaires à la microgravité : techniques avancées pour améliorer la mesure et l'évaluation du risque cardiovaculaire induit par les vols spatiaux pour les équipages de longue durée

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THÈSE

Pour obtenir le diplôme de doctorat

Spécialité RECHERCHE CLINIQUE, INNOVATION TECHNOLOGIQUE, SANTE PUBLIQUE

Préparée au sein de l'Université de Caen Normandie

Désadaptations cardiovasculaires à la microgravité:techniques avancées pour améliorer la mesure et l'évaluation du risque cardiovaculaire induit par les vols spatiaux pour les équipages de longue durée.

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Thèse soutenue publiquement le 16/12/2019 devant le jury composé de		
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UNIVERSITÉ CAEN NORMANDIE

497 NBISE Normande de Biologie Intégrative, Santé, Environnement

COMETE UMR 1075 UNICAEN / INSERM

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Chapitre 1

Introduction

Impact du vol spatial sur les systèmes physiologiques :

Nos travaux actuels portent principalement sur la désadaptation du système cardiovasculaire lors des vols spatiaux. D'autres systèmes physiologiques tels que les os, le métabolisme et le cerveau sont tous affectés par les séjours longue durée en microgravité. Alors que les agences prévoient des missions de longue durée au-delà de l'orbite terrestre basse, la dynamique et la restauration de ces changements deviennent particulierement important. Vico et ses collègues (Vico et al., 2000) ont montré des taux de déminéralisation osseuse spectaculaires dans les os porteurs de la jambe, qui ne se ont pas restaurés immédiatement après vol et qui ont même continué à diminuer pendant des mois. Les auteurs postulent que, chez certains astronautes, la fragilité osseuse peut tout simplement ne jamais se rétablir au cours de leur vie. Deux articles récents indiquent que des maladies cardio-métaboliques peuvent se développer pendant le vol spatial et le décubitus longue durée. Le développement du diabète de type 2 dans ces mêmes conditions est une préoccupation réelle malgré les contre-mesures de type exercice effectuées (Heer et al., 2014; Hughson et al., 2016). Une mauvaise alimentation et de longues périodes d'inactivité entre les exercices sont des facteurs de causalité suggérés.

En plus des os, et du métabolisme glucidique, les structures/organes cervicaux et cérébraux des astronautes sont affectées en vol longue durée. Arbeille et al ont montré un engorgement très important des veines Jugulaires pendant toute la durée de vols spatial de 6 mois ainsi qu'une augmentation de la vitesse dans les veines intracérébrales qui suggère une compression de ces dernière suite aune augmentation de pression intra crânienne (Arbeille, Provost, & Zuj, 2016; Roberts et al., 2017)ont récemment démontré après un vol de 6 mois un déplacement vertical significatif et une compression générale des tissus et vaisseaux cérébraux à l'intérieur des crânes d'astronautes après des missions de six mois. Les IRM ont également montré un rétrécissement important des sillon cérébraux après un vol spatial de longue durée. L'altération de la vision d'un sous-groupe de membres d'équipage (env 60%) a convaincu la NASA d'examiner en vol et post vol les structures internes de l'œil, y compris l'œdème du disque optique, la taille et la morphologie du nerf optique afin de mieux appréhender l'impact du transfert liquidien sur les structures oculaires et cérébrales. Les changements de vision sont associés à un profil génétique : tous les équipages ayant des problèmes de vision et un œdème de disque optique lors d'un vol spatial portent le gène de la variante phénotypique du métabolisme du 1-carbone (Zwart et al., 2017).

En vol et en décubitus de longue durée on observe une atrophie myocardique, une diminution des volumes cardiaques et l'action de pompage est moins efficace (Arbeille et al., 1987; M. Bungo & Charles, 1985; Perhonen, Franco, et al., 2001) ce qui nécessite une pratique suffisante de contre-mesures comme l'exercice aérobique.

Les artères deviennent plus épaisses et plus rigides (Arbeille, Provost, et al., 2016; Hughson et al., 2016) avec des impacts potentiels sur la cognition (Iulita, Noriega de la Colina, & Girouard, 2018; Pase et al., 2016). L'épaisseur de la paroi artérielle est également augmentée en confinement de longue durée (MARS 500 jours, CELSS 180 jours), ce qui indique que l'épaississement de la paroi artérielle n'est pas lié uniquement a la microgravité mais pourrait peut-être être favorisé par le stress environnemental present en vol spatial confinement, via un processus inflammatoire. (Arbeille, Provost, Vincent, & Aubert, 2014) (Yuan et al., 2019).

Comme mentionné ci-dessus, les agences spatiales ont réalisé depuis 1984 que les membres d'équipage doivent s'imposer d'avoir une activité physique en orbite pour atténuer le déconditionnement cardiaque (Arbeille et al., 1987). Actuellement, tous les astronautes font de l'exercice lorsqu'ils se trouvent sur la Station spatiale internationale, mais la quantité, la durée et le type d'exercice varient selon les équipages et les conseils de leur Médecins au sol. Le matériel utilisé comprend : le tapis roulant de course à pied T avec des bandes élastiques de tension fixée aux membres, un ergomètre et un dispositif d'exercice résistif ARED. Pour les expériences de simulation, les procédures sont différentes. D'une part, il n'y a pas de contre-mesure « exercice » dans les études d'immersion sèche d'autre part, le HDTBR offre de nombreuses possibilités en matière de contre-mesures, dont les exercices de résistance en position allongée (D. K. Greaves, Arbeille, & Hughson, 2007; Rittweger et al., 2006), le tapis roulant de course a pied en position allongé (D. K. Greaves et al., 2007), une plateforme de vibrations plantaire résistive (D. Greaves et al., 2019), une plateforme de sauts « squats test » (Linnarsson et al., 2015) et une centrifugeuse a bras court (2m) (Clement et al., 2016).

Generalites sur l’adaptation à la microgravite reelle (vol spatial) et simulée (decubitus, immersion, confinement) - Methodologie et appareillage Ultrasonore

L'immersion sèche (DI) (immersion dans un bain sans contact du sujet avec l’eau) et le décubitus anti orthostatique (Tete plus basse que les pieds à moins 6 degrés ou HDBR) sont couramment utilisés dans la recherche spatiale comme modèle pour simuler les effets de la microgravité (Linossier et al., 2017; Watenpaugh, 2016).

L’objectif de cette thèse est de présenter 3 études consacrées à l’étude de l’adaptation cardiaque, artérielle, et veineuse, réalisées à l’aide des 2 méthodes mentionnées ci-dessus : le Décubitus (HDBR) et Immersion sèche. Les résultats de ces études sont présentés dans 3 chapitres suivants.

Le premier chapitre s'intitule « Effets de l'exercice physique sur la contractilité myocardique évaluée par échographie 4D et speckle tracking lors d’un HDBR de 21 jours ». Dans cette étude, nous présentons la méthode Echo 4D speckle tracking qui permet de quantifier la contractilité myocardique sans avoir recours à l’IRM, et qui a déjà été utilisée sur des patients cardiologiques mais pas encore en physiologie spatiale. Cet article a été publié dans le European Journal of Applied Physiology (D. Greaves, Arbeille, Guillon, Zuj, & Caiani, 2019).

Le deuxième chapitre s'intitule « Structure et modifications cardiaques et artérielles après quatre jours en immersion sèche avec et sans brassards de cuisse ». Dans cette étude, nous présentons les résultats des investigations cardiaques et artérielle réalisées sur des sujets placés en immersion pendant 4 jours, la moitié d'entre eux portant des brassards de cuisse le jour dans le but de réduire l'importance du transfert des fluides induit par l'immersion du bas vers le haut du corps. En début d'un vol spatial les brassards de cuisse permettent de réduire l'encombrement de la sphère ORL, les maux de tête et l'dème facial. Un article a été soumis à Acta Astronautica (16 octobre 2019).

Enfin, le troisième chapitre s'intitule « Effet des brassards de cuisse sur la redistribution veineuse pendant 4 jours en immersion sèche ». L'objectif était de recréer un transfert liquidien important vers les régions thoraco céphaliques, d'en évaluer les conséquences au niveau cérébral et de tester l'efficacité des brassard de cuisse comme réducteur de ces effets. Un article a été soumis pour publication à Aerospace Medicine & Human Performance (20 Octobre 2019).

Nouvelle méthode d'investigation ultrasonore des organes et vaisseaux superficiels et profonds en vol spatial et simulation

Actuellement, la plupart des programmes de recherche en physiologie spatiale font appel à l'échographie. En effet l'Echographe est le seul appareil d'imagerie médicale qui peut être installé à bord de la station internationale puisqu'il fonctionne sur une alimentation électrique de 28 volts contrairement aux appareils à rayons « X » (Scanner) et à l'IRM.

Actuellement l'astronaute doit être entrainé (a) configurer l'appareil en fonction de l'organe, (b) pour localiser la sonde d'échographie en regard de l'organe (c) pour orienter la sonde afin d'obtenir une vue parfaite de l'organe en vue axiale ou transverse, (d) pour optimiser l'image en ajustant les réglages de l'échographe (gain, profondeur), (e) pour activer les diverses fonctions de l'échographe comme le Doppler, Temps mouvement, 3D. (f) pour enregistrer les images et vidéo. Pour toutes ces taches l'astronaute est guidé à la voix par un expert depuis la Terre et, parce que la tâche est compliquée et sa formation pré-vol limitée (peu d'heures d'entrainement pré vol) il faut souvent plusieurs minutes pour obtenir la vue échographique attendue. Le principal problème est qu'il est très difficile de guider à distance un sujet non-échographiste (astronaute) pour lui faire réaliser une rotation, ou inclinaison de la sonde de quelques degrés (2-3 degrés).

Pour cette raison nous avons conçu un nouveau dispositif grâce auquel la majeure partie des manouvres (a, c, d, e, f) peut être accomplie directement par l'Expert à distance en utilisant la télé-opération donc avec une participation limitée de l'astronaute de l'ISS   Ce nouveau système 1) réduit considérablement le temps de formation pour l'astronaute en pré vol parce moins de manœuvres à apprendre, 2) permet à l'expert de déclencher les fonctions échographiques et les captures de données a des instants plus opportuns et donc d'opérer une meilleure sélection des données collectées, 3) n'exige pas la présence d'un 2^{ième} operateur assistant pour gérer les fonctions de l'Echographe comme c'est le cas actuellement.

L'Echographe spatial a été développé à partir d'un modèle commercial (Orchéolite Sonoscanner Paris), auquel un ensemble de fonctions a été ajouté (3D, RF signal, elastographie) et modifié pour que toutes ses réglages (gain, profondeur), fonctions (Doppler pulse ou couleur, 3D, RF) puissent être télé-opérés à distance en utilisant des soft spécialement développés par Teamviewer (Goppingen, Germany) et Optimalog (St Cyr/Loire, France).

Au site Expert l'échographiste ajuste les réglages de l'image échographique qu'il reçoit du site distant (ISS) et active les fonctions (Doppler pulse, couleur 3D) à partir du clavier de son PC. Chaque réglage est identifié par une touche du clavier, <F6> et <F7> augmente et diminue le gain ultrason, <F4> active la fonction Doppler Pulsé (O) active l'Echographie 3D. Le design, l'encombrement (40x36x8cm) ou le poids (6kg) de l'appareil n'ont pas été modifiés.

Quatre sondes bi-motorisées ont été développées par Vermon (Tours, France) pour cet Echographe. Elles sont pourvues de transducteurs motorisés dont l'expert peut modifier l'orientation à distance à l'aide d’une sonde fictive dont les mouvements sont transmis à la sonde réelle distante. Un premier moteur permet d’incliner le transducteur de +55°à -55°, un 2ième moteur sert à faire tourner le transducteur sur lui-même de -90° à +90°.

Dès que la communication est établie l’Astronaute positionne la sonde à l’endroit indiqué oralement par l’Expert au sol (Dr D Greaves - Pr P Arbeille). L’Expert utilise des références anatomiques simples pour guider l’astronaute (Ligne mammelonaire, sternum, clavicule), puis, dès que l’organe/vaisseaux apparait l’Expert demande à l’astronaute de garder la sonde immobile pendant que depuis le sol il oriente le transducteur (en manipulant la sonde fictive de la main gauche) jusqu’à bien voir l’organe, optimise l’image, puis active des fonctions comme le Doppler, le 3D, le RF, en agissant sur les touches du clavier de sa main droite.


a


b

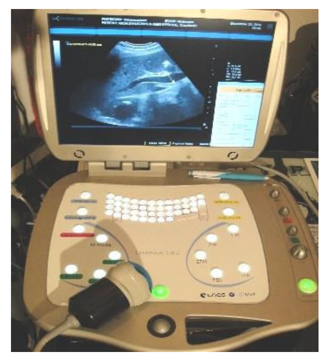

c

Fig. 1.1. (a) Sonde motorisée (400cm3 and 430g). Le transducteur (3,5MHz curved array) peut etre incliné et tourné (fleches) a distance par l’expert en manipulant (b) la sonde fictive (fleches) (c) L’Echographe télé opérable (6kg) avec la sonde egalement tele-operable.

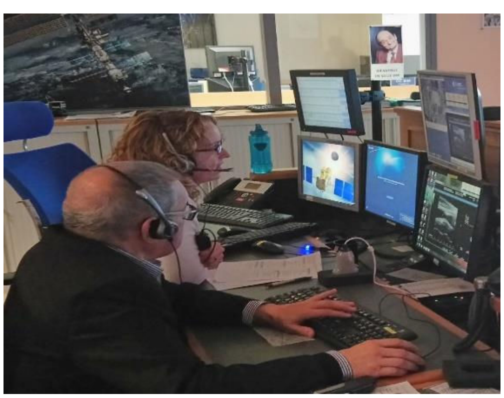


Figure 1.2. Poste Expert au CNES (Toulouse) en liaison directe avec l'ISS. Clavier et sonde de commande

Figure 1.3: Veine cave inferieure et carotide commune avec détection de l'Intima media (liseré rouge).

Thèse Hypothèses Générales

L'objectif général de ce document est d'étudier la manière dont le système cardiovasculaire s'adapte aux environnements de simulation d'un vol spatiale. Nous avons étudié deux 2 modalités HDTBR (Alitement anti orthostatique) et DI (Dry immersion) pour la simulation des effets des vols spatiaux.

Les hypothèses spécifiques étaient les suivantes :

1. Le suivi des speckle (points singuliers du myocarde) en échographie 4D qui permet une évaluation quantitative de la contractilité myocardique HDTBR de 5 jours ;
2. L'effet des brassards de cuisse portés lors d'une DI de 4 jours pour s'assurer qu'ils atténuent le déconditionnement artériel attendu ;
3. L'effet des brassards de cuisse portés au cours d'une DI de 4 jours pour vérifier qu' ils atténuent le transfert liquidien vers les régions céphaliques et cérébrales.

Résumé du Chapitre 2 (Paper 1): Effects of exercise countermeasure on myocardial contractility measured by 4D speckle tracking during a 21-day head-down bed rest

L'objectif était de quantifier les modifications de la contractilité cardiaque au cours d'un bedrest de 21 jours (HDBR) par la méthode speckle tracking 4D et de déterminer si la contre-mesure « exercice » était capable de préserver cette contractilité cardiaque. Les méthodes traditionnelles 2D ne mesurent qu'une variation de la taille du ventricule de la systole à la diastole et ne suivent pas la cinétique des mouvements de contractilité à l'intérieur de la paroi. De plus l'échographie 2D ne permet d'accéder qu'a la contractilité longitudinale globale par la mesure de la distance Apex-Valve mitrale. Le suivi des mouvements des speckles (points singuliers à l'intérieur du myocarde) en 4D montre que la contractilité radiale diminuée significativement pendant le HDTBR chez les sujets témoins alors qu'elle est conservée dans le groupe exercice. Par contre la contractilité longitudinale n'est pas affectée dans aucun des 2 groupes. Bien sûr, l'IRM pourrait fournir des données similaires, mais il n'est pas possible à ce jour d'imaginer avoir une IRM a bord de l'ISS dans un futur proche. A la suite de ces résultats nous avons mis au point un algorithme de traitement des vidéos cardiaque qui permet d'accéder à la contractilité radiale et longitudinale en vol (prog Vasc-Aging en cours)

Résumé du Chapitre 3 (Paper 2): Cardiac and arterial structure and functional changes after four days of dry immersion with and without thigh cuffs

Dans le deuxième chapitre, nous présentons les résultats de mesures cardiaques, et artérielles réalisée a 4 jours d'immersion sèche. Au matin du 4ieme jour on observe une diminution significative du volume du ventricule gauche, du volume éjection et de la fraction d'éjection qui montrent que quatre jours en immersion est suffisant pour induire une réduction du volume plasmatique et donc des volumes cardiaques. Ceci est en accord avec les résultats obtenus en immersion sèche en HDBR et vol spatial historique pour DI (Navasiolava et al., 2011; Watenpaugh, 2016) ainsi qu'avec les mesures directes du volume plasmatique effectuées au cours de cette étude. La masse cardiaque montre une tendance à diminuer. Par contre au matin du 4ieme jours d'immersion les flux artériels chez les sujets portant les brassards de cuisse le jour, après la nuit sans les brassards sont redistribué comme chez les sujets contrôle. De plus le port des brassards de cuisse pendant 8h ne modifie pas de manière significative les paramètres cardiaques ou artériels. Il apparait donc que le port de brassard de cuisse toute la journée n'a pas entraîné d'« effet mémoire» ni d'« effet chronique » des brassards. Si plus de participants avaient eu le cœur sportif (comme les astronautes), nous aurions certainement observé une perte de masse myocardique plus importante. On observe aussi des signes de remaniement vasculaire, avec une augmentation de l'IMT fémorales (Intima media thickness) et d'augmentation de la rigidité artérielle au niveau Carotidien. Les débite artériels périphériques (Carotide Fémorale) sont resté stables pendant la durée de l'immersion sèche. La durée du séjour en immersion sèche était d'une durée probablement insuffisante pour induire des modifications cellulaires majeures des parois périphériques comme celles observées en HDBR et vol spatial. Le port de brassards de cuisse n'a eu aucune incidence sur l'adaptation cardiaque ni artérielle a l'immersion.

Introduction du Chapter 4 (Paper 3): Effect of thigh cuffs on the venous redistribution during 4 days in dry immersion

L'objectif de l'expérimentation était de montrer que quatre jours en immersion sèche suffisaient pour réaliser un transfert liquidien important vers les régions céphaliques comparable à celui observé en vol spatial. Notre protocole consistait donc à mesurer les volumes veineux au niveau cervical cérébral et porte au début de la période en immersion (à 2h) puis a 4 jours d'immersion. Compte tenu des problèmes engendrés par ce transfert liquidien en vol nous avions proposé de tester la capacité des brassards de cuisse à réduire l'amplitude du transfert veineux. Les résultats montrent que l'immersion provoque un transfert de sang veineux au niveau cervical maximal à 2H et que les Brassards de cuisse réduisent significativement ce transfert dans cette phase précoce. Par contre a 4 jours d'immersion l'amplitude du transfert sanguin est considérablement diminuée (bien que toujours présente) et les brassards de cuisse n'ont pas d'effet visible à ce moment-là. En fait le volume plasmatique décroit significativement à la fin du premier jour (env. 20%) des lors la masse de sang déplacées vers la tête par l'immersion est insuffisante pour générer une stase importante au niveau cervical comme à 2h d'immersion. Pour cette même raison la vitesse dans les veines cérébrales n'est pas augmentée à 4 jours d'immersion contrairement à ce qu'on avait observé à 2h d'immersion lors d'une précédente étude. Donc le modèle immersion sèche est un modèle pour étudier les transferts liquidiens en microgravité mais seulement en début de phase d'immersion. Sur cette période de temps, les Brassards de cuisse ont bien un effet protecteur pour les organes de la zone céphalique.

Chapitre 2

Effets de la contre-mesure d'exercice sur la contractilité myocardique, mesurée par échographie 4D et speckle tracking pendant un décubitus à -6 degrés de 21 jours / Effects of exercise countermeasure on myocardial contractility measured by 4D speckle tracking during a 21-day head-down bed rest

PMID: 31531733

ABSTRACT

Objective: to evaluate functional myocardial contractility after 21 days of head-down bed rest (HDTBR) in sedentary control (CON) or with a resistive vibration exercise (RVE) countermeasure (CM) applied, by using 4D echocardiographic (4D Echo) imaging and speckle tracking strain quantification.

Methods: Twelve volunteers were enrolled in a crossover HDTBR design, and 4D Echo was performed in supine position (REST) at BDC-2 and at R+2, and in -6° HDTBR (on day 18), and also during the first and the last minute of the 80° head-up step of Standard Measures tilt test, performed at both BDC-2 and R+2. Radial (Rad-Str), longitudinal (Lg-Str) and twist (Tw-Str) strain were measured by 4D speckle tracking, as well as left ventricle diastolic volume (LVDV) and mass (LVmass).

Results: On day 18: in the CON group, LVDV and LVmass were reduced ($p<0.05$), the Rad-Str decreased ($p<0.05$) and Tw-Str showed a tendency to increase ($p< 0.11$), with no changes in Lg-Str. In RVE group, LVDV and LV mass, as well as all the strain parameters remained unchanged.

On R+2: in the CON group, LVDV and LVmass were not recovered in all subjects compared to pre-HDTBR ($p<0.08$), Rad-Str was still decreased ($p<0.05$), while Tw-Str tended to increase ($p<0.09$). These parameters remained unchanged in the RVE group.

Tilt 80°: Rad-Str and Lg-Str values at 80° tilt were similar post HDT in both groups.

Conclusion: 4D Echo and speckle tracking analysis showed that in the CON group, Rad-Str decreased concomitant with LVmass and LVDV with HDTBR, but this observation did not support the hypothesis that this HDTBR induced remodelling or a muscle atrophy. RVE acted to preserve both LVmass, LVDV and contractility during HDTBR, thus proving its effectiveness to this aim. Nevertheless, the significant HDTBR-induced changes observed in the CON group had only a limited effect on the cardiac contractile response as observed during post HDTBR tilt test. The level of contractility at 80° Tilt position was not affected neither by HDTBR nor by RVE CM.

Key words: Echocardiography, head-down tilt bedrest, resistive exercise, cardiac contractility, cardiac strain, speckle tracking, ultrasound.

INTRODUCTION

Head-down tilt bed rest (HDTBR) represents an experimental model commonly used to simulate the effect of microgravity on Earth. This model is considered as an effective microgravity simulation for most physiological effects of spaceflight such as muscular, metabolic and cardiovascular changes (Demontis et al., 2017). For the cardiovascular aspect, it leads to fluid shift from the legs to the chest, causing an increase in left ventricular transmural pressure, end diastolic volume (LVDV), and stroke volume (Fortney, Schneider, & Greenleaf, 1996) that activate short-term volume regulatory mechanisms resulting in plasma volume loss, with the achievement of a new hemodynamic steady state within 48 h characterized by decreased volume loading of the heart similar to what reported during space-flight (Arbeille et al., 2001; Levine, Zuckerman, & Pawelczyk, 1997).

Echocardiography is an imaging technique that has been performed since the beginning of manned spaceflight, thus allowing to observe a reduction in left ventricular (LVDV) volume accompanied by a reduction in plasma volume due to space flight (Martin, South, Garcia, & Arbeille, 2003). This cardiac adaptation persisted throughout both short-duration and long-duration spaceflight missions, and HDTBR studies, due to insufficient or inadequate effectiveness of applied exercise countermeasures performed at that time. (Arbeille et al., 1987; M. Bungo & Charles, 1985; M. W. Bungo, Charles, & Johnson, 1985; Herault et al., 2000) (Dorfman et al., 2007).

In order to compensate or minimize the effects of cardiac deconditioning, additional countermeasures (CM) have since been developed and studied, with the specific aim to maintain or restore cardiac volume and mass during both real and simulated microgravity exposure. These CM have included pharmaceuticals, short-arm centrifugation (ground only), lower-body negative pressure, nutritional supplementations and, as in focus of the current study, aerobic and resistive exercise. The majority of these CM have been shown to be at least partially effective (Ferrando, Tipton, Bamman, & Wolfe, 1997) (P. Arbeille, P. Kerbeci, L. Mattar, J. K. Shoemaker, & R. L. Hughson, 2008b) (Caiani, Massabuau, Weinert, Vaida, & Lang, 2014; Hargens & Richardson, 2009; Ploutz-Snyder et al., 2014).

In the field of muscle-skeletal deconditioning, skeletal muscle atrophy has been associated with a reduced protein synthesis rate and redistribution of muscle fiber types: both issues can be mitigated by an approach that combines amino acid supplementation and resistive exercise. However, in contrast to what is known about skeletal muscle, little is known regarding potential changes to myocardial tissue structure or changes to myocyte metabolism (Bennet, Connacher, Scrimgeour, Smith, & Rennie, 1989; Kumar et al., 2009).

Methodological limitations in directly detecting changes in cardiac contractility in a non-invasive way have produced a yearly paradox in the literature: the cardiac mass is known to decrease due to spaceflight, but with no concomitant changes observed in contractility (Negishi et al., 2017), Levine et al unpublished data from Integrated Cardiovascular Study, a 6-month ISS flight experiment). Indeed, measurements of contractility (strain) were indirectly performed using 2D Tissue Doppler Imaging (DTI), that measures the contractile performance only along parallel directions to the ultrasound beam, thus allowing measurement of longitudinal strain only, but the sensitivity of this parameter was insufficient to detect significant changes associated to space flight. As with any one-dimensional Doppler technique, DTI is angle-dependent, and regional velocity estimates can be influenced by overall heart motion, cardiac rotation, and contraction in adjacent segments. In addition, it is sensitive only along parallel directions to the ultrasound beam, thus allowing measurement of longitudinal strain only.

As the cardiac motion is intrinsically 3D, other imaging techniques are needed to fully investigate strain along other directions (i.e., radially or due to twist), to test for possible changes induced by microgravity.

Four-dimensional echocardiographic (4D Echo) imaging is a relatively new technique that allows acquisition of a 3D volume of the whole heart over an entire cardiac cycle, with time representing the fourth dimension. The cardiac structures can be visualized in 3D in real-time or can be visualized as any 2D cut-plane selected within the 3D volume. By 4D speckle tracking processing, it is possible to achieve improved assessments of contractility along various axes (Perez de Isla et al., 2011; Perez de Isla et al., 2010) (Arbeille et al., 2012; Seo, Ishizu, Enomoto, Sugimori, & Aonuma, 2011). This overcomes the limitations of the traditional DTI method, thus giving 4D Echo datasets and speckle tracking a clear advantage.

Our hypothesis was that changes in contractility do indeed accompany the previously documented changes in left ventricular mass occurring with spaceflight and HDTBR (in non-countermeasure groups). Using an improved echocardiographic imaging technique (4D speckle tracking), previous limitations of 2D imaging could be overcome, thus allowing demonstrating for the first time the expected changes in strain outcome associated with the observed decrease in cardiac mass.

Accordingly, the aim of this study was to assess the effects of mid-duration (21 days) HDTBR on the left ventricular volume, mass, and myocardial contractility along three components (i.e., radial, longitudinal, and ventricular twist) 4D Echo and speckle tracking, and evaluate the effectiveness of resistive exercise in acting as a countermeasure on these outcomes.

METHODS

Subjects:

Twelve healthy male volunteers participated in this study. All were non-smokers with no pre-existing medical conditions, were taking no medications and had all parameters, for hematology, blood chemistry and standard clinical exams, in the respective range of normality defined by clinical practice and relevant guidelines. All participants gave informed, written consent to participate in the study. This experiment was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and approved by the local institutional ethics committee (CPP Sud-Ouest Outre-Mer I) as well as by the Government of France Health Authority. The study was performed at the Institute for Space Medicine and Physiology (MEDES-IMPS) in Toulouse, France.

General protocol:

Subjects were enrolled in a crossover design with a washout period of 4 months between two consecutive campaigns, with one sedentary control (CON) group and two countermeasure (CM) interventions, either resistive vibration exercise group (RVE), or RVE plus nutrition supplementation (NEX). The order of inclusion in CON, RVE or NEX group was randomly assigned to each subject at the beginning of the bed rest, with 4 subjects assigned to each group in each campaign. All subjects adhered to a strict 6° head-down tilt bed rest for 21 days (HDTBR) for each campaign. Subjects were acclimated to the bed rest unit for 7 days before initiating uninterrupted bed rest, monitored 24 h a day, and provided with strictly controlled diet aimed at preventing body weight changes. Daily cycle started each day at 7:00 AM and ended at 11:00 PM, with no napping allowed during the day. After completing the 21-days of bed rest, subjects remained in the facility for an additional 7 days for further testing. In the ambulatory periods preceding and following HDTBR, lying in bed during the day was not allowed. In this way, each campaign spanned 35 days in-clinic.

All exercise training was performed on an integrated training device supplied by Novotec Medical (Pforzheim, Germany). The vibration platform (Galileo® Fitness, Novotec, Germany) was combined with a system designed to allow exercise training in -6° head down position. RVE sessions were spaced away from meals performed twice per week with three to four-day intervals, starting at HDTBR day two.

In the NEX group, this training was complemented with daily high protein intake (1.2 g/kg body weight /d plus 0.6 g/kg body weight/d whey protein) with alkaline salts (90 mmol potassium bicarbonate /d)

At BDC-2 and R+2, participant underwent progressive head-up tilt test consisting of 3 steps (20°, 45°, 80°) of 3 min duration each (Fig. 2.5a).

During the bed rest campaigns, four subjects in the NEX group withdraw for personal reasons from the study. In addition, for technical problems, we were not able to acquire good quality data in both pre-HDTBR, HDTBR, or post-HDTBR in other three subjects of the same group, thus precluding paired analysis between a NEX gr of 5 subjects and the other group of 11 and 12 subjects respectively. For this reason, we are not reporting results relevant to the NEX countermeasure, but only results relevant to the CON and RVE groups.

Echocardiographic imaging protocol:

Echocardiographic imaging using an ARTIDA (Toshiba Medical, Amsterdam NL) equipment was performed in supine position (REST) at BDC-2 and at R+2, and in -6° HDTBR on day 18. In addition, image acquisition was also performed during the first and the last minute of the 80° head-up step of the Standard Measures Tilt test, at both BDC-2 and R+2 (Fig. 2.5). For each session, three 4D volume scans (3D over time) of the left ventricle, each representing a cardiac cycle, were acquired. In particular, the first 4D capture was stored as raw data to be processed off-line by 4D speckle tracking analysis. The same device settings (i.e. gain, depth, resolution) were used on a given volunteer across acquisition sessions.

Echocardiographic measurements:

Left ventricular diastolic volume (LVDV) and mass (LVmass) were also calculated both by 3D (by automatic contouring) and 2D method (Simpson's bi-plane).

Cardiac contractility was quantified by measuring radial strain (Rad-Str), longitudinal strain (Lg-Str), and twist strain (Tw-Str), using speckle tracking processing of the 4D scan of the left ventricle. The 4D speckle tracking echocardiographic mode allows simultaneous visualization of left ventricular myocardial strain changes in real-time, on both apical 4- and 2-chambers views, as well as on 3 transverse views of the left ventricle at apical, middle, and sub mitral level. The software uses conventional gray-scale B-mode recordings to automatically detect the internal and external contours of the left ventricle and tracks myocardial speckles, which serve as natural acoustic markers. In case of poor echogenicity resulting in a sub-optimal view, background noise may interfere with the automated detection of the endocardium. In this case, the left ventricle internal contour was manually corrected. At each point of the myocardium on these 5 cut-planes, the computed strain value is displayed using a parametric color scale (from yellow the highest, to blue the lowest), and all this information is projected on a polar view of the left ventricle divided in 17 segments (Fig. 2.1), according to the AHA model (Cerqueira et al., 2002). The percent displacement of each speckle in 3 directions (longitudinal, radial and twist strain) was used to quantify the strain value for each of the 17 segments. This percent value represents the contractility of each segment in each direction (Perez de Isla et al., 2010), the 4D strain being the evolution of these (3D) strain values over time.

To evaluate changes in myocardium contractility between pre HDTBR and day 18, and between the CON and RVE groups, we defined total strain as the sum of the % values in all segments, and mean strain as their average, with arbitrary units, to differentiate from the original strain values. The total strain represents an index of the whole contractility of the heart, while the mean strain gives a qualitative evaluation of such contractility. Accordingly, mean and total radial strain (Rad-Str), longitudinal strain (Lg-Str), and twist (Tw-Str) strain, were computed and presented in the results. (Figs. 2.1, 2.3 and 2.4)

Statistical analysis:

The effects of HDTBR and the exercise countermeasure on cardiac contractility were assessed in a supine and a head-up tilt 80° position independently. Two-way repeated measures ANOVAs were used to test for main effects of HDTBR and the exercise countermeasure on cardiac contractility in both body positions. (SigmaPlot 12.5, Systat Software Inc, Chicago IL, USA).

RESULTS

All subjects, while in CON and RVE groups, successfully completed the HDTBR. Image quality of the acquired images allowed obtaining reliable measurements for comparison among the different time point in 11/12 subjects in the CON group and 12/12 subjects in the RVE group. During the Tilt there was not enough time during the 3 min at 80° to perform 4D analysis of Rad-St, Lg-Str and Tw-Str. The Tw-Str parameter could not be collected in good condition in all subjects.

Effects of bed rest on LV function and strain

In Fig. 2.1, an example of speckle tracking analysis performed off-line on the acquired 4D volumetric echo in one subject before HDTBR in supine position and at HDT18 at -6° head-down is reported for radial strain. Note the reduction in yellow areas (higher strain values) with bed rest, confirmed by a reduction in total strain for this subject at HDT18.

In Fig. 2.2, the cumulative results relevant to LVDV and LVmass in both CON and RVE groups are presented. In the CON group, compared to BDC-2, at HDT18, LVDV was significantly reduced by 15% (98 to 83 ml) and LV mass by 17% (192 to 160 gr) ($p<0.05$). On the contrary, no changes were visible in the RVE group. After bed rest, at R+2, in the CON group, LVDV showed incomplete recovery to baseline levels in all subjects (86ml, -13% from pre HDTBR, $p<0.09$) as well as LVmass (174mg, -9%, $p<0.08$).

In Fig., 2.3, the cumulative results relevant to Total Rad-Str, Total Lg-Sr and Total Tw-Str are shown. In the CON group, Total Rad-Str at HDT18 was found decreased by 26% (from 431 to 321 a.u, $p<0.05$), and it was not completely restored to pre-HDTBR values at R+2 (350 a.u, -18%, $p=0.05$).

While Total Lg-Str did not change for both groups, neither at HDT18 nor at POST, for the CON group an apparent increase in Tw-Str at both HDT18 (from 4 to 13 a.u, $p<0.10$) and at R+2 (4 to 42 a.u., $p<0.11$) was noticed, while no changes were visible for the RVE group.

As from the previous results, the main effect of bed rest was noticeable on Total radial strain, we conducted a segmental analysis for this strain component in order to evaluate changes at segmental level. The results of this analysis are reported in Fig. 2.4, separately for the CON and the RVE group. In both groups, a lower strain associated with apical segments was visible already before HDTBR. At HDT18, a decrease in Radial strain in both basal and mid ventricular segments was visible in the CON group, while no apparent segmental changes were present in the RVE group.

Contractility at 80° Standard Measures Tilt

Fig. 2.5 summarizes for both CON and RVE groups the results in LVDV, total Rad-Str and total Lg-Str obtained in the first minute of the 80° head-up step of the Tilt, and at conclusion, both at pre-HDTBR and at R+2. The LVDV decreased in similar proportion during both pre and post HDTBR tilt tests in both groups (in CON, pre-HDTBR tilt pre: from 100 to 70ml; post-HDTBR tilt: from 86 to 62ml. In RVE, pre-HDTBR tilt: from 90 to 57ml; post-HDTBR tilt: from 91 to 59ml), thus reaching similar values at pre and post HDTBR tilt despite LVDV measured post HDTBR before tilt test started was lower in CON group than in RVE.

In 10 of the 11 CON subjects, the total Rad-Str decreased significantly ($p<0.05$) during pre HDTBR tilt (from 435 to 299 a.u.) while this was not significant at R+2 (from 346 to 296 a.u.), besides reaching a similar end-tilt value at 80° position pre and post HDTBR. It is worth noticing that at post-HDTBR the Total Rad-Str supine (right before being tilted) was reduced compared to the pre-HDTBR.

In the RVE group, the Total Rad-Str did not decrease during pre HDTBR-tilt (from 389 to 367 a.u.), while it decreased at post-HDTBR tilt (410 to 257 a.u.), however it can be noted that the Rad Str supine (just before being tilted) post-HDTBR was higher than at pre-HDTBR.

For Lg-Str, no changes were observable during Tilt, both pre- and post-HDTBR, in both groups. Thus, the lowest level of Rad strain (at 80° post HDT) was similar for CON and RVE.

DISCUSSION

The present HDTBR study showed that in the control group such position maintained during 21 days induces a decrease in volemia, as exhibited by the significant decrease in left ventricle diastolic volume, in agreement with other reports of several bedrest and inflight studies. Additionally, the left ventricular myocardial mass significantly decreased, consistent with bedrest and spaceflight. (Arbeille et al., 2000; Arbeille et al., 1997; P. Arbeille, P. Kerbeci, L. Mattar, J. K. Shoemaker, & R. Hughson, 2008a; Caiani et al., 2014; Dorfman et al., 2007; Perhonen, Franco, et al., 2001; Perhonen, Zuckerman, & Levine, 2001).

The evaluation of the myocardial contractility along 3 orthogonal components by 4D speckle tracking analysis showed that only the radial contractility was affected by a significant reduction with HDTBR, and this was concomitant with the observed drop in left ventricle volume and mass. Nevertheless, it is difficult to state if such changes in radial strain were due to a real remodelling of the myocardium cellular structure or simply as the consequence of the myocardium atrophy and/or dehydration. Three days after the conclusion of HDTBR (at R+2), the left ventricle mass, end-diastolic volume, and Total Rad-St did not completely recover, in agreement with the results obtained in a 60-days HDTBR (Westby, Martin, Lee, Stenger, & Platts, 2016), thus suggesting that cardiac muscle atrophy could persist into recovery, as a result of real tissue transformation.

On the contrary, in a previous HDTBR study of 5 days duration, the quick decrease in cardiac mass during HDT and the quick recovery within 2 days after the HDTBR supported the hypothesis of a dehydration process related to the fluid shift effect induced by the HDTBR (Caiani et al., 2014).

Most of the longitudinal strain evaluation during HDTBR or spaceflight were performed using the Doppler Tissue Imaging (DTI) modality, reporting a decrease or no change in this parameter. In a 5-days HDTBR, (Caiani et al., 2014) found DTI velocities to reduce significantly after 5 days, and recovering within 3 days after the conclusion, again supporting the hypothesis that the cardiac longitudinal contractility change was related to dehydration induced by fluid shift and the subsequent cardiovascular adaptation to the new homeostatic condition. Conversely, a 6-months spaceflight study (Levine et al, unpublished results from Integrated Cardiovascular) performed on board the International Space Station and a two-week HDTBR study did not found any significant change in longitudinal contractility (Negishi et al., 2017), despite the fluid shift was present both during the flight and with HDTBR, as confirmed by the significant dilation observed by vascular ultrasound in the jugular vein (Arbeille, Zuj, et al., 2016). Lastly, another 70-days HDTBR study recently showed a decrease in Lg Str (also evaluated by DTI) (Scott et al., 2018).

However, the DTI method used in these studies to estimate the longitudinal strain is based on the processing of tissue velocities on 2D views, as opposed to the speckle tracking mode used in this study, which measures movement of speckles over a 3D space: this difference in processing raw data could explain the weaker changes in Lg-Str and Tw-Str that we found in our study.

Two days after the end of the present 21-days HDTBR, the radial strain was not completely recovered, thus not supporting the dehydration hypothesis. On the contrary, the fact that the longitudinal and twist contractility were not affected by HDTBR does not support the hypothesis of true ventricular remodelling, as it should have affected strain in all directions.

As a result, we suggest that the observed changes along different directional strains might be related to different processes during the early period of adaptation and later on. In order to clarify these questions, additional strain assessments are required with longer duration, appropriately powered bed rest studies.

The Rad-Str changes after bed rest in the control group had a similar amplitude changes in each of the 17 cardiac segments. This can be observed from the speckle tracking polar maps (Fig. 2.4). This is true except for the basal segments (#1 and #6) and the apical segments (#14-17). This might partially explain why the longitudinal strain is less affected by HDTBR than the radial strain. Conversely, the remaining segments showed higher strain value (higher radial contractility) and were more affected by the HDTBR.

Conversely, on the Longitudinal strain polar map (not reported), the Lg-Str changes were of low amplitude in most of the segments and more heterogeneously distributed.

Lastly, the changes in radial strain (contractility) were quite homogenous around the left ventricle, which is not the case in coronary patients, where the area affected is exclusively located downstream to the occluded coronary artery. As a result of our observation, in healthy subjects like the astronauts or HDTBR volunteers, if 4D Echo is not available, the radial and longitudinal myocardium contractility could be evaluated using speckle tracking mode applied to a single apical 2-chamber, or multiple (mid and base left ventricle) parasternal short-axis views of the left ventricle. If this methodology were combined with a 4D volume, error from out-of-plane motion of the speckles would be solved.

The 4D Echo and Speckle tracking analysis have been previously validated in coronary patients – this methodology has been proven to be capable of locating the myocardial area with reduced contractility (using a colour scale), evaluating the loss of contractility compared to healthy areas (by strain in each segment), and quantifying the level of recovery (increased strain) after coronary angioplasty. In this experiment, the largest increase was observed in the radial strain, compared to the longitudinal and twist directions, and the changes observed were not associated with myocardial mass change (as observed with bed rest in healthy volunteers) but instead to perfusion restoration via re-vascularisation or liquid transfer (Arbeille et al., 2012). This observation supports the hypothesis that changes in contractility should be related to liquid transfer at the myocardium level (i.e., dehydration) (Caiani et al., 2014) at least between 24hrs and R+2, after the conclusion of HDTBR.

In coronary patients, there is no time for vascular remodelling because the change in strain occurs within 24 hrs from reperfusion. With mid-duration HDTBR (e.g. 21 days) it is arguable that the reduction in radial strain was just related to the myocardium atrophy without remodelling, or if this change represents a significant remodeling, accompanying the myocardial atrophy.

On the other hand, skeletal muscle atrophy during sedentary conditions (HDTBR or Dry immersion) has been associated to real tissue remodeling with a significant atrophy of type I muscle fibers and an increased proportion of hybrid, type I/IIX fiber co-expression. Additionally, after a 1-month spaceflight, leg muscle atrophy in mice was found associated to fiber type redistribution, with structural alterations (Demangel et al., 2017; Tascher et al., 2017). Also a histological study of the myocardium in tail suspended rats (for 30 days) reported the association of myocardium atrophy and deep rearrangement of the intra cellular architecture and some destructive changes of the myocytes ultrastructure (Nepomniashchikh, Kolesnikova, & Nepomniashchikh, 1985). These observations are in favour of a myocardium tissue remodeling explanation but until now no direct or indirect observation has confirmed that for the human heart.

Considering results obtained at the Tilt test (at R+2) both the ejection fraction and the stroke volume were protected in the RVE group, but surprisingly also in the CON group (except for 1 subject), despite the observation that the supine left ventricle volume was significantly lower than pre HDTBR. This is probably due to the limited decrease in contractility.

Contractility is mediated by the sympathetic nervous system, whose balance may be affected by the HDTBR, nevertheless it seems that this contractility during the Standard Measures Tilt was sufficient to prevent orthostatic intolerance the CON subject, despite the fact that his values did not fully recover at R+2.

A similar study, where tilt test was performed after a 2-weeks HDTBR, reported that DTI showed similar changes in contractility during acute fluid shift as at pre HDTBR, while no changes in longitudinal strain were detected. This latter is in agreement with our study, suggesting a stiffer left ventricle after HDTBR (Negishi et al., 2017). On the other hand, during acute fluid shift as that induced during zero G flights, the tissue velocity as measured by DTI was found preload dependent, while strain appeared to be preload independent, probably reflecting intrinsic myocardial properties (Caiani et al., 2007). As a conclusion, strain seems an appropriate parameter, even when measured by DTI, for evaluating changes in cardiac longitudinal contractility.

In the Exercise RVE group, the left ventricle diastolic volume and mass remained unchanged during and after the HDTBR. The radial, Twist and longitudinal strain also remained unchanged which confirm the efficiency of the Resistive vibration exercise as a countermeasure acting as cardiac protector in simulated gravity conditions.

Limitations

While the 4D speckle tracking method permits visualization and quantification of the radial, longitudinal and twist for each cardiac segment, it suffers from some limitations when used under certain conditions, like the tilt test. It was less reliable for Twist strain evaluation likely due to lower absolute values of twist strain changes or perhaps errors in detection of speckle movements.

Acquisition time is slow for 4D speckle and this is an additional limitation. For each individual acquisition, the sonographer must a) locate high-quality 4-chamber apical view to ensure that the ultrasound sweep will cover the whole ventricle, b) wait motionless several seconds for the 4D speckle processing and display, and c) verify the data and repeat as required. Considering that the entire process takes approximately one minute, capturing during a dynamic test can sometimes fail. A third limitation is body position requirement, which for the Standard Measures Tilt is supine, while left-lateral decubitus is preferred for the highest quality images.

Finally, in our analysis we did not focus on other temporal parameters (i.e., time to peak) as previously reported. In those studies, significance was not reached and, in this study,, the computation of these parameters would have been more prone to errors due to the instability of the 4D speckle tracking pattern during the contraction. For these reasons, we decided to focus on the most robust and reliable parameter we could extract in our analysis.

CONCLUSION

The 4D Echo with speckle tracking mode allowed evaluating directly and simultaneously the regional strain values along various directions in the 17 left ventricle myocardial segments, without using any complicated model or assumption, as implied by other 2D speckle tracking or DTI methods.

The 21-days HDTBR induced in the control group a significant reduction in both the left ventricle volume and mass, associated with a significant drop in radial contractility (but not in longitudinal strain and twist). These changes in contractility were quite equally distributed among the basal and mid ventricular myocardial segments, thus suggesting a homogenous remodelling of the cardiac muscle, except at the apex where they were of lower amplitude. Unfortunately, these results do not allow concluding whether HDTBR induced a real cellular remodelling or only a muscle atrophy. Resistive exercise countermeasure was able to preserve both cardiac mass and contractility during HDTBR, thus proving its effectiveness to this aim. Nevertheless, the significant HDTBR-induced changes observed in the CON group had only a limited effect on the level of cardiac contractility observed at the post HDTBR tilt 80° position.

FIGURES

a b

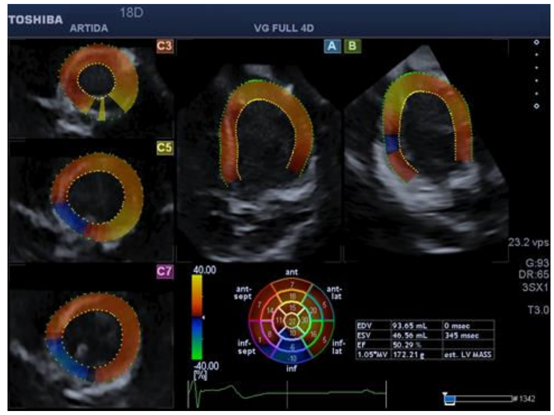


Fig. 2.1: Example of speckle tracking analysis performed off-line on the acquired 4D volumetric echo in one subject before HDTBR in supine position (a) and at HDT18 at -6° head-down (b). Apical long-axis 4- and 2-chamber views, as well as 3 transverse short-axis views of the left ventricle are visualized, each with the myocardial contour identified, and the corresponding color-coded strain computed. The 17 cardiac segments polar map summarizes the strain value (radial strain in this screenshot) in % for each segment in which the left ventricle was automatically subdivided. By comparing pre-HDTBR and HDT18 images, it is possible to evidence a reduction in yellow areas (higher values) with bed rest. This resulted in decrease in total strain from 275 a.u. (19+14+30+29+10+12+20+29+28+16+7+7+11+11+11+19+2) at pre to 178 a.u. (27+15+30+10+11+18+20+16-6+8+14+7+5+5-10+1+7) at HDT18.

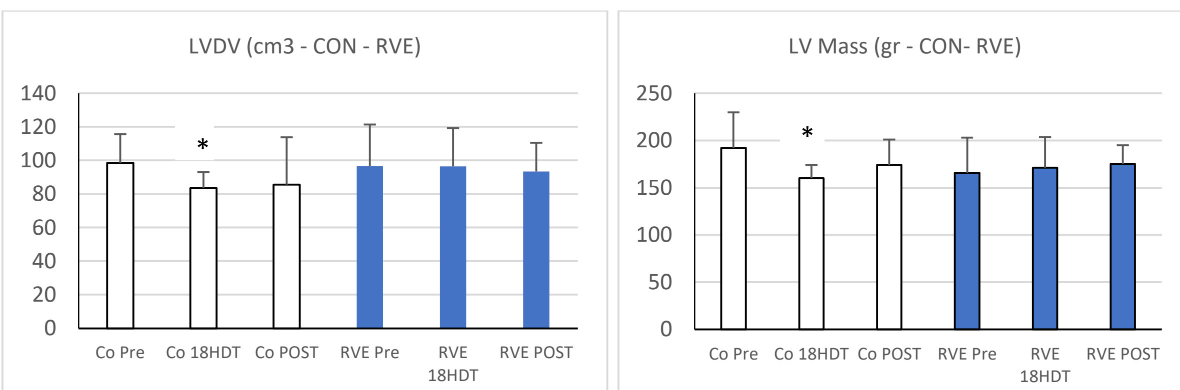


Fig. 2.2. Results obtained in the control (CON, white bars) and countermeasure (RVE, blue bars) groups relevant to left ventricle diastolic volume (LVDV, left panel) and left ventricle mass (right panel), at Pre-HDTBR, at HDT18, and at post. (: p<0.05 vs Pre). Post HDTBR the significance was lower (LVDV p<0,09 LVmass p<0,08 vs pre).*

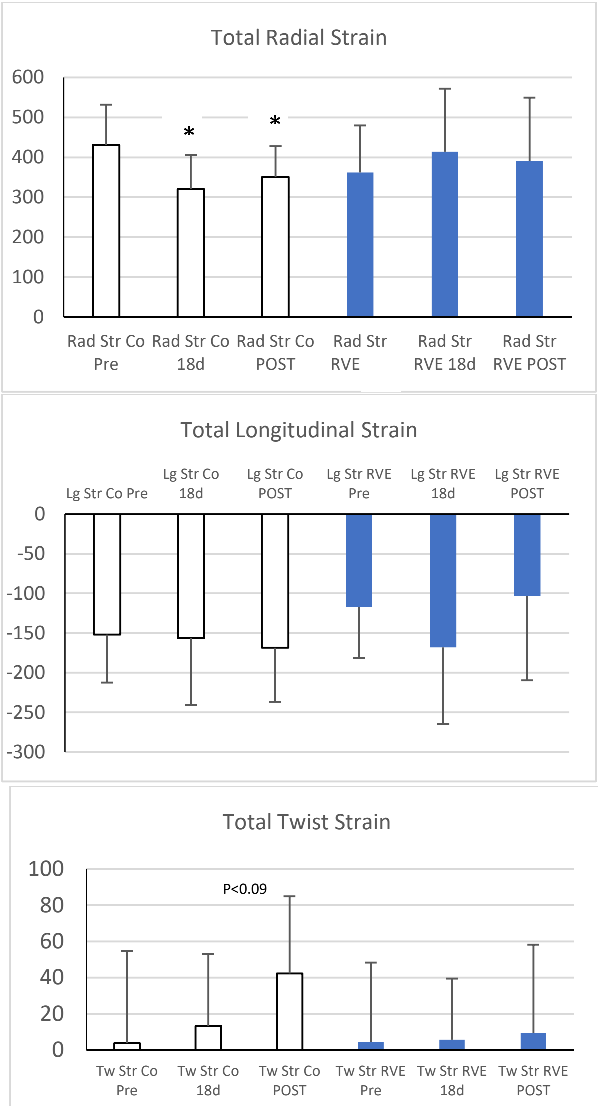


Fig. 2.3. Results obtained in the control (CON, white bars) and countermeasure (RVE, blue bars) groups relevant to left ventricle total radial strain (top panel), total longitudinal strain (center panel), Twist strain (bottom panel) at Pre-HDTBR, at HDT18, and at post, all expressed in arbitrary units. (: $p<.05$ vs Pre).*

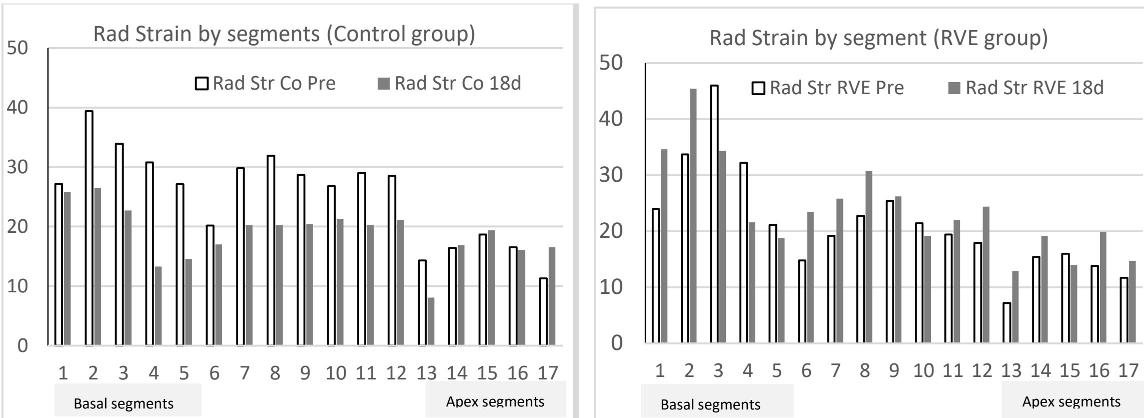
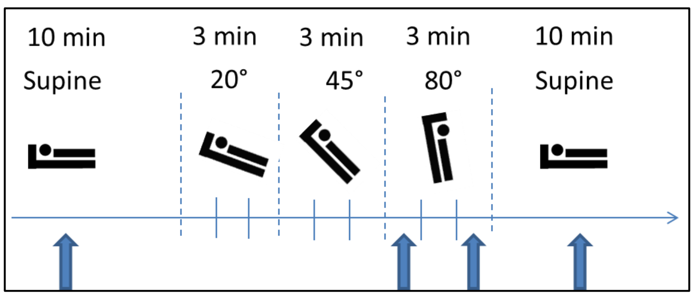
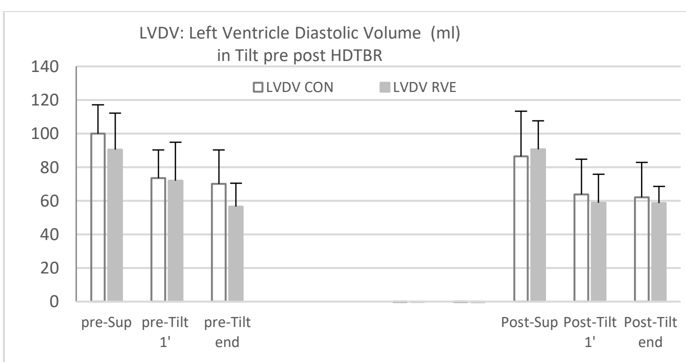


Fig. 2.4. Results obtained in the control (CON, left) and countermeasure (RVE, right) groups relevant to left ventricle radial strain for each of the 17 segments in which the 3D left ventricle was sub-divided, at Pre-HDTBR (in white) and at HDT18 (in dark gray). (in % values).



a



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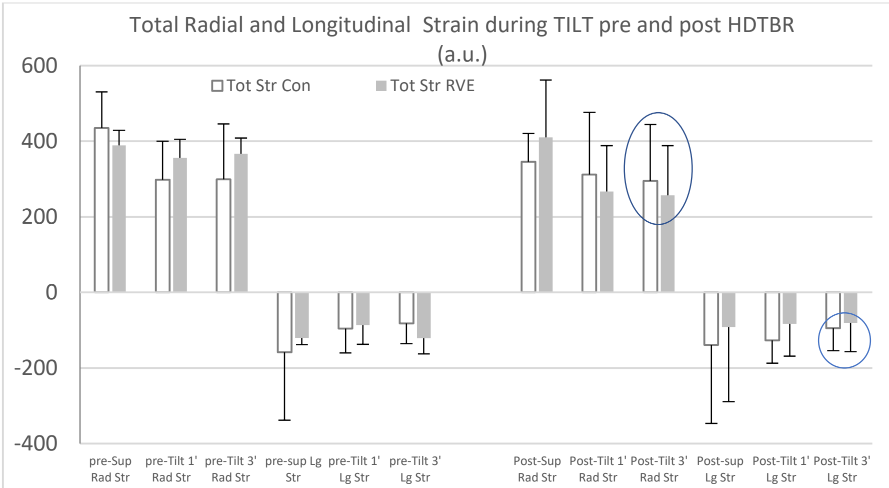


c

Fig. 2.5. Graded Tilt protocol (arrows indicate when 4D volumetric acquisition was performed) (a). Results obtained at Pre-HDTBR (left), and after HDTBR (right). In each case measures were performed before Tilt (supine: Sup), at 1 min of 80° tilt (Tilt 1'), and at the end of the Tilt test (Tilt 3'), in the control (CON, white) and countermeasure (RVE, light gray) groups: Left ventricle diastolic volume (b), and Radial and Longitudinal strains (Rad-Str and Lg-Str (c). Only LVDV and Rad-Str (supine) in the control gr were significantly different pre vs post. No significant difference were found for the Rad-Str nor Lg-Str at post HDTBR Tilt 80° position between the CON and RVE groups (circle).

Chapitre 3

Modifications cardiaque et artérielle morphologiques et fonctionnelles après quatre jours en immersion sèche avec et sans brassards de cuisse / Cardiac and arterial structure and functional changes after four days of dry immersion with and without thigh cuffs

ABSTRACT

Objective: a) to evaluate the cardiac and vascular changes induced by 5 days in Dry immersion (DI) b) test the efficiency of thigh cuff worn during the day at reducing the DI effect.

Method: Nine control subjects were immersed 5 days in a DI tank; nine treatment subjects were also immersed in the DI for five days but wore thigh cuffs during the day. Cardiac and vascular targets were assessed by ultrasound at the following timepoints: pre-DI, at day 4 AM (before donning cuffs for the day) and PM.

Results: No difference was found between the two treatment groups for any parameter. From Pre to Day 4 AM, the left ventricle volume stroke volume and ejection fraction all decreased significantly ($p<0.001$) while cardiac mass tended to decrease ($p=0.06$). Carotid intima media thickness (IMT) did not change while the femoral IMT increased ($p<0.05$) by Day 4 AM. The carotid distensibility decreased (i.e. stiffness increased) significantly ($p<0.05$). The carotid-femoral pulse wave velocity (PWV) and carotid-tibial PWV showed a decrease in half of the subjects (i.e. suggesting increased stiffness).

Both carotid and femoral flow volume as well as the flow redistribution index (carotid/femoral flow) remained unchanged. The intracranial flow velocity decreased and also the cerebral and carotid vascular resistance indices ($p<0.05$). Femoral and tibial resistance indices tended to decrease.

Conclusion: DI induced a) a reduction in cardiac volume that corresponds with a reduction in plasma volume, b) an increase in stiffness or wall thickness in some vessels probably explained by hypokinesia and environmental stress. The daytime thigh cuffs had no acute or chronic impact on the cardiac and arterial adaptation to DI.

Keywords: dry immersion; thigh cuffs; cardiac; vascular; echography.

INTRODUCTION

Several years ago, significant cardiovascular changes were reported during spaceflights, and head down bed rests (HDTBR) such as decreases in left ventricle diastolic volume, stroke volume, decreases in limb arterial vascular resistance or alterations in the orthostatic intolerance. (Arbeille et al., 2001; Arbeille et al., 2008a; M. Bungo & Charles, 1985; M. W. Bungo et al., 1985). Such changes occurred within the first day of HDTBR or spaceflight and were related to the abrupt cephalad fluid transfer induced by the environment (microgravity) or the position (head-down position) and the subsequent adaptation. Later on, cardiac mass decrease was measured which corresponded to a cellular adaptation to the new environmental condition, which included hypovolemia and the absence of exercise (Arbeille et al., 2008b; Dorfman et al., 2007; Perhonen, Franco, et al., 2001).

More recently, carotid and femoral intima media thickness (IMT) were found to be increased and the wall distensibility decreased in long-duration confinement (1G) and longer-duration spaceflight (0G (Arbeille et al., 2014; Arbeille, Provost, & Zuj, 2017; Yuan et al., 2019). The ground-based confinement results, in particular, could not be explained by fluid transfer (as in spaceflight), and subsequent flow and pressure redistribution. Moreover, they could not be explained exclusively by deconditioning nor to an abnormal nutritional regime; exercise and malnutrition are supposedly well-controlled for in spaceflight and confinement studies. On the other hand, a significant increase in carotid artery wall stiffness was found alongside disturbances in glucose metabolism (Hughson et al., 2016). This result suggests that several factors could be at least partially responsible for the accelerated aging of the arterial wall including inflammatory processes, deconditioning, environmental and psychological stresses.

Dry immersion (DI) has been proposed to simulate the fluid-shift related adaptations of the cardiac and arterial system. DI induces a sustained and prolonged pressure over the body from the neck down, causing a fluid transfer in the cephalad direction sustained over several days (Navasiolava et al., 2011; Watenpaugh, 2016). In a previous three day DI study, a drop in volemia and stroke volume was reported along with other changes to the venous system (Arbeille, Avan, et al., 2017). In the present five-day DI study, our objective was to detect and measure any changes in cardiac volume, carotid, femoral and tibial wall properties, regional flow redistribution and vascular resistance. Secondarily, the objective was to evaluate and quantify the efficiency of thigh cuffs when used during daytime only, similar to what is currently done in the Russian and USOS segments on ISS.

METHODS

Eighteen healthy male participants (33.4 $\pm$ 5.6 yr; height, 178.0 + 5.8 cm; weight 74.5 + 8.0 kg; 23.5 + 1.8 BMI; 46.1 + 5.4 VO_2max; 117 + 8 mmHg SBP; 65 +7 mmHg DBP; 59 + 9 BPM HR; study intake means + SD, see Table 3.1) underwent four days of dry immersion (DI) at the MEDES Space Clinic in Toulouse, France following methodology as previously described (Navasiolava et al., 2011). Two campaigns ran from November 2018 to March 2019. All participants completed a medical questionnaire, a lifestyle questionnaire and attended the facility for a medical screening battery prior to the study. All participants gave informed, written consent to participate in the study. This experiment was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and approved by the local institutional ethics committee (CPP Sud-Ouest Outre-Mer I) as well as the Government of France Health Authority.

Participants were assigned into either the control or cuffs group (9/9 split). The cuffs group wore the Russian Braslets device ("cuffs"; (Kozlovskaya, Grigoriev, & Stepantzov, 1995)) around both upper thighs tightened to 30 mmHg. Calibration was performed using (1) a strain gauge combined with (2) direct ultrasound measurements of the popliteal vein diameter. Cuffs were worn for eight consecutive daytime hours only, while immersed to the neck in the tank. The control group wore no cuffs while in the tank. Ultrasound measurements were taken (Orcheo-Lite, Sonoscanner, Paris, France) three days before entering the tank (Pre) in a semi-recumbent position to simulate the DI posture without immersion. Measurements were repeated again twice more on the fourth day in the tank: in the morning (D4 AM) prior to donning the cuffs for the day (cuffs group) and again in the afternoon (D4 PM) after having worn the cuffs for eight hours (cuffs group).

Participants were passively lifted from the tank once per day in the morning for showering and toileting while remaining supine during their entire time out of the tank. Since other experiments required additional out-of-tank time, the total out-of-bath time was kept to approximately one hour per day (or less) between days one four. Participants were not permitted caffeine, alcohol or any strenuous physical activity for 24 hrs prior to the ultrasound sessions. There was no physical exercise in the tank.

Data Analysis:

Diameters were measured manually from the B-mode images using calipers placed by the same trained sonographer while IMT measurements were semi-automated using the RF-based, region-of-interest method in the software provided (Sonoscanner Version 8-3-101). Peak systole and min diastole pulse-wave velocities were chosen manually with calipers.

Arterial flows were calculated using these velocities multiplied by the cross-sectional area. Vascular resistance was calculated differently for the low resistance/cerebrovascular (MCA, CCA) and high resistance/peripheral beds (femoral, tibial) (Arbeille & Herault, 1997).

- Cerebrovascular resistance = (Vs-Vd)/Vs and Lower limb vascular resistance = Vd/Vs

Where Vs = maximum velocity at systole Vd = minimum velocity at diastole

Flow volume in the main peripheral arteries and cerebral arteries and flow redistribution ratio

Common Carotid: Qcc (ml/min) = mean velocity * vessel x-sectional area

Superficial Femoral artery Qfem = Mean velocity x *vessel x-sectional area

Middle cerebral artery flow Fmca = Mean velocity only (due to vessel x-section not being measurable) (Aaslid, Markwalder, & Nornes, 1982).

Flow redistribution ratio = Qcc/Qfem

Distensibility Index was calculated using the following formula (Arbeille, Avan, et al., 2017):

- DI = (Dd-Ds)/Ds, Where Dd = arterial diameter at end diastole and Ds = arterial diameter at end systole

Cardiac volume and mass were calculated:

-Left ventricle diastolic volume: LVDV(cm^3)= [(7 x $LVDD^3$)/(2,4+LVDD)] with LVDD and LVSD left ventricle diastolic and systolic diameter (Teichholz, Cohen, Sonnenblick, & Gorlin, 1974)

- Left ventricle mass: LVmass(g) =0.80[1.04[$(PWT+LVDD+SWT)^3$ -$LVID^3$)]+0.6

SWT = septal wall thickness PWT = posterior wall thickness LVDD = left ventricle internal diameter (Myerson, Montgomery, World, & Pennell, 2002)

Statistical Analysis:

To test the hypothesis that wearing the cuffs for eight hours during dry immersion affected cardiac function, arterial wall properties and arterial blood flow properties, a dependent t-test was used to compare D 4AM to D 4PM, preceded by a Shapiro test for normality. To test the hypothesis that four days of dry immersion affected these main outcomes, a 2X2 Repeated Measures ANOVA was used to compare Pre to D 4AM with a main effects analysis for time and condition, followed by a Shapiro test for normality on the residuals. Significance was set at <0.05; means are reported as ± standard deviations. All tests were coded in R 3.6.0 (R Core Team, Netherlands).

Table 3.1. Participant characteristics at time of selection visit.

	Treatment	Age (y)	Height (cm)	Weight (kg)	BMI	VO_2max	SBP (mmHg)	DBP (mmHg)	HR (BPM)
Mean	All subject	33.4	178.0	74.5	23.5	46.1	116.6	64.9	58.5
SD		5.36	5.76	8.03	1.83	5.43	8.41	6.53	8.49
Mean	Cuff group	33.6	180.4	74.3	22.8	43.7	115.3	63.7	60.7
SD		3.44	4.14	9.00	1.71	2.49	8.56	6.70	8.22
Mean	Control gr	33.3	175.6	74.8	24.2	48.6	117.8	66.1	56.3
SD		6.75	6.11	6.91	1.67	6.38	8.08	6.12	8.21

RESULTS

Subjects: Participant characteristics are listed in Table 3.1.

Cardiac and Vascular data after 4 days in Immersion (D4 AM): The first hypothesis was to test the chronic effect of the dry immersion with and without daytime thigh cuffs. This was achieved by testing baseline (Pre) against the fourth day, in the morning (D4 AM) with main effect of time and interaction effect of condition. None of the cardiac or vascular parameters had a significant interaction effect, meaning it made no difference if the cuffs were worn for the previous three daytime periods or not. As such, subsequent results will be reported as pooled for all 18 participants.

Cardiac-Structure and Function (Fig. 3.1):
At D4 AM: left ventricular diastolic volume was significantly lowered from 164.6 ± 42.9 ml to 152.5 ± 37.2 ml (mean = -8% loss; $p=0.0293$) while left ventricular systolic volume was unchanged ($p>0.05$). Stroke volume was significantly reduced (108.4 ± 27.5 ml to 93.3 ± 22.7 ml; mean -14% $p<0.001$) and also the ejection fraction (0.66 ± 0.06% to 0.62 ± 0.07%, mean -6% $p<0.01$).

Cardiac mass showed a tendency to decrease (200 +/- 60g to 180+/-40g mean -7% p=0.0613 - 11/18 Subjects).

Arterial Wall Properties (Fig. 3.2): Carotid artery distensibility index dropped significantly from 0.108 ± 0.024 units to 0.097 ± 0.026 units (mean -9% p=0.041) while the carotid-femoral pulse wave velocity and carotid-tibial pulse wave velocity tended to decrease in 11/18 subjects (p=0.07).

The intima media thickness (IMT) of the superficial femoral artery was, on average, 4% thicker (0.42 ± 0.056 mm to 0.44 ± 0.063 mm; p<0.05), whereas he carotid IMT did not show significant change (Fig. 3.2).

Resistivity index (RI) and arterial hemodynamic (Fig. 3.3): Middle cerebral artery mean velocity was significantly lower at D4 AM compared to Pre (mean -16% p=0.0416). The common carotid resistance index (RI) was lower (0.825 ± 0.037 to 0.794 ± 0.028 units mean -4%, p=0.0023) while RI of the tibial artery also trended towards a decrease (mean -7% p=0.0683 on 11/18 subjects). RI calculated for MCA and SFA were not found to be statistically different (p>0.05), thought it could be noted that these parameters did decrease in 9/18 subjects. Flows volume in the common carotid and superficial femoral arteries were unchanged after four days in dry immersion (all p>0.05, Fig. 3.3). The flow redistribution ratio (carotid flow/femoral flow) did not change significantly.

Cardiac and Vascular data at D4 PM compare to D4 AM: The second hypothesis was to test the effect of wearing the cuff during the day and this test was done on Day 4 of the immersion by comparing morning (before donning cuffs: D4 AM) to afternoon (after having worn the cuffs for eight hours D4 PM). Only the SV tended to increase in 12 of the 18 subjects (p<0.09); none of the other parameters mentioned above showed significant change.

DISCUSSION

By the fourth day in the morning (D4 AM), the dry immersion participants showed significant decreases in left ventricle volume and stroke volume (approx. -14% $p<0.05$) which corresponded to the drop of approximately 20% in plasma volume (Navasiolava & Custaud submitted). It has been shown previously that dry immersion, along with head-down tilt bed rest, induces hypovolemia via a neuro-hormonal response mediated by the carotid and cardio-pulmonary baroreceptors (Hughson et al., 1995) (Watenpaugh, 2016). It follows that the left ventricle filling pressure would be reduced, explaining the significant reduction in ejection fraction observed. It seems unlikely that this is due to a decrease in contractility as there has been very little time for remodeling of the cardiac myocytes. While not significant, there was a trend (11/18 subjects; $p=0.06$) for lower left ventricular mass (approx. -7%).

At D4 AM, no difference in LVDV, SV, LVmass was found between treatment groups, implying there is no "memory" effect of having worn the cuffs during the day for the previous three days. Everything "resets" overnight. Nevertheless, there is some (albeit rather weak) evidence of a daytime effect on cardiopulmonary function: during the daytime period (8h am to 6pm) the SV tended to increase in 12 of the 18 subjects ($p<0.09$) 6 in the control (no cuffs) group. During previous HDTBR and spaceflight experiments, the left ventricle volume was restored to pre HDTBR/pre-flight values after 8h wearing cuffs and this is in contradiction with the present DI study where no significant change was found with cuff intervention (Herault et al., 2000) (Arbeille, Diridillou, et al., 1999).

These trends to decrease observed for the cardiac volume, are probably related, again, to the aforementioned hypovolemia, reduced preload and deconditioning; there is no exercise at all while in the tank. From Table 3.1., it can be noted that none of these participants were athletes of the caliber of many long-duration ISS crews. If DI were indeed performed on athletes with VO2max and heart mass matched to current ISS crew, we would expect larger heart mass decreases in DI, which is, after all, a no-exercise model of space simulation. Since all crew are prescribed a custom exercise countermeasure to perform while in microgravity, we suggest developing the DI space analog model to include exercise of similar duration, intensity and type as what is currently performed on ISS. For studies looking to simulate sojourns beyond low-Earth orbit, we further suggest an exercise DI model that matches what is currently in work at the agencies for exercise countermeasure planning.

The novel observations of this study are, instead, related to neck level (carotid stiffness) changes as well as leg level (femoral IMT) changes to the artery wall. Common carotid artery distensibility index decreased, suggesting increased stiffness in the vessel wall. This distensibility measure is conservative because it assumes no change in carotid distending pressure from Pre to Day 4AM & PM. In spaceflight, carotid distending pressure would have been expected to increase compared to pre-flight (standing) due to fluid shift induced pressure redistribution, but in the DI model the hydrostatic pressure remains unchanged at the neck level. The scans were done in the same semi-recumbent position between Pre and Day 4 AM & PM. So, to see a change in distensibility on the fourth day, while assuming no change in carotid distending pressure, suggests that even 4 days of DI is sufficient to induce arterial stiffness increase. Nevertheless, the change in distensibility were far below the magnitude expected (Arbeille, Avan, et al., 2017) (Hughson et al., 2016), indicating that the DI stimulus was not sufficient to reproduce the published effects observed with spaceflight. There was no cumulative, or “memory” effect of wearing cuffs during the day for three days in DI on the carotid stiffness. There was also no acute effect after 8h.

While the carotid stiffness increased, the carotid IMT did not change significantly (increase in 4/18 subject only). This is contrary to what observed on 75% of the subjects in long duration spaceflight (6 month) and confinement (520 day and 180 days; (Arbeille et al., 2014; Arbeille, Provost, et al., 2016; Yuan et al., 2019). Carotid stiffness and IMT has been shown to not be correlated in space studies (Arbeille, Avan, et al., 2017), meaning that the mechanisms underlying these two process are likely different.

Nevertheless, we did expect to see increases in carotid to mirror the observed femoral IMT increase. This speaks to our concern that the stimulus was insufficient to gain significance but perhaps sufficient to start the physiological process(es) in some participants. Given a stronger DI stimulus i.e. more time in the tank or deeper body immersion), it seems logical to expect that the carotid IMT would likely have followed the femoral IMT. For IMT to change, cellular remodeling must have occurred, which appears to require more than four days in DI to get underway in the carotids of most participants. It is helpful to keep in mind that microgravity alone cannot explain why the carotid and femoral IMT changes as increased IMT is also observed in Earth-based confinement. IMT remodeling, then, appears to have more to do with hypoactivity, nutrition, stress than with any pressure or flow redistribution that microgravity will induce.

Carotid and femoral flows (ml/min) did not change after four days in immersion, nor did the carotid to femoral flow ratio. This was expected because, previous HDTBR and DI studies, showed that 2-3 hours in the tank induces notable fluid shifts towards the head and thorax with the internal jugular vein significantly enlarged and the intracranial pressure increased in 50% of the subjects, but the carotid flow remains stable even after this period when the subject is already becoming hypovolemic (Arbeille, Avan, et al., 2017).

After Day one, the participants had three additional days with lower overall blood volumes but no pressure or flow redistribution. In addition, downstream vascular resistance (i.e. the areas supplied by the carotids and femorals) decreased or at least showed a tendency to decrease which may have contributed to maintaining the flow into these areas. The cuffs did not affect femoral flow because they were of low pressure and only superficial leg veins were compressed. The venous return through the deep veins remained unchanged and therefore the arterial flow proceeded unaffected.

Conversely, the mean flow velocity in the MCA was reduced with DI which means that, barring any diameter change, the flow volume in the MCA should also have been reduced (around 15%) in these subjects. This may be related to the slight increase in cerebral resistance index present in 9/18 subjects. The cerebral resistance index ((S-D)/S) measures the proportion of diastolic flow (D) compared to systolic (S) and the increase of the resistance index correspond to a decrease in cerebral diastolic flow. In the present study, the reduction in cerebral diastolic velocity was consistent with the reduction in stroke volume and plasma volume. Finally, the cerebral flow was slightly reduced at Day 4 in the morning in all subjects but showed a tendency to increase during daytime (8AM to 6PM) in both treatment groups. Such an increase was concomitant with the increase in stroke volume during the same period, probably related to daytime activity. Again, the thigh cuffs had no effect on the arterial cerebral flow.

During short-duration bedrest or short-duration confinement (4 days), the carotid and femoral vascular resistance and flow also remained unchanged or showed very limited variation, similar to the current study. The arterial response to orthostatic test after the 4 days was, however, affected in the previous work. (Arbeille et al., 1998). This reinforces the idea that four days of either dry immersion, confinement, bedrest is not long enough to induce remodeling and significant hemodynamic changes at rest, but can still have an impact on arterial dynamic function such as active vasoconstriction or dilatory capacity in response to acute fluid transfer (mediated by tilt or LBNP for example).

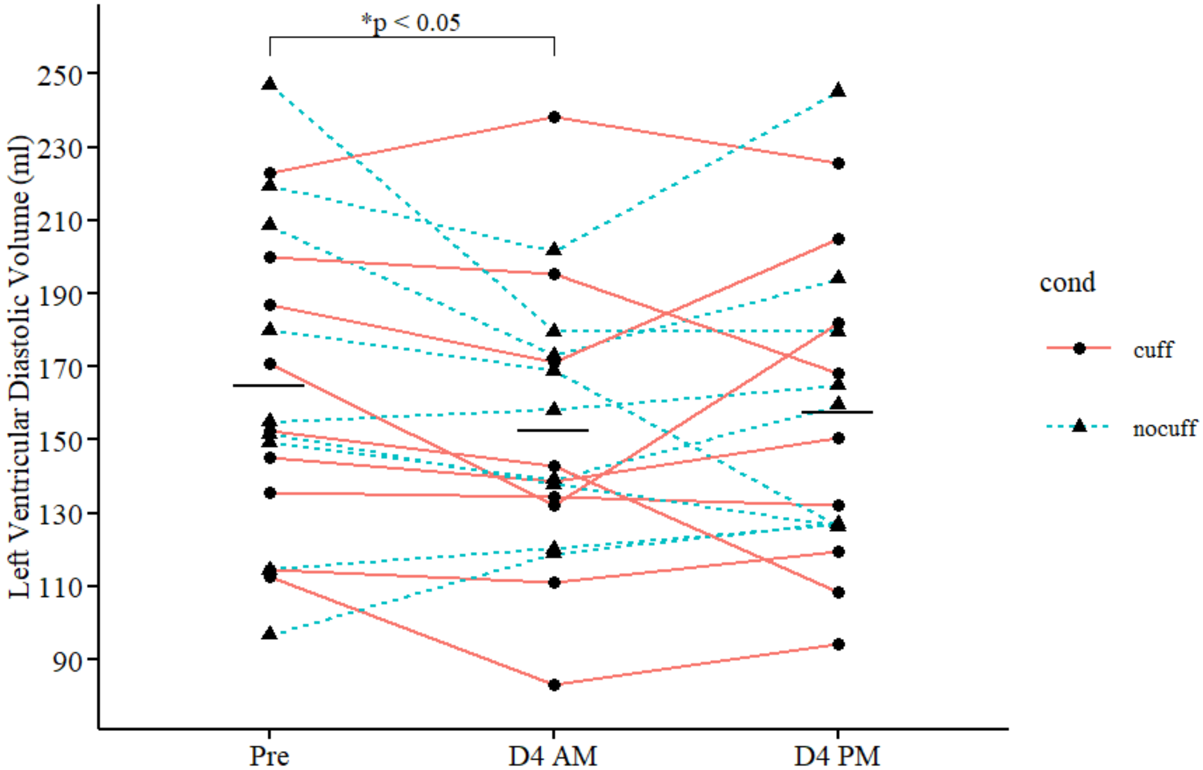
The thigh cuff countermeasure was proposed for the current study because it is used extensively in-flight, particularly in the Russian segment but also by USOS crew. Personalized cuffs launch in the personal kit items of every crewmember. The cuffs are either self-prescribed or recommended by crew surgeons to reduce the cephalad fluid shift and mitigate headache, full sinuses and other general “head stuffiness” symptoms. In the present experiment, the thigh cuffs were worn for eight hours per day and had a limited impact on the arterial network. At Day 4 in the morning before donning the cuffs, none of the arterial parameters presented above showed a cumulative cuff effect; the treatment groups were indistinguishable by the next morning. Moreover, the trends and tendencies observed in some parameters were often equally distributed between the treatment groups among the two groups, supporting the explanation that the countermeasure had limited impact on the arterial network.

Previously, the same cuff countermeasure was tested during a 7-day bedrest and 6-month spaceflights, and again, no effect was detected on the arterial hemodynamics (specifically carotid and femoral flows) and no “cuff memory” effect was found at Day 7 in the morning after a night without cuffs, or at the end of spaceflight mission. This is consistent with our observations after 4 days in DI. On the other hand, a reduction in cerebral resistance index, together with the stroke volume (hypovolemia) were also measured in both studies (Herault et al., 2000) (Arbeille, Herault, et al., 1999). Nevertheless, in bed rest or spaceflight the thigh cuff countermeasure induced more change after 8h compared to what observed after 8h with cuff in DI. This might be explained by the fact that in head down bedrest the fluid transfer towards the head induced by the head down tilt position is facilitated by the gravity vector from feet to head and during spaceflight by the suppression of gravity, while in DI the gravity vector is opposite and counteracts the cephalad fluid shift.

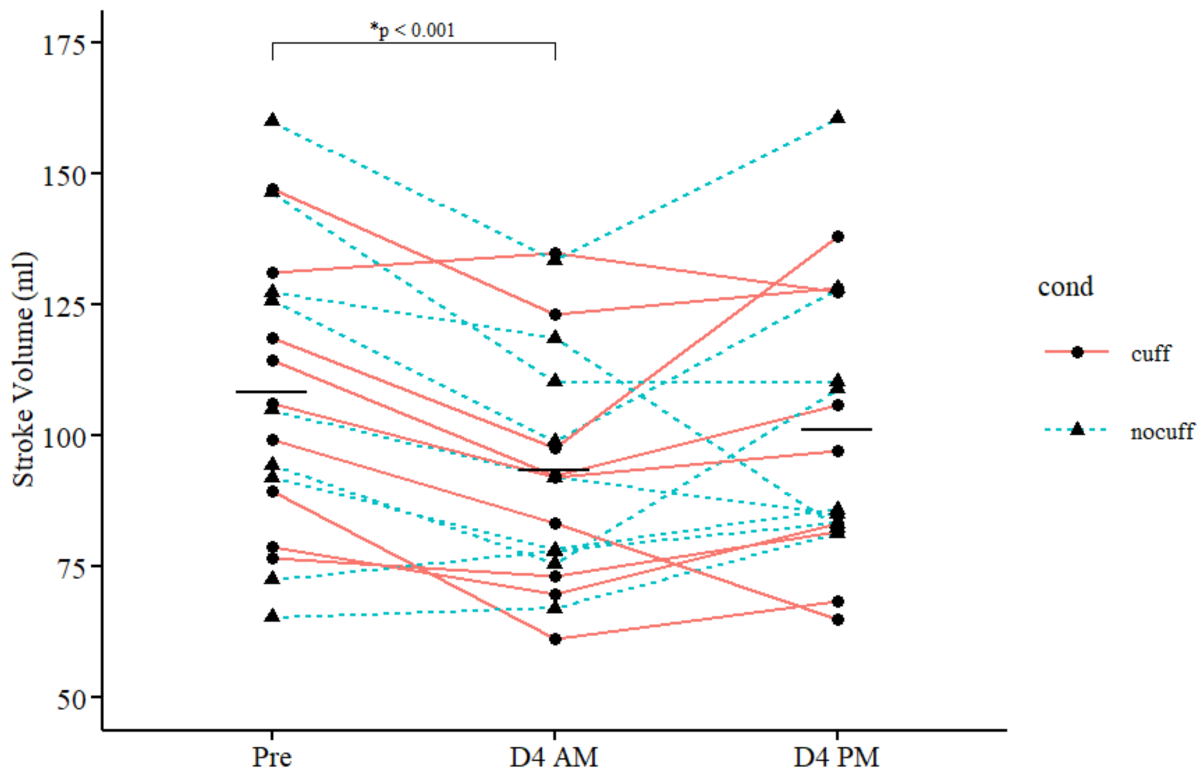
CONCLUSION

Dry immersion induced a cardiac volume decrease without evidence of contractility decrease. It also triggered a decrease in arterial distensibility and large artery IMT changes, at least in half the population both at carotid and femoral level, while the corresponding peripheral flows remained unchanged. We suggest that the duration of this DI (only four days) was too short for cardiac and arterial remodeling that has already been observed in long duration spaceflight, confinement, and HDT. Lastly, the cuff countermeasure worn for 8 hours per day had no “cuff memory effect” after 4 days on the cardiac nor the arterial parameters (as observed in a 7 day HDTBR and 6 months of spaceflight) and it tended to partially restore these parameters while in HDT and spaceflight it normalized them.

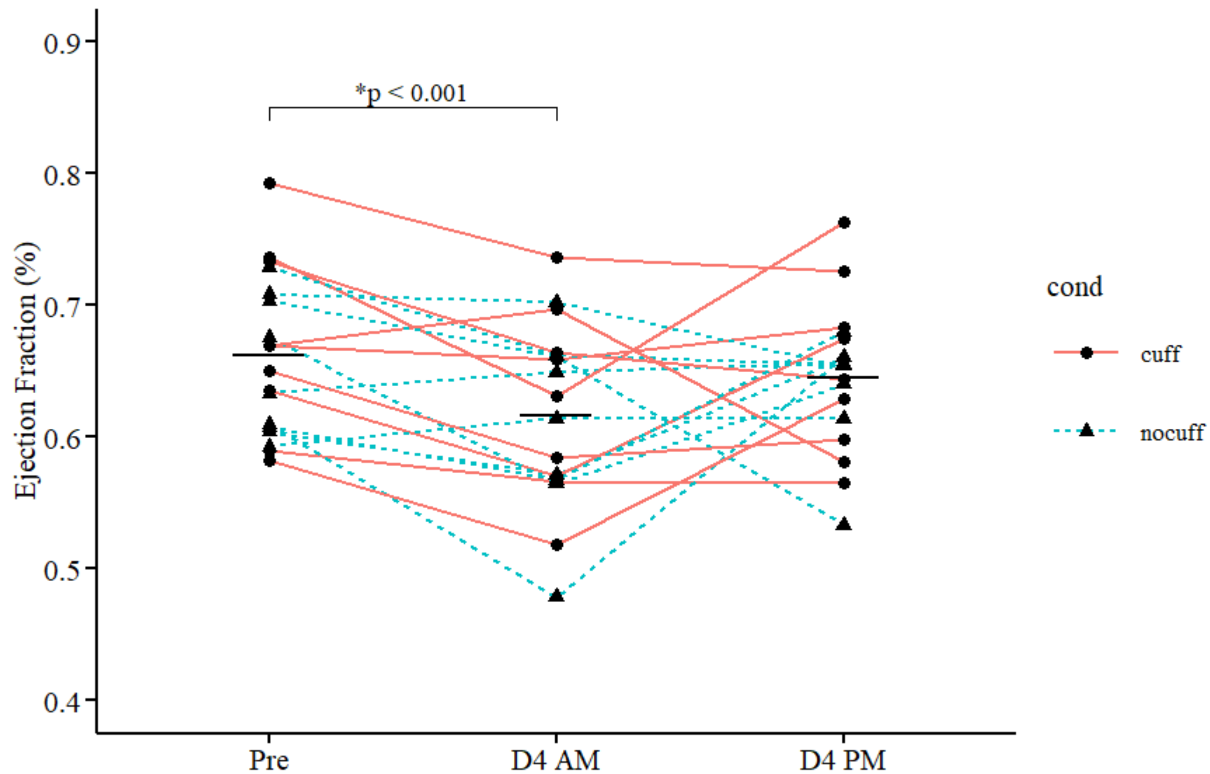
FIGURES



*p < 0.05
Left Ventricular Diastolic Volume (ml)
250
230
210
190
170
150
130
110
90
Pre
D4 AM
D4 PM
cond
cuff
nocuff



*p < 0.001
Stroke Volume (ml)
175
150
125
100
75
50
Pre
D4 AM
D4 PM
cond
cuff
nocuff


*p < 0.001
0.9
0.8
0.7
0.6
0.5
0.4
Ejection Fraction (%)
Pre
D4 AM
D4 PM
cond
cuff
nocuff

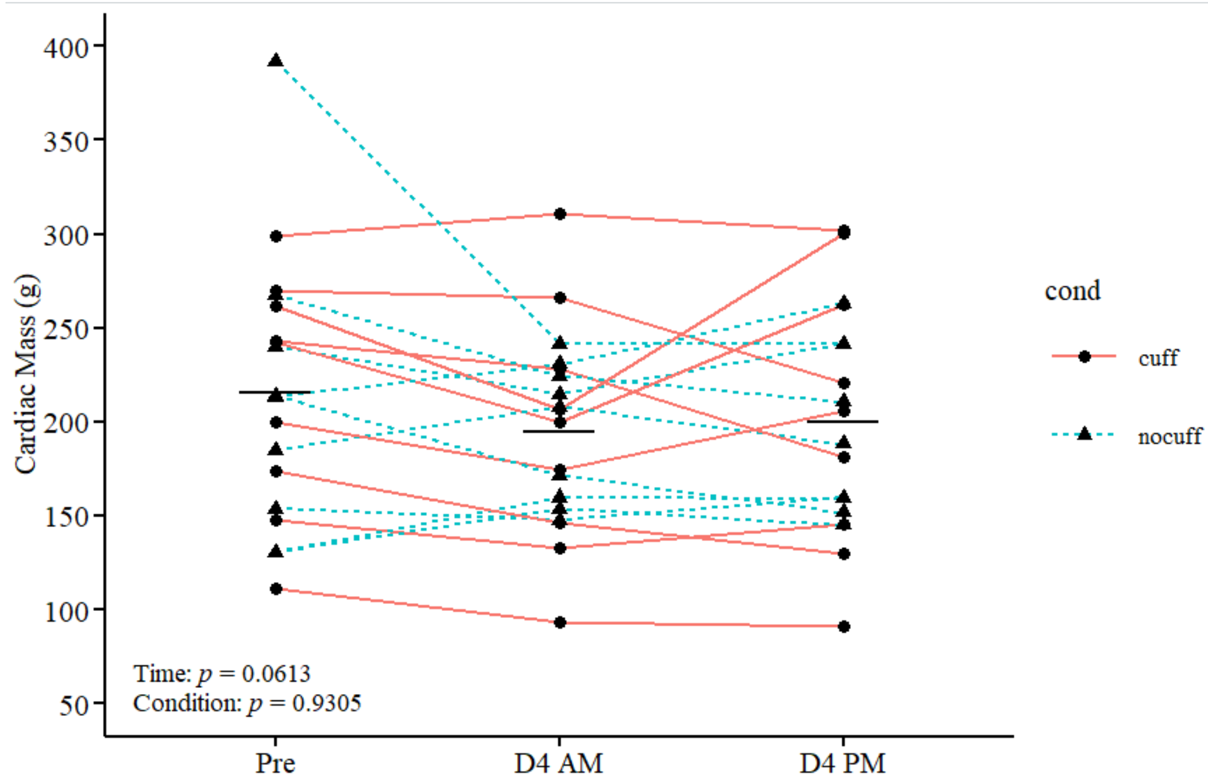
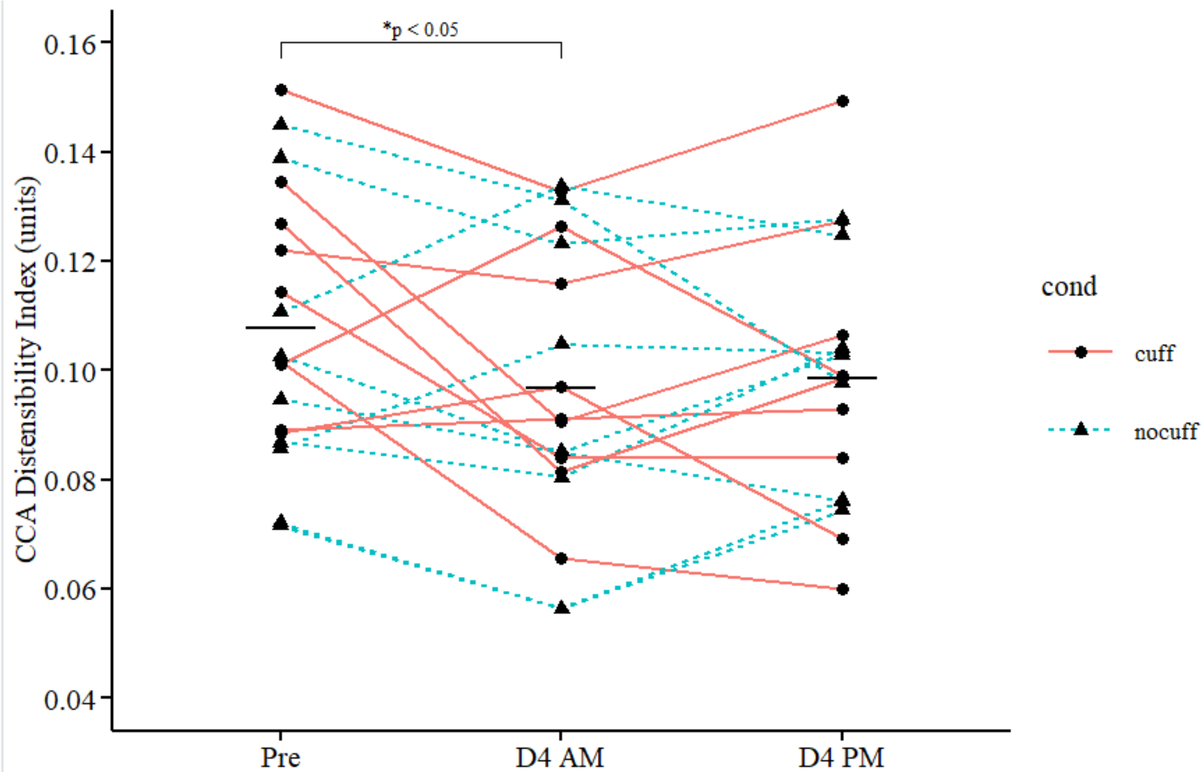
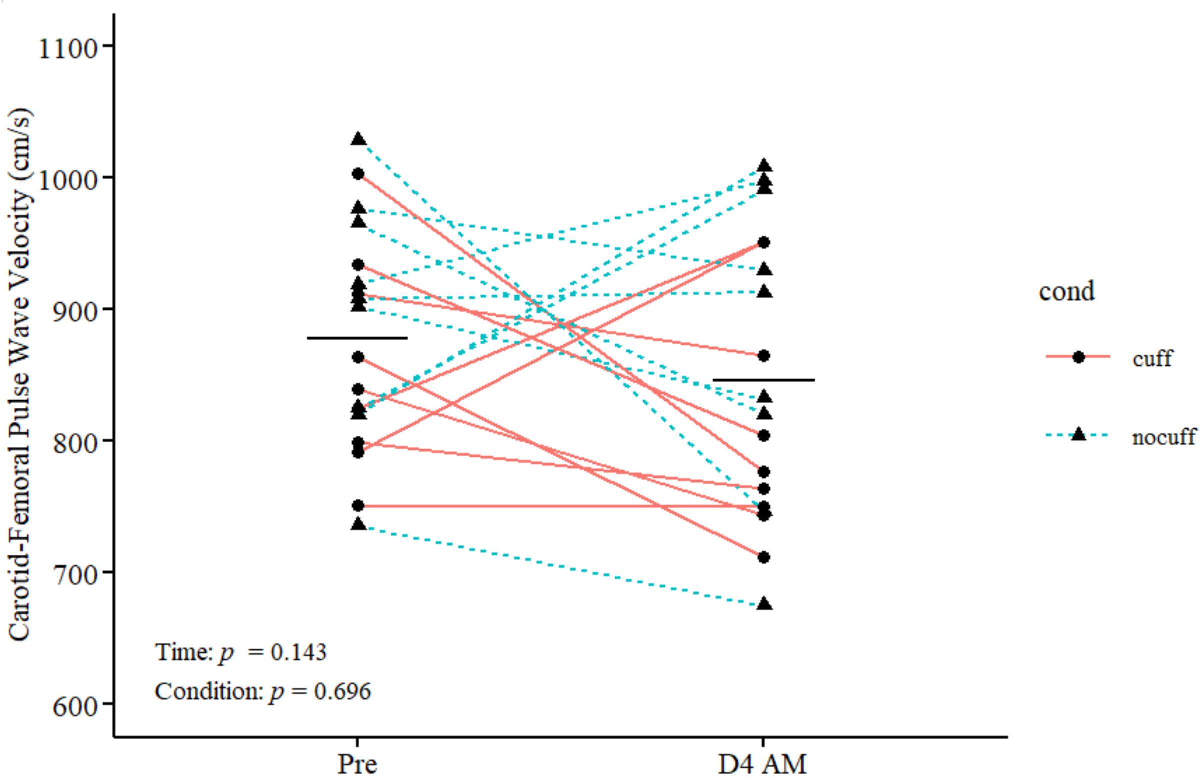

400
350
300
250
200
150
100
50
Cardiac Mass (g)
Time: p = 0.0613
Condition: p = 0.9305
Pre
D4 AM
D4 PM
cond
cuff
nocuff

Fig. 3.1. Cardiac function outcomes from four days of dry immersion. Horizontal black bars represent the mean. Day0 was prior to dry immersion; day4AM represents four days of dry immersion prior to donning cuffs for the day. Time effect tests the treatment of day0 to day4AM; Condition is the interaction effect of being in the cuff or control group against time.



*p < 0.05
0.16
0.14
0.12
0.10
0.08
0.06
0.04
CCA Distensibility Index (units)
Pre
D4 AM
D4 PM
cond
cuff
nocuff



1100
1000
900
800
700
600
Carotid-Femoral Pulse Wave Velocity (cm/s)
Time: p = 0.143
Condition: p = 0.696
Pre
D4 AM
cond
cuff
nocuff

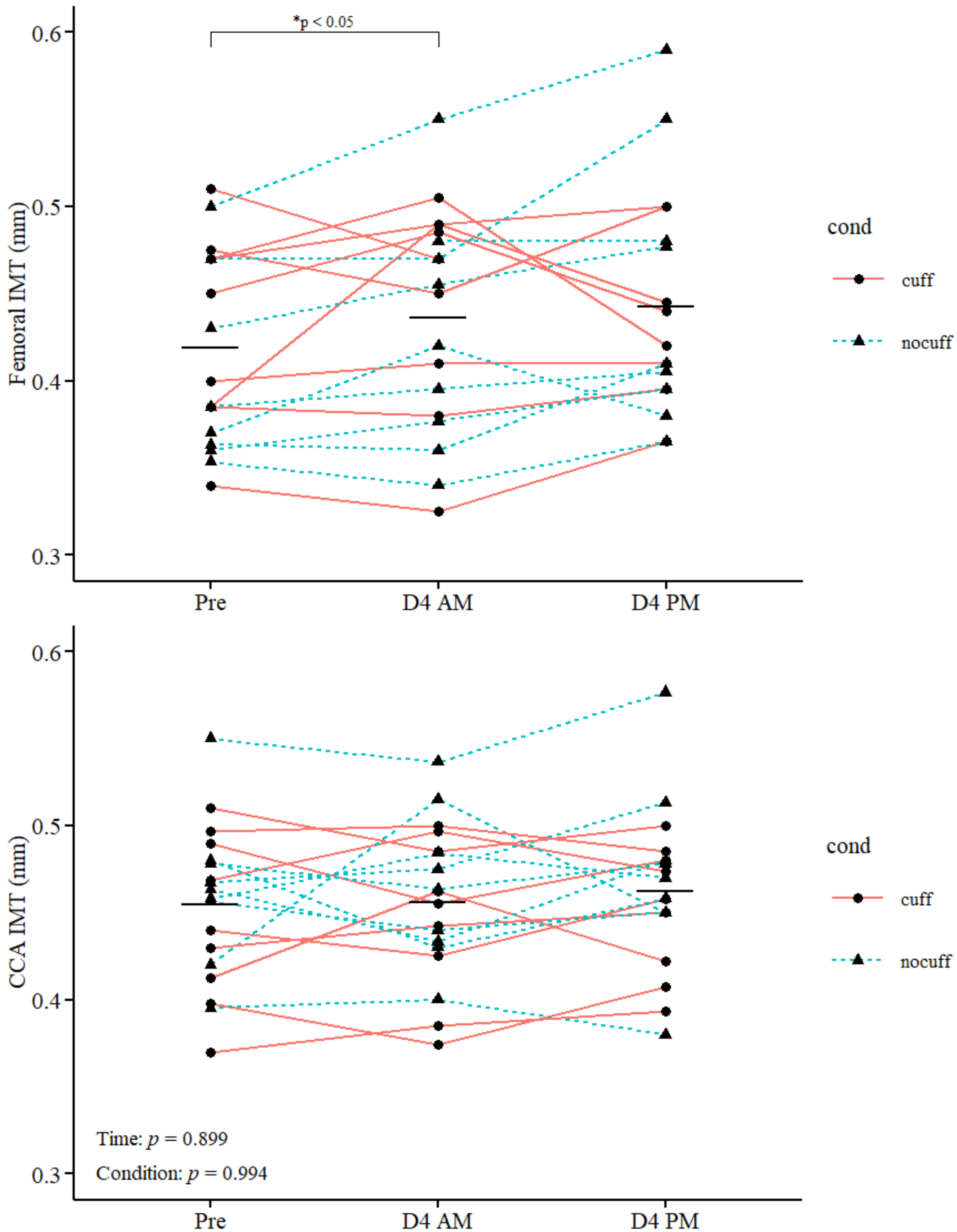
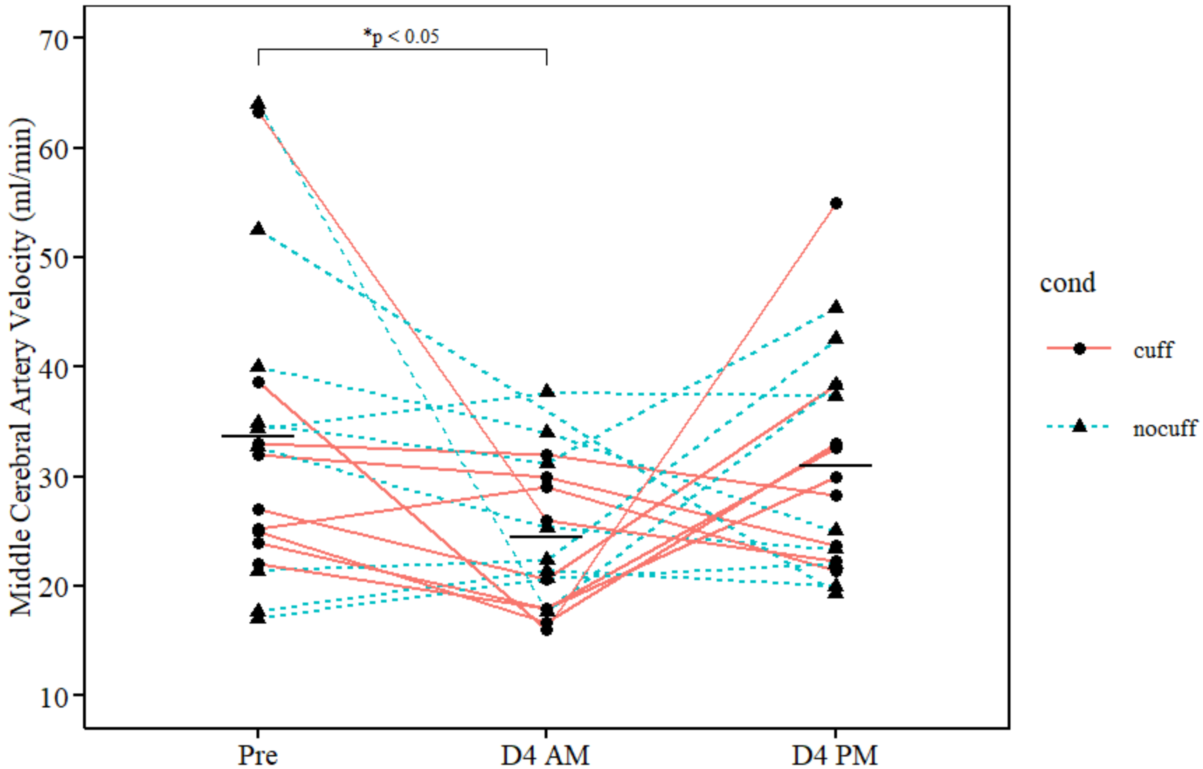
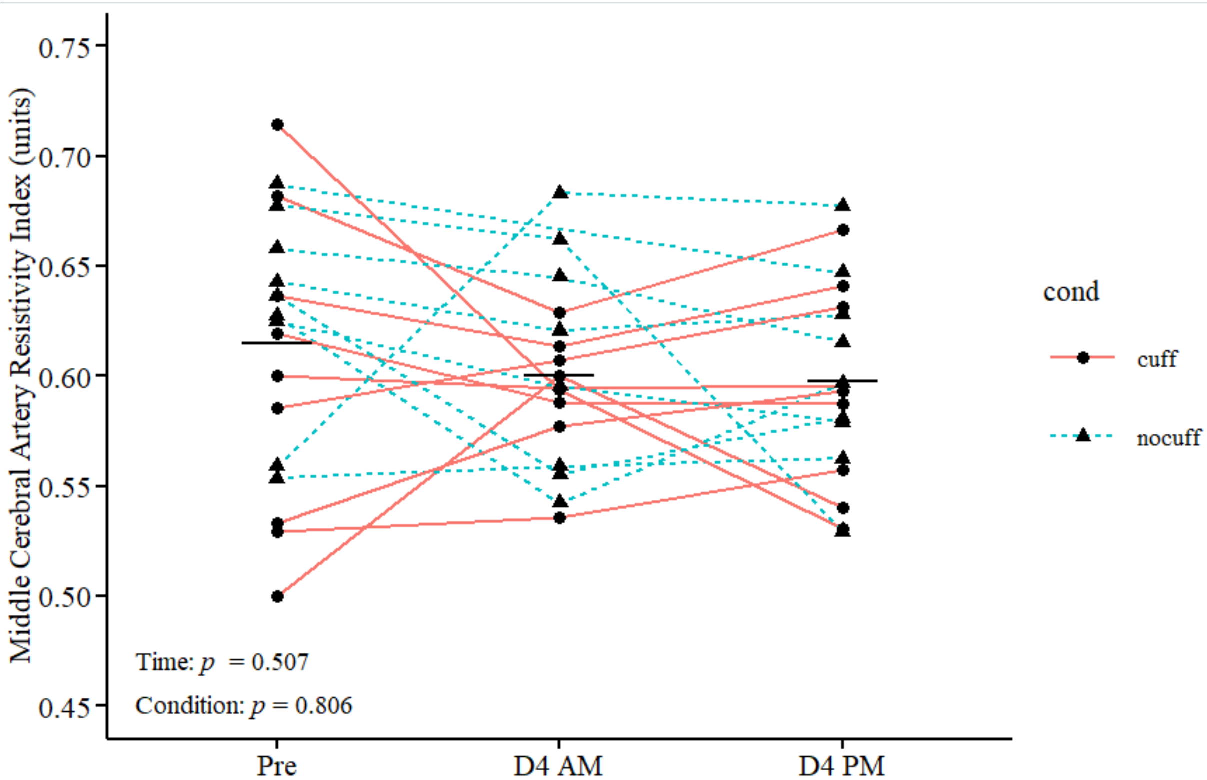
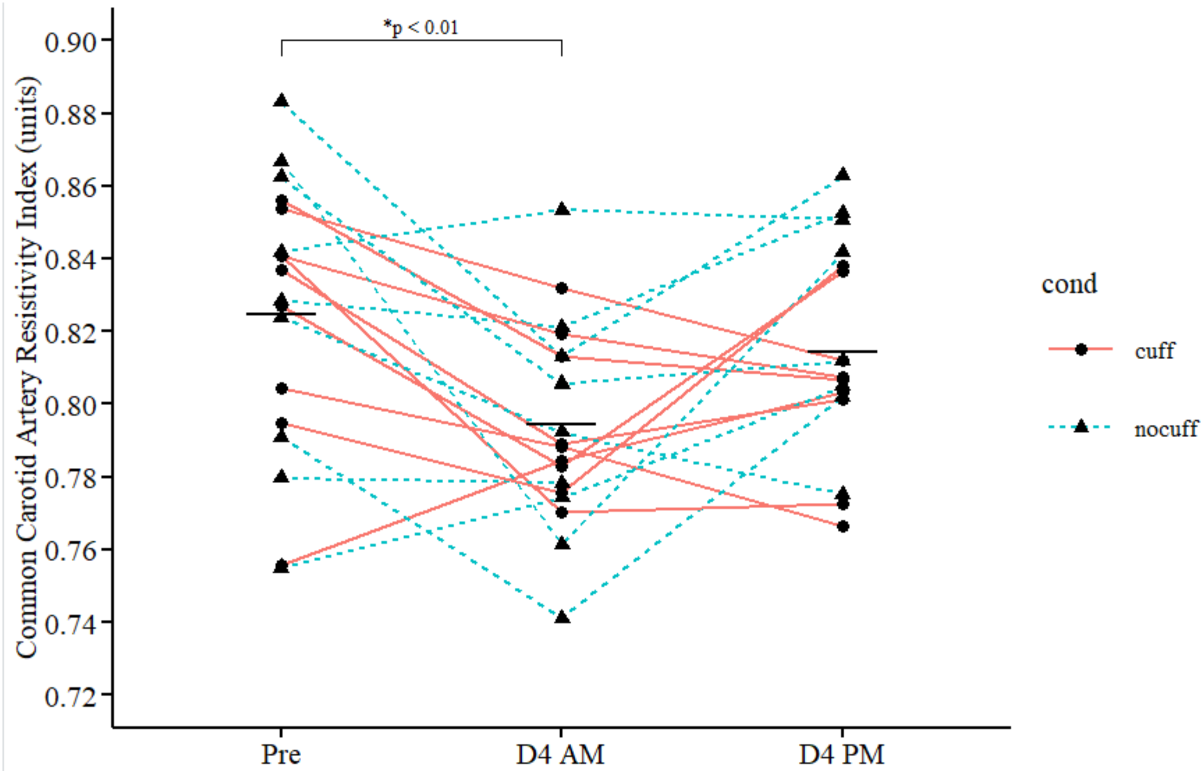


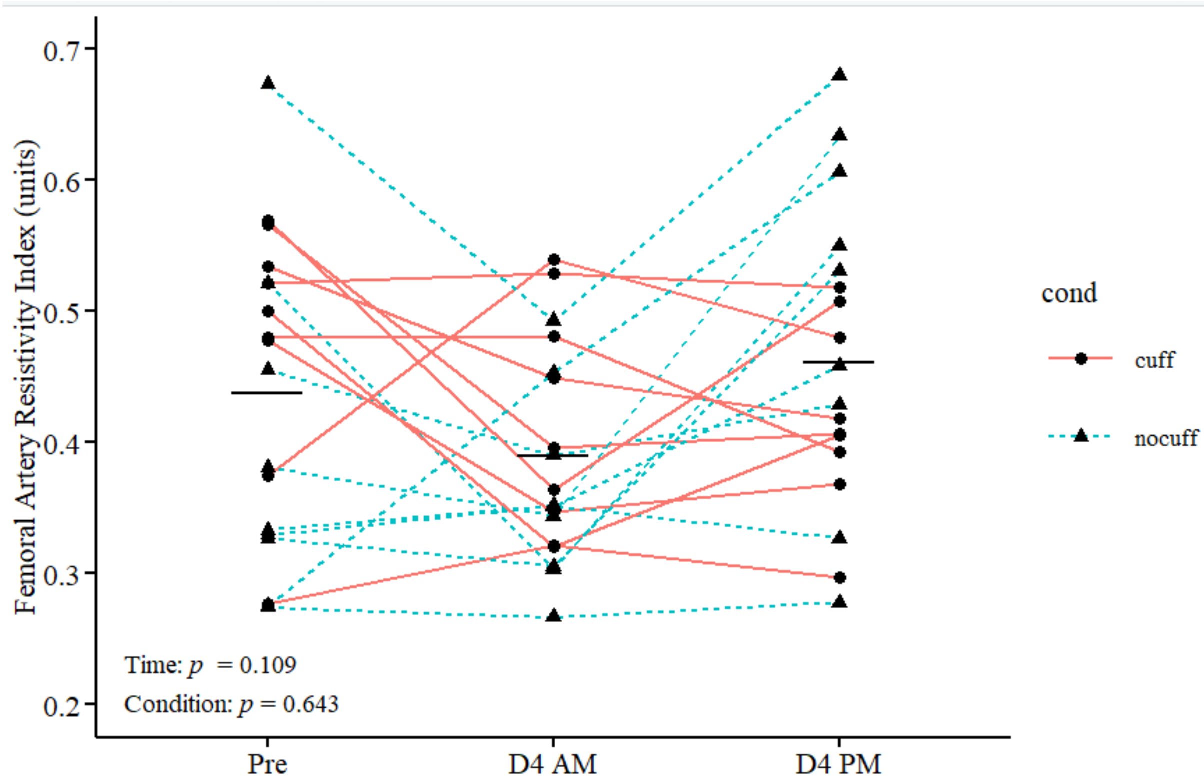
Fig. 3.2. Arterial wall properties after four days of dry immersion. Horizontal black bars represent the mean. Day0 was prior to dry immersion; day4AM represents four days of dry immersion prior

to donning cuffs for the day. Time effect tests the treatment of day0 to day4AM; Condition is the interaction effect of being in the cuff or control group against time.






*p < 0.01
Common Carotid Artery Resistivity Index (units)
0.90
0.88
0.86
0.84
0.82
0.80
0.78
0.76
0.74
0.72
Pre
D4 AM
D4 PM
cond
cuff
nocuff


Femoral Artery Resistivity Index (units)
0.7
0.6
0.5
0.4
0.3
0.2
Time: p = 0.109
Condition: p = 0.643
Pre
D4 AM
D4 PM
cond
cuff
nocuff

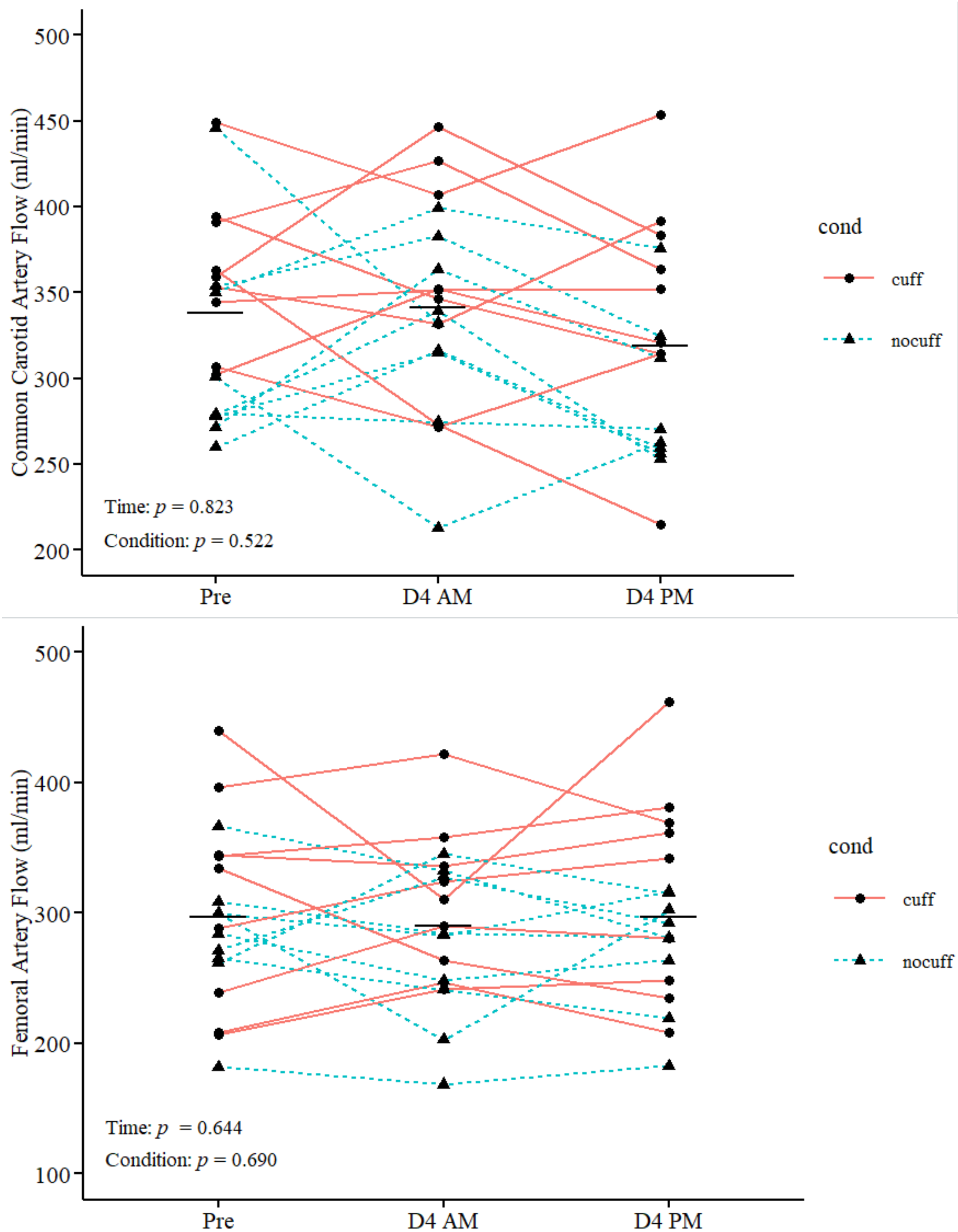


Fig. 3.3. Resistivity indices, flows and cerebral flow velocity after four days of dry immersion. Horizontal black bars represent the mean. Day0 was prior to dry immersion; day4AM represents four days of dry immersion prior to donning cuffs for the day. Time effect tests the treatment of

day0 to day4AM; Condition is the interaction effect of being in the cuff or control group against time.

Chapitre 4

Effet des brassarts de cuisses sur la redistribution veineuse pendant 4 jours en immersion sèche / Effect of thigh cuffs on venous redistribution during 4 days in dry immersion

ABSTRACT

Purpose: The objective was to quantify the venous redistribution during a 4-day dry immersion (DI) and evaluate the effect of thigh cuffs.

Methods: The study included 9 control (Co) and 9 subjects wearing thigh cuffs during daytime hours (CU). Ultrasound images were collected Pre DI, on the fourth day in the morning (D4 AM) and on the fourth day in the afternoon (D4 PM), to assess the following outcome variables: left ventricle dimension, stroke volume, and ejection fraction (LVD, SV, EF), jugular vein volume (JV), portal vein dimension (PV), middle cerebral vein velocity (MCVv). An additional measure of JV dimension was performed on the first day after having worn the cuffs for two hours (D1 2H).

Results: The JV volume increased significantly from Pre to D1 2H in both groups, but increased more in the Co compare to the CU subjects (Co: 0,27+/0.15cm^3 to 0.94+/-0;22 cm^3;P<0.01 CU: 0,32+/-0.13 cm^3 to 0.64+/-0.32 cm^3 P<0.042).

At D4 AM no difference was found between the two treatment groups for any of the parameters listed above.

Stroke volume and EF decreased from Pre (SV:111+/-23cm^3 to 93+/-24 cm^3 p<0.05; EF:0.66+/-0.07 to 0.62+/-0.07 p<0.05). JV volume was slightly, but significantly increased (Co: 0.47+/-0.22cm^3 CU:0.35+/-014cm^3 P<0.05), while MCVv and PV remained unchanged from Pre DI. From D4 AM to PM these parameters did not show any significant change.

Conclusion: The results confirm that DI induces, during the first 2-3 h, a significant cephalic fluid shift as observed in spaceflight. During this early phase the thigh cuffs reduced the amplitude of the fluid shift towards the head, but after 4 days in DI there was only a slight memory (residual) effect of DI on the jugular volume and no residual effect of thigh cuffs.

Keywords: Dry immersion, Jugular vein, Cerebral vein, Portal vein

INTRODUCTION

Some astronauts reported vision problems during long duration spaceflights onboard the International Space Station (ISS) which has led to the hypothesis that vision problems may be caused by cephalic fluid shifts induced by the absence of gravity resulting in an increased intraocular pressure (IOP) and intracranial pressure (ICP). A recent study has provided support for this hypothesis demonstrating an increase in ICP and IOP with cephalic fluid shifts induced by head down tilt and a reduction in ICP and IOP when fluid was shifted away from the head using lower body negative pressure (Macias, Liu, Grande-Gutierrez, & Hargens, 2015).

Dry immersion (DI) has been proposed as method of mimicking the effects of microgravity exposure on Earth (E. Shulzhenko, Vil-Vilyams, Grigoryev, Gogolev, & Khudyakova, 1977) with various durations of use (10 hours to 28 days). During DI, the subject is seated in a semi-recumbent position inside of a water tank (Fig. 4.1). Bags are used to separate the subject from the water such that the subject is not in contact with the water. The subject is submerged up to the neck level with the water pressure on the body promoting the transfer of interstitial fluid into the vascular system and a total shift of fluid towards the cephalic area (Miki, Klocke, Hong, & Krasney, 1989; Navasiolava et al., 2011). During the first four hours of immersion, cardiac stroke volume has been found to increase with peripheral vascular resistance (Navasiolava et al., 2011) and the Jugular vein volume, to increase significantly (Arbeille, Avan, et al., 2017). After 1 day, plasma volume has been found to be significantly reduced with further reductions seen after three days

(E. B. Shulzhenko, Tigranyan, Panfilov, & Bzhalava, 1980). However, there is currently no published data on the central or peripheral venous flow changes after 1 day in DI nor on any counter measure to reduce the venous redistribution.

The purpose of the current study was to quantify changes in venous volume and flow after four days in DI with and without the effect of wearing the Russian Braslets system (thigh cuffs). These cuffs are carried by all crew on ISS (USOS and Russian) as part of their personal items and are worn during day to alleviate venous congestion symptoms. DI, like microgravity, induces a fluid shift towards the head. Previous work has shown that, without thigh cuffs, D1 increases with jugular vein volume (JVvol), Middle cerebral vein velocity (MCVv) and Portal vein diameter (PV) significantly increased (Arbeille, Avan, et al., 2017). We hypothesized (a) that both the JV, MCVv, and PV would again exhibit an increased volume in the control group, similar to what has been observed with spaceflight (Arbeille, Provost, Zuj, & Vincent, 2015) and (b) that thigh cuffs may mitigate the cephalad fluid transfer , reflected in attenuated changes to the JV, MCVv, and PV.

METHODS

Subjects:

Eighteen healthy male participants (33.4 ± 5.6 yr; height, 178.0 + 5.8 cm; weight 74.5 + 8.0 kg; 23.5 + 1.8 BMI; 46.1 + 5.4 VO_2max; 117 + 8 mmHg SBP; 65 +7 mmHg DBP; 59 + 9 BPM HR; study intake means + SD, see Table 3.1) underwent four days of dry immersion (DI) at the MEDES Space Clinic in Toulouse, France following methodology as previously described (Navasiolava et al., 2011). Two campaigns ran from November 2018 to March 2019. All participants completed a medical questionnaire, a lifestyle questionnaire and attended the facility for a medical screening battery prior to the study. All participants gave informed, written consent to participate in the study. This experiment was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and approved by the local institutional ethics committee (CPP Sud-Ouest Outre-Mer I) as well as the Government of France Health Authority.

Participants were assigned into either the control (Co) or cuffs (CU) group (9/9 split). The CU group wore the Russian Braslets device (Kozlovskaya et al., 1995) around both upper thighs tightened to 30 mmHg that was calibrated using a strain gauge combined with measurements of the popliteal vein cross section diameter by ultrasound. Cuffs were worn for eight consecutive daytime hours only, while immersed to the neck in the tank. The Co group wore no cuffs while in the tank.

Participants were passively lifted from the tank once per day for some minutes in the morning to shower and defecate while remaining supine during their entire time out of the tank. Since other experiments required additional out-of-tank time, the total out-of-bath time was approximately 1h per day from D1 to D4. Participants were not permitted caffeine, alcohol or any strenuous physical activity for 24 hrs prior to the ultrasound sessions. There was no physical exercise in the tank.

Measurements:

Ultrasound measurements were performed with the Echograph Orcheo-Lite (Sonoscanner, Paris, France, ISS Version: 8.3.101) equipped with three motorized 3D probes. One Superficial motorized probe with a linear array transducer (17MHz) for superficial organs and vessels, a Cardiac/Transcranial motorized probe with a phased array transducer (1.5-3.5MHz) for the heart and intracranial vessels. An abdominal motorized probe with a curved array transducer (3-5MHz) for abdominal organs and vessels. These three probes were located on the acoustic window of each organ/vessel, then the operator activated an automated motorized sweep (Tilt +/45° from vertical to the skin) in order to capture an integrated video. In this video, all of the sequential images of the organs under the probe head (+/1 45°) are included, as well as a 3D reconstruction of the organ. This automated motorized process allowed quick and efficient quantification of the target. (Arbeille et al., 2018).

Cardiac volumes: Standard left ventricle systolic and diastolic volumes were evaluated from the time motion trace (m-mode) taken on the left ventricle parasternal long axis view, right below the mitral valve (Teichholz et al., 1974). Stroke volume (SV) was calculated as (left ventricle diastolic - systolic volume) and ejection fraction (EF) as (SV/left ventricle diastolic volume).

Jugular vein volume (JVvol) was measured from both the long axis and short axis views of the right internal jugular vein. Since the IJV is an irregular, non-circular 3D object, an estimate based on the mean of several x-sectional diameters was used. First, the largest JV volume in the video was identified and a length measurement taken. Then several measurements were taken of the JV cross in x-section area at each change in diameter on the JV long axis view. The probe location was standardized as follows. The bottom of the probe was seated firmly in contact with the collarbone, the medial side in contact with the trachea. One automated sweep was performed, then the probe was rotated 90° without moving the location. Then the second sweep was performed. From these two sweeps the long axis and short axis views required for JVvol calculation were captured. Minimal pressure was applied on the skin by the probe to avoid compressing and changing the JV cross section.

Middle cerebral vein velocity (MCVv): The intracranial veins are usually not investigated clinically in adults and are not easy to visualize using transcranial ultrasound with PW or color Doppler. The strategy used in the current study was to locate, first, the middle cerebral artery (MCA), by placing the phased-array probe at the temple between ear and eye, while keeping in contact with the zygomatic arch and scanning using the color Doppler. The Doppler filter must be set low because of the low venous blood velocities. The sample volume must be set high to facilitate the detection of any flow in the vicinity of the MCA. The maximal velocity was measured using manual calipers from the PW Doppler trace of the middle cerebral vein (MCV).

Portal vein diameter (PV) was measured at the main trunk using the biliary duct as the definitive landmark differentiating a branch from the trunk. The abdominal probe was located at the intersection of the mammillary and xiphoid lines and oriented with the probe marker at a 45° counterclockwise rotation from the vertical.

Procedure:

This experiment consisted of a 3-day ambulatory control period followed by DI. During the 4 days in DI, the subjects remained in a semi-recumbent position in a controlled, thermoneutral (33±0.5°C) bath. Waterproof bags were used to contain the bath water and separate the subject from the liquid, maintaining a dry environment.

Ultrasound measurements were conducted before DI (Pre) in a semi recumbent position as in the bath, and at day 4 inside the bath, D4 AM (prior to donning the cuffs for the day for the cuffs subjects) and D4 PM (with the cuffs still on for the cuff subjects) for the JVvol, MCVv and PV. An additional JV vol measurement was performed at Day 1 in the bath after 2h in DI (D1 +2H), with the cuff on for the cuff subjects.

All study measurements were conducted in a quiet room at a temperature of ~25°C.

Data Analysis:

To test the hypothesis that wearing Braslets for eight hours during DI affected cardiac function and venous redistribution, a dependent t-test was used to compare D4 AM to D4 PM, preceded by a Shapiro test for normality.

To test the hypothesis that four days of DI affected these main outcomes, a 2x2 Repeated Measures ANOVA was used to compare Pre to D4 AM with a main effects analysis for time (pre and D4 AM) and condition (Control or Cuff), followed by a Shapiro test for normality on the residuals. Significance was set at $p<0.05$; means are reported as ± standard deviations. All tests were coded in R 3.6.0 (R Core Team, Netherlands).

RESULTS

Cardiac volume (Fig. 4.2):

At Day 4 AM of immersion SV and EF reduced significantly in both groups with no difference between the 2 groups (SV:111+/-23cm^3 to 93+/-24 cm^3 P<0,05); EF:0.66+/-0.07 to 0.62+/-0.07 P<0.05) At D4 PM, there was no significant difference observed for SV and EF compared to D4 AM.

Jugular vein (Fig. 4.3):

On Day 1 after 2H in immersion (DI +2H), JVvol increased significantly compared to Pre in both groups (P<0.001). During these 2H wearing cuffs attenuatedthis increase in JVvol (Co: 0.27+/0.15cm^3 to 0.94+/-0.22 cm^3 p<0.01; CU: 0.32+/-0.13 cm^3 to 064+/-0.32 cm^3 p<0.04).

At D4 AM, JVvol increased significantly in both groups compared to Pre (Co: 0.47+/-0.22cm^3 CU:0.35+/-014cm^3 p<0.05), with no significant treatment effect Wearing cuffs for two days previously during daytime hours had no residual or “memory” effect on JVvol by D4 AM.

From D4 AM to D4 PM, JVvol was not significantly different.

Middle cerebral vein (Fig. 4.4):

At D4 AM, the velocity in the middle cerebral artery (MCVv) was not significantly different from Pre, and no difference was found between the twogroups..

From D4 AM to D4 PM, MCVv did not show any significant change.

Portal vein (Fig. 4.5):

At D4 AM, the PV diameter did not show any significant change from Pre, with no condition effect. From D4AM to D4PM PV diameter did not show any significant change, with no condition effect.

DISCUSSION

Earth-based spaceflight simulation studies have primarily utilized head-down bed rest as a model of microgravity exposure due, in part, to fluid shifts towards the cephalic and thoracic regions. The use of DI has been proposed as an alternative, more "intense" model of microgravity exposure; however, studies investigating fluid shifts and resulting hemodynamic response are limited. After one day of DI, a marked reduction in plasma volume (16-30%) has been previously reported (Fomin, Orlov, Radzevich, & Leskin, 1985) which is similar to what has been observed with spaceflight (Arbeille et al., 2001). Therefore, the current study investigated potential fluid shifts during the early (two days) and late (four days) adaptation phase to DI. A fluid shift from feet to head similar to what occurs in space flight and bedrest was expected, but the present results show that adaptation is swift, being present mainly during the first hours in DI and become minor at least at Day 4.

Cardiac stroke volume (SV) decreased significantly during the four days in immersion which corresponds well with the decrease in plasma volume measured (Custaud & Navasiolava submitted). SV and EF did not differ between the two treatment groups; thus, the thigh cuffs intervention had no chronic effect on the cardiac volumes, despite being worn for eight hours per day during their four days in the tank. It is noteworthy that the measurements at D4 AM were performed after a night without thigh cuff on both groups; indeed, measurements were completed immediately prior to donning the thigh cuffs for the day (for the cuff treatment group). Thus, even if the thigh cuff were to have had an acute effect between morning and evening, these results clearly indicate that any such effect is lost, or "forgotten" overnight. Moreover, the results confirm that the cuffs applied for 8 hours betweenD4 AM to PM did not induced any significant cardiac volume change. Thus, we did not observe any "memory" or residual effect of cuff on the cardiac parameters.

These results appear to be in contrast to previous work, indeed a 6-month spaceflight sojourn and longer-duration head-down tilt bed rest (HDTBR) studies reported partial restoration of cardiac volume (which had decreased in-flight) after having worn the thigh cuffs for eight hours during the day (Arbeille, Diridillou, et al., 1999; Herault et al., 2000). To explain this, recall that DI is a different model: (1) the fluids shift earlier, since the first day that exist in DI since day 1, due to the plasma volume loss and (2) the fluids shift with less magnitude because the 1Gz still present in DI which confounds the fluid shift migration induced by the water pressure applied on the lower body, the abdomen and the chest. Conversely inflight, despite similar reductions in plasma volume , the complete loss of the Gz gravity vector means that fluids are pushed strongly from the trunk and lower body liquids towards the thoracic, cervical, head areas as confirmed by the jugular vein distension (Arbeille et al., 2001; Arbeille et al., 2015).

<u>On Day1 after 2HR in DI:</u> JVvol increased significantly D1 2HR compared to Pre in both groups, confirming that DI induced a measurable and important fluid shift from the lower part of the body to the cervical area, causing the internal jugular vein to distend. This is in agreement with a previous three-day DI (Arbeille, Avan, et al., 2017). Nevertheless, JVvol increase observed after two hours in the tank was of lesser amplitude than during this previous study. The reason could be methodological: the pressure applied on the body by fabric may have been less. Alternatively, the participants may have been submerged further under the water. The exact pressure at any point along the surface of the body is equal to *pgh* where *p*=density of the fluid, *g*=acceleration due to gravity and *h*=height of the fluid column. That is, the height of the water column an important determinant of pressure and thus our physiological stimulus. Submersion distance and fabric are important considerations when comparing across DI studies.

After two hours in the tank, the JV vol was less distended in those subjects wearing the cuffs. This indicates that that the thigh cuffs trapped a significant amount of fluid in the lower limbs. This is in agreement with what is observed in flight and in bedrest when using the same thigh cuff device and procedure (Arbeille, Herault, et al., 1999; Herault et al., 2000). The thigh cuffs do have an acute and sustained effect, at least while they are actually worn in microgravity conditions.

Lastly, this fluid shift effect was concomitant with the increase in SV during the early phase of DI, and this is consistent with previous DI studies (Navasiolava et al., 2011). However since the SV was found to be reduced after the first day (E. B. Shulzhenko et al., 1980), present study) we did not expect to have a significant JV vol increase by day four.

At D4 AM JVvol the had begun to reduce again, compared to the first day (2 hours in the tank) but was still significantly higher compared to Pre DI. Thus, there is a chronic DI effect (i.e. the fluid shift) but any cuff effect was lost. DI induced a major fluidshift effect on the JVvol after only two hours of immersion; this fluid shift effect was still present after 4 days, but of much lower amplitude.

Additionally, from Day4 AM to Day4 PM JVvol was not significantly different between the two groups.

Because plasma volume and cardiac SV were reduced at by the fourth day and the vertical 1G gravity still pushing the liquid towards the feet, the quantity of fluid shifted towards the head was reduced. Consequently, the cervical (JV) vein was not as distended as during the first day. Consequently, the effect of trapping a lower overall blood volume portion in the legs had lesser impact on the upper body veins measured on the fourth day compared to the first.

Lastly, the fluid shift at day 4 is less important compared to in-flight and HTDBR bedrest because the cuff effect was not visible while evident inflight (Arbeille, Diridillou, et al., 1999; Herault et al., 2000).

The cerebral and splanchnic veins showed no change by the fourth day with DI, but we did not measure these parameters during the early DI phase. So, these results are in contrast to previous studies that collected in the early DI phase. Those studies interestingly observed an increase in intra cranial pressure index (optoacoustic method) in 2/3 of the subjects (Arbeille, Avan, et al., 2017). Again, the overall decrease in fluids available to be shifted by the fourth day is probably responsible for this difference.

CONCLUSION

The DI model seems to be well adapted for quantifying the acute effect of fluids shifting into the cardiac, cervical and cerebral areas but is not an ideal model for studying the chronic effect of fluids shifting over several days or, indeed, not an ideal model to test the effect of any counter measures. This is because the fluid shift disappears after several hours in DI. Nevertheless, DI remains a model of no exercise.

FIGURES

Fig. 4.1: Photograph of a participant submerged in the DI tank. Waterproof bags are used to contain the water and to provide a dry environment for the participant.

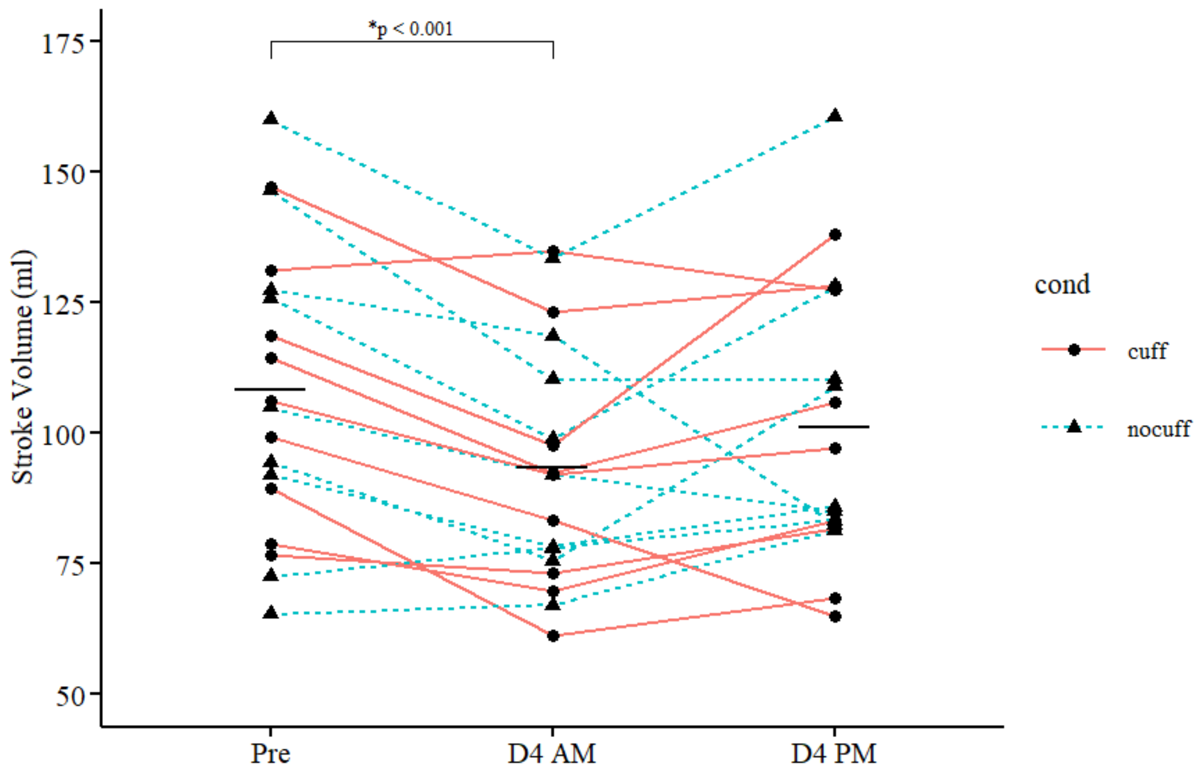


Fig. 4.2: Stroke volume (SV) measured at pre-DI, at D4 morning (AM) without cuff for the cuff subjects, and at D4 evening (PM) after 8h with cuffs on for the cuff subjects, both in control (Co) and cuffs (CU) subjects (P<0.05). DI effect significant at D4 AM in both groups. No significant effect of Thigh cuff.*

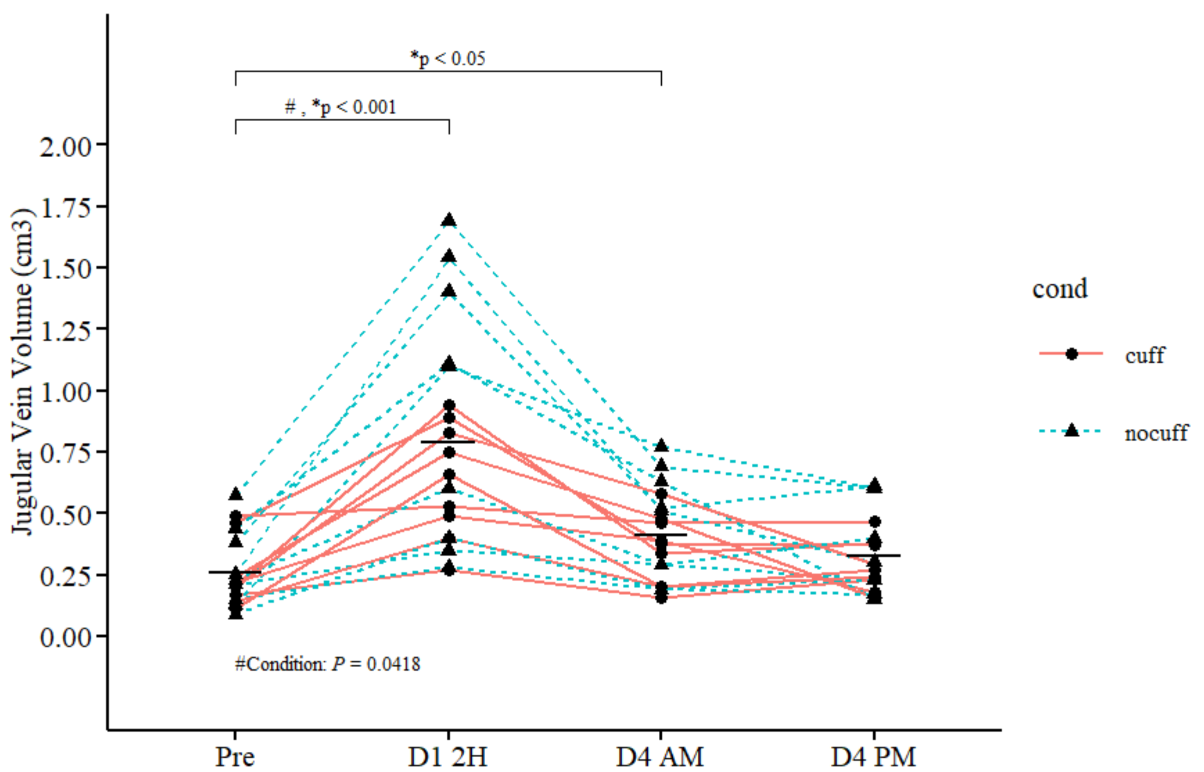


Fig. 4.3: Jugular vein volume (cm3) measured at pre DI, after 2H in DI, at D4 morning (AM) without cuff for the cuff subjects, and at D4 evening (PM) after 8h with cuffs on for the cuff subjects, both in control (Co) and cuffs (CU) subjects (P<0.05). DI effect significant at D1+2H and D4 AM in both groups. Thigh cuff effect significant at D1 2H only.*

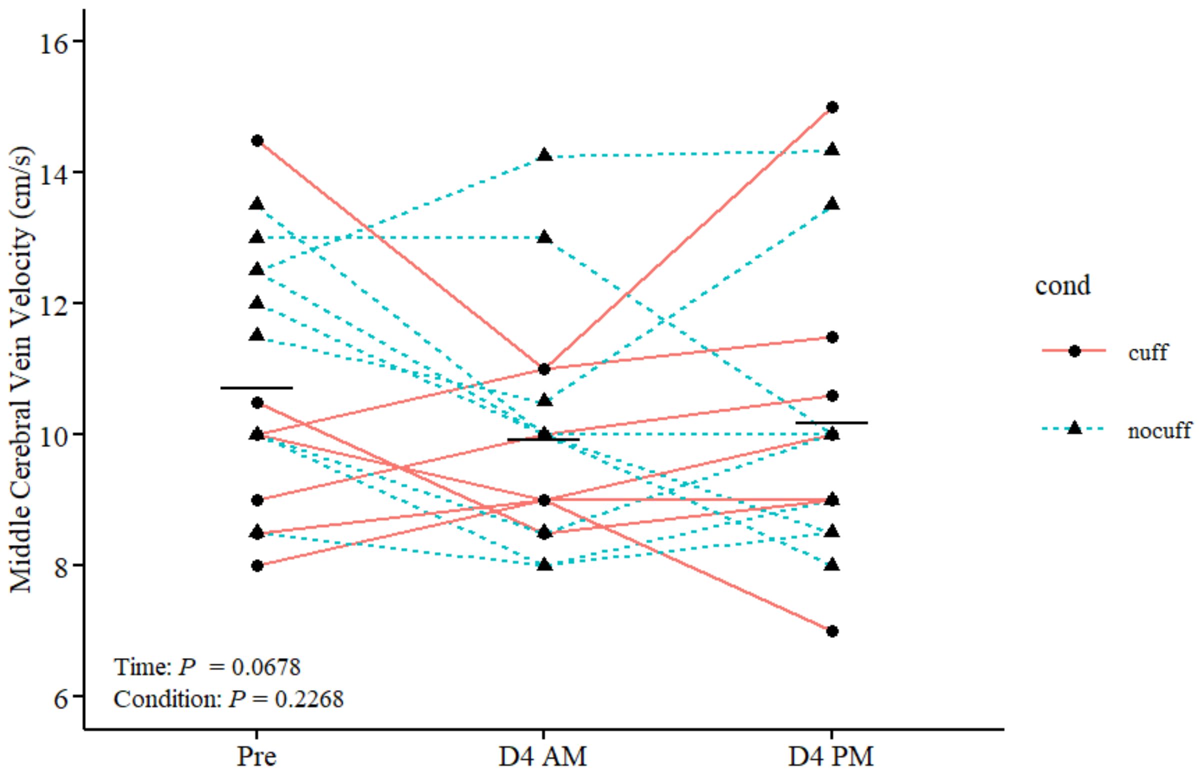


Fig. 4.4: Middle cerebral vein velocity (MCVv cm/s) measured at pre DI, at D4 morning (AM) without cuff for the cuff subjects, and at D4 evening (PM) after 8h with cuffs on for the cuff subjects, both in control (Co) and cuffs (CU) subjects (P<0.05). No significant DI effect on MCVv at D4 AM nor DI PM in any of the 2 groups. No significant Thigh cuff effect on MCVv*

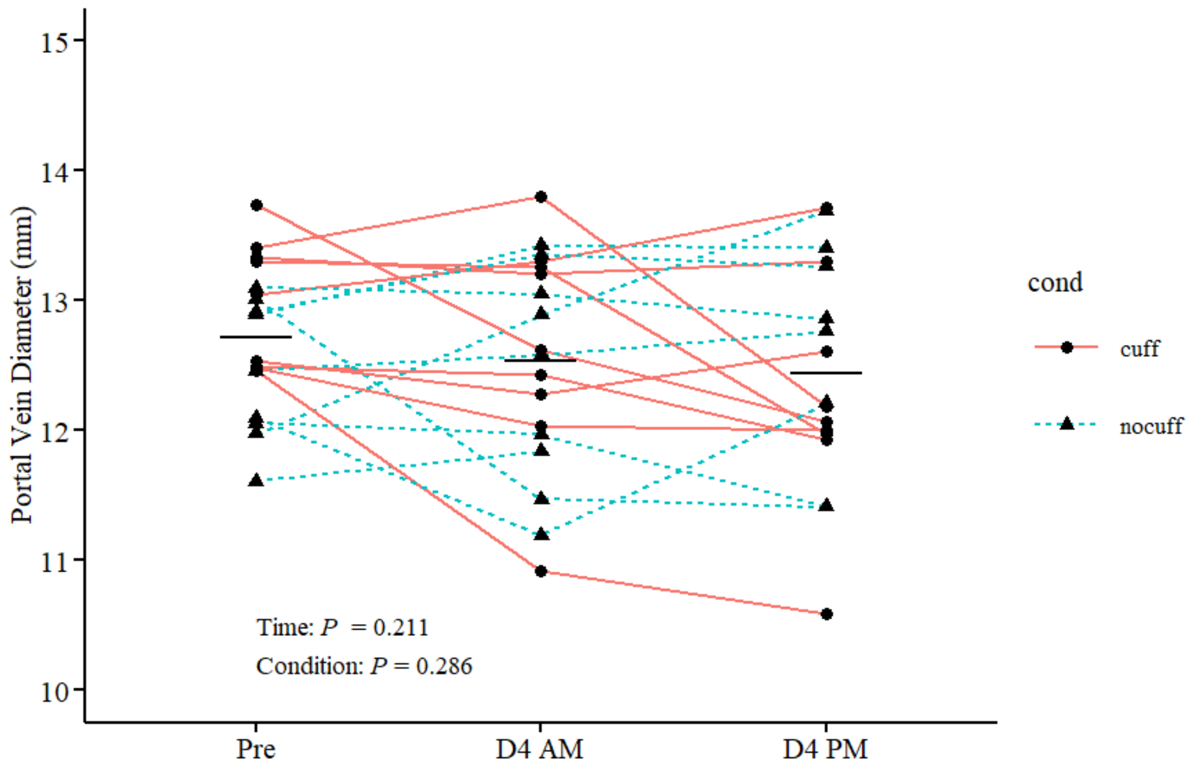


Fig. 4.5: Portal vein diameter (PV mm) measured at pre DI, at D4 morning (AM) without cuff for the cuff subjects, and at D4 evening (PM) after 8h with cuffs on for the cuff subjects, both in control (Co) and cuffs (CU) subjects (P<0.05). No significant DI effect on PV at D4 AM nor DI PM in any of the 2 groups. No significant Thigh cuff effect on PV.*

Chapitre 5

Synthèse & Conclusion

Synthèse immersion sèche et Décubitus a -6 degré

Les 2 expériences menées avec ces modelés de simulation des effets de la microgravité ont permis de montrer que les volumes, la masse, et la contractilité myocardique était affectée significativement par l'immobilité en position anti orthostatique (-6°) mais que la contre mesure exercice permettait de restaurer efficacement l'ensemble de ces paramètres dont il est important qu'ils soient au moins partiellement restaurés lors du retour au sol. L'étude HDBR 21 jours a été l'occasion de mettre en pratique une nouvelle méthode d'investigation cardiaque (4D speckle tracking) et de développer un algorithme pour l'évaluation de la contractilité radiale et longitudinale en Echographie 2 dimensions. Cet algorithme mis au point avec le LIPADE (Pr N Vincent - Paris V) est en cours d'utilisation pour le programme « Vasc Aging » en cours à bord de l'ISS.

L'expérience immersion sèche n'a pas permis de mettre en évidence de modifications importantes de la structure des parois artérielles (épaisseur) ni d'augmentation importante de leur rigidité comme déjà observé en vol spatial. Toutefois une évolution dans ce sens a été mise en évidence qui suggère que la durée de 4 jours (pourtant en hypokinésie complète) n'est pas suffisante pour voir apparaitre un phénomène de transformation cellulaire d'importance (Remodeling).

L'immersion sèche a par contre généré un transfert liquidien (veineux) très important du moins dans le 2 premières heures, qui simule le transfert veineux vers les régions céphaliques tel qu'observé en vol spatial. Dans cette phase précoce les brassards de cuisse ont montré leur efficacité pour limiter ce transfert dont on sait les problèmes qu'il pose au niveau oculaire et cérébral en vol (Edme, perte de vision, déplacement des structures cérébrales...). Par contre en immersion sèche le volume plasmatique chute fortement en fin du premier jour et la masse de sang qui migre vers la région céphalique devient insuffisante pour provoquer une stase veineuse au niveau céphalique et cérébral. Donc l'immersion est un modèle de simulation des effets du transfert liquidien lors des premières heures d’immersion, mais pas au-delà, du fait de l’hypovolémie. Une augmentation de la pression de l’eau sur le corps pourrait augmenter le transfert liquidien mais pas nécessairement au-delà du premier jour.

Limitation des méthodes de simulation des effets du vol spatial

Pour la plupart des expériences en simulation les caractéristiques des sujets ne sont pas toujours homogènes et représentative de la population des astronautes. Les caractéristiques suivantes sont en général prises en compte : forme physique (VO2max), sexe et âge. Les équipages de l'ISS sont généralement plus âgés, souvent formés sur le plan militaire et généralement beaucoup plus sportifs que les recrues pour les expériences de simulation (Bedrests confinement, immersion). Si l'objectif est d'améliorer / de mieux comprendre les risques pour la santé des astronautes, nous devons étudier des sujets « quasi-astronautes » dans les expériences de simulation des effets des vols spatiaux.

Enfin, Il n’existe aucune étude d’étalonnage de l’immersion sèche ou du HDBR par rapport au vol spatial réel. Nous ne connaissons pas la « dose/durée équivalente correcte » pour reproduire les mêmes effets avec chaque méthode. De plus les différents systèmes, neurologiques, cardiovasculaire, nutrition, etc., sont touchés différemment dans chacune de ces simulations. Ainsi, si, par exemple, deux jours en immersion équivalent à une semaine en HDTBR, et à un mois en ISS pour la perte de volume plasmatique, ces proportions ne sont pas transférables à la perte osseuse, au remodelage artériel ou à l’évolution psychique et cognitive. Un travail doit être entrepris de mieux déterminer et comparer les effets de chacune des conditions analogues à la micropesanteur pour chaque système physiologique et neurophysiologie donné sans oublier d’y ajouter l’approche intégrative cerveau-corps. De nos données et étude bibliographique nous avons défini différents points. L’immersion sèche est un modèle d’absence totale d’activité physique avec un transfert liquidien de faible amplitude, et de faible durée. Le décubitus est aussi un modèle de restriction moindre d’activité physique mais avec transfert liquidien céphalique significatif, et de longue durée. Le confinement est un modèle avec activité physique normale, gravite normale, mais avec un fort effet confinement (stress). Enfin le vol spatial se caractérise par l'absence de gravite, un transfert liquidien céphalique fort et constant, une activité physique très réduite et un effet confinement.

Prolongement du travail de Thèse : Activité de recherche en cours de réalisation (par Danielle Greaves)

Etude du remodeling arteriel et perturbations métaboliques associées (Participation à des programmes spatiaux)

Je participe actuellement à 2 études en vol spatial sur des astronautes de la Station spatiale internationale (ISS). Les programmes « Vascular Echo » et « Vascular Aging » (PI = Richard Hughson, Co-I P Arbeille) sont en cours (recueil de données). Mon rôle principal dans ces études est de collecter des données échographiques soit en pré, post vol, soit pendant le vol. En vol je guide l'équipage à la voix pour trouver la fenêtre acoustique, puis je contrôle l'orientation de la sonde et les fonctions de l'Echographe depuis le Centre Spatial de Toulouse. Pour les mesures pré et post vol je me rends à Houston et à Cologne.

Vasculaire Echo Main Hypothèses

L'objectif est de mesurer et de quantifier les changements structurels et fonctionnels cardiaques et vasculaires et évaluer les biomarqueurs associés à ces modifications pendant les mois de vol spatial et jusqu'à un an de récupération. Les objectifs spécifiques de cette étude sont de collecter des données sur les points suivants :

1. La contractilité radiale et longitudinale myocardique du ventricule gauche.
2. Les vaisseaux sanguins (artères et veines) pour obtenir des données sur les changements structurels au niveau cellulaire et les dimensions au repos et assis (1G). Quatre caractéristiques de la fonction vasculaire seront étudiées.

a. Les parois artérielles peuvent être plus rigides : les indices de mouvement de paroi axiale et radiale sont collectés et analysés pour quantifier la rigidité
b. La capacité des parois artérielles à se dilater en réponse à un problème de débit sanguin élevé : le débit sanguin artériel et la dilatation sont surveillés après une occlusion circulatoire de l'avant-bras de 5 minutes
c. La réponse du flux sanguin à l'exercice peut être altérée : la vitesse du flux sanguin dans l'artère fémorale est surveillée après un exercice sub maximal
d. Les artères et les veines peuvent ne pas se contracter de manière appropriée pour réguler la pression artérielle et préserver la répartition du volume sanguin : Les propriétés vasculaires sont surveillées en réponse à une compression non occlusive circulatoire (env. 30mmHg) de 3 heures à la cuisse

3. Marqueurs biochimiques dans le sang circulant reflétant le métabolisme cardiovasculaire, la croissance, l'inflammation et le stress oxydatif sont mesurés. Des périodes prolongées d'activité physique réduite peuvent affecter plusieurs marqueurs suggérant le développement d'une résistance à l'insuline
4. La longueur des télomères dans les leucocytes reflète les mécanismes cellulaires régulant l'équilibre entre dégradation et réparation.
5. Une surveillance ambulatoire de la pression artérielle pendant 24h avec une estimation de la pression artérielle centrale afin d'obtenir une estimation de la rigidité artérielle globale

L'étude de la récupération des paramètres cardiovasculaire ~~étendues~~ jusqu'à 12 mois après l'atterrissage

Vasculaire Aging Main Hyptheses

1. Identifier le (s) mécanisme (s) d'augmentation de la rigidité artérielle ;

2. Confirmer si la résistance à l'insuline se développe lors d'un vol spatial et identifier les conséquences cardio-métaboliques ;
3. Identifier les interactions entre le statut cardio-métabolique et le métabolisme osseux ;
4. Identifier les interactions entre les radiations et l'état du système cardiovasculaire vasculaire en cours d'un vol spatial.

Deux autres études de vols spatiaux auxquelles je participe sont en phase de planification et d'intégration et doivent débuter en 2020. Il s'agit du programme « Vasculaire Calcium » (PI = R Hughson, Co-I, D Greaves, P Arbeille …) et du programme PMU (PI = Ph Arbeille, Co-I D Greaves, R Hughson, A Hargens et al.). En tant que Co-investigateur, je dois contribuer aux télé-opérations Echographiques en vol ainsi qu'aux mesures pre post vol. Ces 2 programmes font partie des 14 programmes selectionnés pour le programme ONE YEAR MISSION mis en place par la NASA.

Participation au développement de nouvelles méthodes d’investigation (par Danielle Greaves)

Nous travaillons activement à trois projets de développement de nouvelles méthodes d’investigation du système cardiovasculaire. Le premier est une méthode basée sur le traitement des signaux de radiofréquence (RF) pour mesurer l'épaisseur de paroi de l'artère carotide et en suivre l’évolution au cours du cycle cardiaque. RF est le signal ultrasonore natif, qui permet d’obtenir des données complètement basiques qui n'ont pas été lissées, filtrées, ou traitées par un logiciel particulier. Avec l’aide de l’entreprise, Sonoscanner (Paris), qui produit l’Echographe spatial, nous avons mis au point un outil robuste, basé sur le signal RF, dont le lancement est prévu pour ISS dans les mois à venir.

Le deuxième projet est la mesure du temps de transit des ondes artérielles pulsées (PWTT). Le PWTT est une mesure indirecte de la rigidité locale du vaisseau. Au cours du cycle cardiaque les parois se déforment au passage de l’onde de pression. Un algorithme RF permet de mesurer le temps nécessaire à l'onde de pression pour parcourir une distance donnée, ce temps est directement lié au changements de la rigidité artérielle en fonction du temps passé par l’astronaute dans l’ISS. Ce logiciel RF, sera également chargé sur l’ISS dans les prochains mois.

Le dernier projet prospectif consiste à créer un outil de visualisation et de mesure de la veine jugulaire. Le drainage cérébro-vasculaire crânien ne peut être correctement mesuré que si la forme et l'écoulement à l'intérieur de la veine jugulaire interne sont connus. L'échographie-Doppler fournit une visualisation et une quantification du flux en temps réel. Elle est actuellement disponible sur ISS. Il est donc possible d’utiliser efficacement les ultrasons pour évaluer, par exemple, les contre-mesures prescrites aux membres de l’équipage. L'imagerie de la veine jugulaire interne (VJI) pose un défi intéressant en raison de sa forme unique et irrégulière de cette veine et de ses flux sanguins multidirectionnels. Nous pensons que la meilleure visualisation est possible en 3D (et non en 2D) et que la meilleure technologie pour le visualiser est actuellement un affichage holographique.

Liste des Publication de D Greaves 2012 – 2019

Soumis:

1. Greaves DK, Guillon L, Besnard S, Navasiolava N, Arbeille P. Cardiac and arterial structure and functional changes after four days of dry immersion with and without thigh cuffs (Acta Astronautica)

2. Arbeille P, Greaves DK, Guillon L, Besnard S. Effect of thigh cuff on venous flow redistribution during 4 days in Dry immersion. Soumis Aerospace medicine and Human performance Oct 2019 (Aerospace Medicine and Human performance)

Publiés (2012-2019 Annotated List):

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2. Fraser KS, Greaves DK, Shoemaker JK, Blaber AP, Hughson RL. Heart rate and daily physical activity with long-duration habitation of the International Space Station. Aviat Space Environ Med 83: 577-584, 2012 PMID: 22764612

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Poster #1 – Présenté en Septembre 2019 Cerebral Autoregulation Network, Leuven, Belgique

Poster #207

Vascular Echo: Stiffer arteries and increased pulsatility index in astronauts after five months on the International Space Station

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Background & Hypotheses

Central artery stiffness is associated with cerebrovascular pulsatility resulting in structural and functional consequences. Spaceflight is a unique stress that causes accelerated vascular "aging-like" changes reflected by reduced carotid distensibility equivalent to aging 20 years during 6-months. In this study, we report the first measurements during spaceflight of arterial stiffness by direct measurement of pulse wave arrival time at the carotid (CCA), superficial femoral (SFA) and tibial (TIB) arteries. Pulse wave arrival time was measured from the R-wave of the ECG to the onset of the Doppler velocity wave. Using remote guidance and the ECHO robotically-controlled ultrasound, five male astronauts completed sessions pre-flight, within one month of arrival on the International Space Station, again in their fifth month in space and then again after landing. After one month on ISS, both the CCA-SFA pulse wave velocity (PWV) and the CCA-TIB PWV were faster (+16.45 ± 7.29% and +9.30 ± 8.3%, mean ± SEM), compared to pre-flight values. Post-flight at 60 days, the change was down to pre-flight values again. Cerebral blood flow velocity was measured by transcranial Doppler ultrasound before flight and post-flight. The pulsatility index increased from 0.80 ± 0.05 to 0.85 ± 0.01 at three days post-flight. The faster PWV was consistent with previous findings from pulse arrival time and the increase in pulsatility index was

anticipated with the increased arterial stiffness. The potential long-term consequences for cerebrovascular and cognitive health of astronauts remains to be established. Nine crew are planned, with observations out to 1-YR. If the changes observed are not permanent, this indicates that the underlying mechanism for arterial stiffening may be different than typical age-related and sedentary lifestyle-related stiffening observed in population studies here on Earth.

Methods

5M crewmembers processed; collection is ongoing and 5 additional crew have been recruited

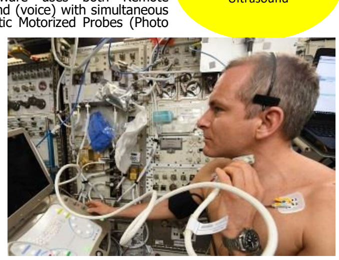
Data takes: Pre-flight, Early mission, Late mission and Post-flight Day 3

Remote-guided ultrasound [GE Vivid, Orcheo Lite Sonoscanner] & Transcranial Doppler [Atys]

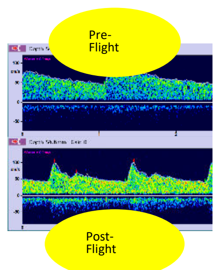
Pulse wave velocity calculated from PW Doppler ultrasound images and the ECG at 3 sites: carotid, sup. femoral & post. tibial arteries

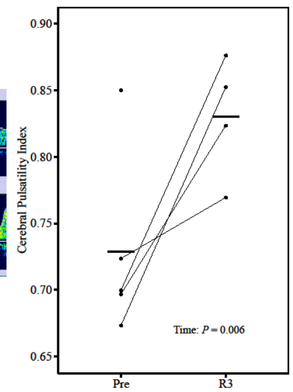
Robotic Space Ultrasound

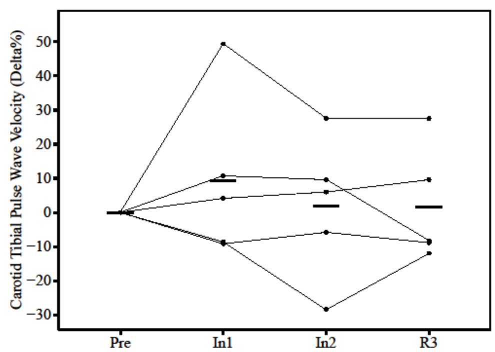
ESA ECHO hardware uses both Remote Guidance Ultrasound (voice) with simultaneous operation of Robotic Motorized Probes (Photo credit: D. Chaput)

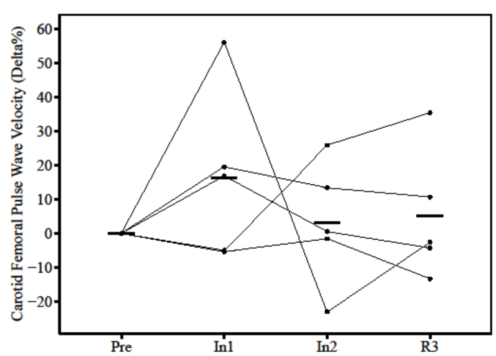


Results & Discussion









Cerebral pulsatility increases after spaceflight indicates increased cerebrovascular resistance

Percent change in PWV from preflight indicates arterial stiffening on orbit

By expressing as CCA-TIB velocity, any potential confounding change in pre-ejection time is avoided

Individual data shown

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Hughson RL, Robertson AD, Arbeille P, Shoemaker JK, Rush JW, Fraser KS, Greaves DK. Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. Am J Physiol Heart Circ Physiol. 2016 Mar 1;310(5):H628-38. doi: 10.1152/ajpheart.00802.2015. Epub 2016 Jan 8. PubMed PMID: 26747504.

Baevsky RM, Baranov VM, Funtova II, Diedrich A, Pashenko AV, Chernikova AG, Drescher J, Jordan J, Tank J. Autonomic cardiovascular and respiratory control during prolonged spaceflights aboard the International Space Station. J Appl Physiol (2007);103(1):156-61. Epub 2007 Apr 19

Poster #2 – Présenté en Juin 2019 International Society for Gravitational Physiology, Noordwijk, Le Pays Bas

Vascular Echo – Faster central and peripheral pulse wave velocity in astronauts while on International Space Station

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Background & Hypotheses

Pulse wave transit time (PWTT) has been used to quantify stiffening of the arterial tree. Arteries that are more flexible and youthful have longer transit times and slower velocities due to the dampening effect on the pulsatile force of blood during systole.

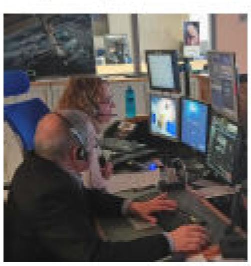
In this study, transit time was measured using pulsed wave ultrasound. Arrival times of velocity waveforms were measured from the R-wave of the ECG to the common carotid, superficial femoral and posterior tibial arteries respectively. The time lag between pulse arrival between the carotid artery and the other two sites was calculated and divided by segment length to calculate pulse wave velocity (PWV). The session was repeated pre-flight and twice in-flight, within the first and final month of their mission.

Data from four male astronauts recruited into the Vascular Echo study showed, on average, a 20.0 +/- 10.6% change in CCA-SFA velocity and an 18.2 +/- 5.9% change in CCA-TIB velocity compared to pre-flight values.

These faster velocities are consistent with previous findings from PWTT (Baevsky et al., 2007, Hughson et al. 2016) but the added value here is that we have, for the first time, measured pulse wave velocity to eliminate any potential impact of changes in pre-ejection period in the previous calculations of PWTT. The similar changes in PWV for the "gold standard" carotid-femoral measurement and for the carotid-tibial artery suggest that arterial stiffness is occurring in central (elastic) as well as peripheral (more muscular) arteries. These results point to more widespread vascular changes during spaceflight and indicate that increased hydrostatic pressure theory alone is inadequate to explain the apparent vascular stiffening in both the carotid and peripheral arteries during 6-month missions to ISS. Instead, the explanation may well be multifactorial, including factors such as calcium mobilization, insulin resistance, physical inactivity, nutrition and radiation.

Methods

- 4M crewmembers processed; collection is ongoing and 5 additional crew have been recruited
- Data takes: Pre, L+30, R-30, R+4
- Remote-guided GE Vivid (HRF US2) and Orcheo Lite Sonoscanner (ESA ECHO)

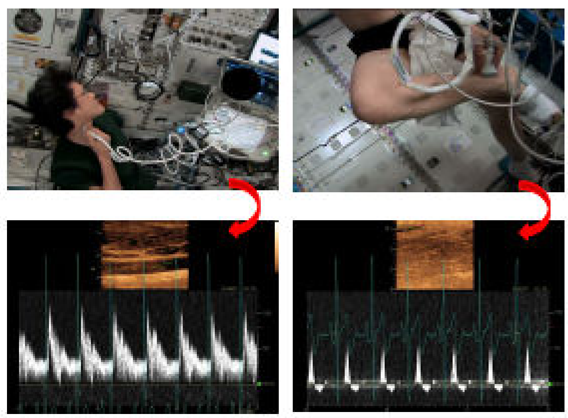


ESA ECHO Hardware utilises both Remote Guidance Ultrasound (voice) with simultaneous operation of Robotic Motorised Probe (Photo credit: D. Chaput)

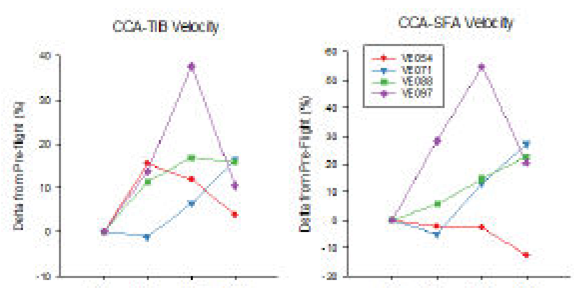
Results & Discussion

- Increased arterial stiffness is an established risk factor for cardiovascular and cerebrovascular disease potentially leading to stroke, kidney disease, and cognitive dysfunction
- Cumulative risk exists for 1-YR+ ISS crew
- For non-ISS exploratory missions that leave low earth orbit, risk may be much greater - if radiation is partly to blame
- Current exercise and other countermeasures insufficient to mitigate
- Early post-flight data indicates the effect may reverse with return to 1G

Results & Discussion Cont'd



Pulse wave transit time was calculated from pulse-wave Doppler ultrasound images and the ECG at 3 sites: carotid, superficial femoral and posterior tibial arteries. By expressing as CCA-TIB velocity, any potential confounding change in pre-ejection time is avoided.



Percent change in velocity from preflight to three time points indicates arterial stiffening on orbit. Individual data shown.

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Poster #3 – Présenté en Janvier 2019 NASA Human Research Science Symposium, Galveston, Texas

Poster #4 – Sera Présenté en Janvier 2020 NASA Human Research Science Symposium, Galveston, Texas

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