Atherosclerosis 243 (2015) 462–465

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Associations of non-invasive measures of arterial structure and function, and traditional indicators of cardiovascular risk in adults with cerebral palsy

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ARTICLE INFO

Article history:
Received 18 July 2015
Received in revised form
11 September 2015
Accepted 29 September 2015
Available online 9 October 2015

Keywords:
Cerebral palsy
Adult
Arterial stiffness
Endothelial function
Carotid intima media thickness
Cardiovascular health

ABSTRACT

Background: Persons with cerebral palsy (CP) have mobility limitations and may be at increased risk for cardiovascular disease (CVD).
Aims: To determine the feasibility of assessing novel CVD risk indicators and to identify predictors of CVD risk in a clinic-based group of adults with CP.
Methods: In an observational study, we examined 42 adults with CP (mean age 33.5 ± 12.3 yr). Traditional (resting blood pressure, smoking status and lipids) and novel CVD risk indicators (endothelial function, arterial stiffness, and carotid wall thickness) were assessed.
Results: Measures of endothelial function and central arterial stiffness were conducted in 100% and 83% of participants, respectively. Age was the strongest independent predictor of vascular health (cIMT, *Age*, R square = 0.576, $p = 0.001$).
Conclusion: Non-invasive measures of arterial structure and function are feasible to assess and may assist in the prediction of CVD risk in adults with CP.

1. Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide [1]. The development of CVD may be prevented by addressing risk factors such as physical inactivity [2]. It is approximated that up to 30–40% of the CVD risk reduction associated with increased physical activity (PA) is not explained by changes in traditional risk factors [3,4]. Alternatively, structural and functional adaptations to the vascular wall may explain some of the PA related CVD risk reduction [4].

Cerebral palsy (CP) leads to mobility limitations that impact a person throughout their lifespan [5]. It has been identified that PA levels of individuals with CP are related to their mobility level and decline with advancing age [6]. It remains to be determined if lifelong decreases in PA could put adults with CP at an elevated risk of CVD [7].

To our knowledge, only one previous study has examined endothelial function and arterial stiffness in ambulatory adolescents with CP (mean age 13.2 ± 2.1 yr) compared to their typically developing peers, and determined that there were no differences [8]. However, that study did not capture these novel CVD risk indicators across the entire mobility spectrum on a five-level ordinal scale, the Gross Motor Function Classification System (GMFCS) [9] (Level I representing the best mobility; Level V the least).

Despite some literature describing causes of mortality [7,10], predictors of cardiometabolic risk [11–13], and coronary risk evaluation [14] in adults with CP, there have been no assessments of both traditional and novel CVD risk indicators in adults with CP. Such an evaluation may help inform clinical practice aimed at the early detection of CVD and in the evaluation of interventions for attenuating CVD risk.

The objectives of this study were to determine the feasibility of

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http://dx.doi.org/10.1016/j.atherosclerosis.2015.09.035
0021-9150/

assessing novel CVD risk indicators, including arterial stiffness and endothelial function, and to identify predictors of CVD risk in a clinic-based group of adults with CP across the mobility spectrum.

2. Methods

Forty-two adults with CP (mean 33.5 ± 12.3 yr; range 18–75 yr) were recruited from across Ontario, Canada. Inclusion criteria consisted of a GMFCS level I–V, regardless of intellectual ability. The Hamilton Integrated Research Ethics Board granted study approval and written consent was obtained for this cross-sectional, observational design study.

The study protocol consisted of PA monitoring followed by one visit to the Vascular Dynamics Laboratory at McMaster University. Methods for anthropometric data collection and cardiometabolic markers analysis are described elsewhere [15]. Vascular measures were obtained in a temperature-controlled room (23.2 ± .9 °C) with the participant in a supine position. All participants were assessed at least 12 h postprandial and instructed to abstain from vigorous PA at least 12 h prior to data collection. All vascular signals were acquired using a data acquisition system (Powerlab model ML795; ADInstruments, Colorado Springs, CO, USA) and software program (LabChart 7; ADInstruments Inc., Colorado Springs, CO, USA). Carotid distensibility ($mmHg^{-1}$), an indicator of local carotid artery stiffness [16], was acquired using brightness mode ultrasound with a 12 MHz probe (Vivid Q; GE Medical Systems, Horten, Norway) and simultaneous applanation tonometry (model SPT-301; Millar Instruments, Houston, TX, USA). The same ultrasound images were used to calculate carotid artery intima media thickness (cIMT) as previously described [8]. Central pulse-wave velocity (cPWV, m/s), indicative of regional artery stiffness [17], was determined from 20 continuous heart cycles and arterial pressure waveforms from the common carotid and femoral arteries, and was calculated by dividing the superficial distance between the two sites by the time it takes for the pulse-wave to travel that distance. Flow-mediated dilation (FMD), indicative of brachial artery endothelial function [18], was determined using duplex ultrasonography of the dominant arm brachial artery approximately 10 cm proximal to the antecubital fossa. Brachial artery absolute and relative FMD (%FMD) were calculated as previously described [18]. PA was measured for seven consecutive days using an ActiGraph GT3X accelerometer (ActiGraph, Pensacola, FL, USA) [19].

One independent investigator (First author, PM) performed the analysis of all vascular indices. PM received formal training from the senior author (MM) and adhered to standard operating procedures pertaining to the analysis of the non-invasive measures. Test-retest reliability in our lab for the FMD assessment in a mobility limited population (spinal cord injury) resulted inan intraclass correlation coefficient of 0.90 and CV of 9%. The reproducibility of cPWV [20] and cIMT [21] has been reported in other studies using the same methods, with correlation coefficients of 0.97 and 0.97, respectively.

Statistical analysis was performed using Statistical Package for the Social Sciences software (SPSS 20. IBM, Armonk, NY, USA). Feasibility of the non-invasive measures was determined as a percentage of those who had the measure successfully performed relative to the number of participants tested. Participant data were separated into two groups based on whether participants were community ambulatory (GMFCS I-II) or non-ambulatory (GMFCS III-V). Upon separation into two groups, differences in all measures were analyzed using independent t-tests.

To determine the independent contribution of traditional CVD risk indicators (age and waist circumference) as well as mobility grouping (ambulatory or non-ambulatory) on vascular outcomes, separate multiple regression analyses were conducted for each dependent variable using a backward regression model. Data are reported as means ± SD. A minimum criterion alpha level of $p \leq 0.05$ was used to determine statistical significance. As this was a feasibility study, no formal sample size calculations were performed. Through purposeful sampling, we included at least five participants in each GMFCS level.

3. Results

Participant characteristics are presented in Table 1. None of the participants had a medical history of CVD. No participant described any discomfort during the testing session, which lasted no longer than 3 h. The FMD measurement was performed in all participants, indicating that it was feasible. Distensibility and cIMT measures were feasible in 97% (41 of 42) of participants. One non-ambulatory participant had severe spasticity of the upper extremities resulting in inadequate ultrasound image quality for analysis. cPWV measurement was performed in 35 of 42 participants, identifying that this measure was feasible in 83% of the participants. Missing cPWV data was as a result of spasticity in the lower limbs preventing adequate femoral artery tonometry signals.

The two mobility groups did not differ in absolute or relative FMD, cPWV, carotid distensibility, cIMT or any cardiometabolic marker assessed. The ambulatory group was taller ($p = 0.008$) and had a lower resting HR ($p = 0.04$) (Table 1). Six participants (all in the non-ambulatory group) were hypertensive [15]. The ambulatory group engaged in more moderate-to-vigorous PA (MVPA)/hour ($p < 0.001$) and in less sedentary time/hour ($p < 0.001$) (Table 1).

The relationship between traditional indicators of CVD risk (age and waist circumference) as well as mobility grouping on vascular and metabolic indices is presented in Table 2. When controlling for waist circumference and mobility grouping, age was an independent predictor of systolic blood pressure, mean arterial pressure, cPWV, and cIMT. When controlling for age and mobility grouping, waist circumference was an independent predictor of total cholesterol (TC), HDL-C, LDL-C, triglycerides, and TC/HDL-C ratio (Table 2).

4. Discussion

4.1. Feasibility of novel CVD risk indicators

FMD assessment, a non-invasive measure of brachial artery endothelial function, was 100% feasible while measures of carotid distensibility and cIMT were feasible in 97% in this cohort of adults with CP. Carotid artery distensibility has been shown to increase throughout childhood, plateaus near age 30, and begins to decline thereafter [16]. The lack of group differences in distensibility observed in the current study may be explained due to the relatively young age in both groups. Regarding cIMT, a value greater than 0.82 mm in the typically developing population increases the risk of CVD [22]. Three participants in the non-ambulatory group presented a cIMT greater than 0.82 mm. In the present study, no significant group differences were found for cPWV and our values were comparable to a typically developing population aged 30–39 years (PWV = 6.5 ± 1.4 m/s) [23]. Post hoc power calculations revealed a sample size of 103 participants would be required to achieve statistical differences between groups for cPWV.

4.2. Predictors of CVD risk

Finally, 6 participants (all in the non-ambulatory group) were hypertensive [15]. Age has been previously identified as the strongest independent predictor of cIMT in the general population [24] and in the present study explained 58% of the variance,