Association between occupational, sport and leisure related physical activity and baroreflex sensitivity. The Paris Prospective Study III.

Rachel E. Climie[1, 2, 3], Pierre Boutouyrie[4], Marie-Cecile Perier[1], Edouard Chaussade[5], Mattieu Plichart[5], Lucile Offredo[1], Catherine Guibout[1], Thomas T. van Sloten[1,4,6], Frederique Thomas[7], Bruno Pannier[7], James E. Sharman[3], Stephane Laurent[4], Xavier Jouven[1], and Jean-Philippe Empana[1].

[1]University de Paris, INSERM, U970, Paris Cardiovascular Research Centre (PARCC), Integrative Epidemiology of Cardiovascular Disease Team, Paris, France
[2]Baker Heart and Diabetes Institute; Melbourne, Australia
[3]Menzies Institute for Medical Research, University of Tasmanian, Hobart, Australia
[4]INSERM U970, Department of Pharmacology; APHP; Paris Descartes University, Paris, France
[5]APHP, University de Paris, Paris, France
[6]Cardiovascular Research Institute Maastricht and Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
[7]Investigations Préventives et cliniques (IPC), Paris, France

Running title: Physical activity and baroreflex sensitivity.

Corresponding author:
Doctor Rachel Climie
INSERM U970, Paris Cardiovascular Research Center (PARCC)
Integrative Epidemiology of Cardiovascular Disease Team, University de Paris,
56 rue Leblanc, 75015, Paris, France. tel: 33 1 53 98 79 64 fax: 33 1 53 98 79 54
Email: rachel.climie@inserm.fr

Word count: 4666
Number of tables: 4
Number of figures: 2

Abstract

Physical activity (PA) is a preventative behavior for non-communicable disease. However, little consideration is given as to whether different domains of PA have differing associations with health outcomes. We sought to determine the association between occupational (OPA), sport (SPA), leisure (LPA) and total PA (TPA) with baroreflex sensitivity (BRS), distinguishing between neural (nBRS) and mechanical (mBRS) BRS. In a cross-sectional analysis of 8649 adults aged 50 to 75 years, resting nBRS (estimated by low frequency gain, from carotid distension rate and heart rate) and mBRS (carotid stiffness) were measured by high-precision carotid echotracking. PA was self-reported using the validated Baecke questionnaire. The associations between PA and nBRS and mBRS were quantified using multivariate linear regression analysis, separately in the working and non- working population. In working adults (n=5039), OPA was associated with worse nBRS (unstandardized β=-0.02, 95% confidence interval (CI)-0.04, -0.003, p=0.022), while SPA was associated with better nBRS (β=0.04, 95% CI 0.02, 0.07, p=0.003) and mBRS (β=-0.05, 95% CI -0.09, -0.00001, p=0.049). Neither LPA nor TPA were associated with nBRS or mBRS. In non-working adults (n=3610), SPA and TPA were associated with better mBRS (β=-0.08, 95% CI -0.15, 0.02, p=0.012 and β=-0.05, 95% CI -0.10, 0.009, p=0.018), but not nBRS. These findings suggest differential associations between domains of PA and BRS and may provide insights into the mechanisms underlying the association between OPA and cardiovascular disease.

Keywords: Baroreceptors, blood pressure, hypertension, exercise, profession.

Introduction

Physical activity (PA) is a well-established preventative behavior for non-communicable diseases (1). As such, international PA guidelines, suggest that adults should engage in ≥30 minutes a day of at least moderate intensity activity (2). However, little consideration is given as to whether different domains of PA are differently associated with health (3). For example, while high levels of leisure (LPA) and sport related-PA (SPA) are associated with beneficial outcomes, recent work has suggested that occupation-related PA (OPA; such as static activity) is linked to increased risk of CVD (4-10) and mortality (11). The underlying pathophysiological mechanisms of the detrimental association between occupation-related PA and CVD are not well known.

Baroreflex sensitivity (BRS) is a marker of autonomic function and is crucial for short- term blood pressure (BP) control. Accordingly, reduced BRS function is related to higher risk of cardiac mortality and sudden death (12). Traditionally, autonomic function is assessed via global BRS, which relates changes in BP (often measured non-invasively from the finger) to changes in heart rate. However, baroreceptors respond to deformation and not pressure *per se*, thus for similar changes in BP, a stiff carotid artery will stretch less than an elastic one, which might influence BRS through a mechanical (i.e. vascular, not neural) mechanism. It is now possible to separate BRS into its mechanical (mBRS; dependent on the stiffness of the arterial wall) and neural (nBRS; including afferent and efferent nerves and effectors, namely the heart and blood vessels) components. Previous studies have shown that total (or habitual) PA is associated with better autonomic function as determined via heart rate variability (13-17) and with higher cardiovagal baroreflex function (18, 19). However, these previous

studies have only measured global BRS and, to our knowledge, it is unclear whether PA affects the mechanical or neural component of the BRS pathway, or both. We, therefore, sought to examine the association between the different domains of PA (occupational, sport and leisure) with the mechanical and neural components of BRS. We hypothesized that SPA and LPA would be beneficially associated with nBRS and mBRS, whereas OPA would be related to poorer nBRS and mBRS.

Methods

Data are available on request subject to approval by the Paris Prospective Study III (PPS3) scientific committee.

Study participants and overview. This study was a cross sectional analysis of the PPS3, an ongoing observational prospective study (20, 21). At baseline, 10,157 healthy men and women aged 50 to 75 years were recruited from a large preventative medical center, the Centre d'Investigations Preventives et Cliniques (IPC center) in Paris (France) between May 2008 and June 2012. At recruitment, participants underwent a standard clinical examination, including resting high-resolution carotid echo-tracking to determine nBRS and mBRS in a quiet and temperature controlled room (22±1ºC). Participants completed self-administered questionnaires to derive information on lifestyle (i.e. PA, diet, smoking and alcohol), personal and family medical history, psychological (perceived stress) and socioeconomic data (education, professional occupation category and whether they undertook shift work). Smoking was categorized as non-smoker, former smoker, smoking cessation less than 1 year ago or current smoker, alcohol was categorized as non-drinker, rarely, certain days of the week or almost every day, and education was categorized as tertiary education or higher vs. less than tertiary education. Professional occupation was categorized as

high (eg. managers), medium (eg. clerks or first-line supervisors), low (eg. blue collar workers), no professional activity or unemployed. The non-working population included retired, unemployed and inactive subjects. BP was measured three times using a validated digital electronic blood pressure monitor (A & D TM-2541, A&D Company, Tokyo, Japan), after 10 minutes of supine rest. The mean of the last two measurements was calculated and used in the analysis. Fasting blood samples were taken to assess for standard blood biomarkers. Participants provided informed written consent and the study protocol was approved by the Ethics Committee of the Cochin Hospital (Paris). The study is registered in the international trial registry (NCT00741728).

Physical activity. PA was assessed using the validated Baecke questionnaire (22). The validity of the questionnaire has been confirmed against objectively measured PA and shown to have acceptable reliability and validity (23). The Baecke questionnaire assesses habitual PA across various settings including OPA, SPA, LPA and total PA (TPA). The questionnaire consists of 16 questions relating to the intensity and duration of PA in the different settings, which are scored on a five-point Likert scale. For OPA, data were collected regarding how often participants lifted heavy loads, walked or stood at work. For SPA, data were collected relating to the type of sport(s) practiced, how many hours per week (<1, 1-2, 2-3, 3-4, >4 hours/week) and months per year. Intensity in mega joules per hour (MJ/h) was calculated based on the type of sport (22) and for the analysis was categorized as no sport, light to moderate or high intensity. Finally, for LPA, data pertaining to how often the participants engaged in activities such as gardening or walking in their leisure time were collected. By

combining the relevant information described above, the OPA, SPA and LPA scores were calculated. TPA is the combination of OPA, SPA and LPA.

Carotid echo-tracking derived neural baroreflex sensitivity. Because baroreceptors are sensitive to arterial stretch (i.e. deformation) not pressure, BRS can be investigated via spectral analysis of the spontaneous carotid distension fluctuations (input signal) and R-R intervals (output signal) using noninvasive high-resolution ultrasound carotid echo-tracking, as described previously (21, 24). Briefly, measurements were performed at the right common carotid artery, one cm proximal from the carotid bulb bifurcation using the ArtLab® (Esaote) high-resolution echo-tracking technology after 10 minutes of rest in a supine position. Carotid diameter, distension and heart rate were continuously recorded for five-minutes: cross-spectral analysis of distension rate and heart rate was performed, extracting low frequency (LF) and high frequency (HF) variability of distension waveform and heart rate. The transfer function magnitude between input (carotid distension rate) and output (R-R interval) within the frequency band of 0.04-0.15 Hz defined the LF gain and corresponds to the nBRS. Using this method, Kornet et al. (24) showed that variability in carotid distension rate is a more accurate predictor of R-R interval variability compared to variability in systolic finger pressure.

Mechanical baroreflex sensitivity. From the same ultrasound measurement used to derive nBRS, the mechanical component of BRS (mBRS) was determined. As the mBRS depends on the stretch of the carotid artery, carotid stiffness was used in the current study to represent mBRS. The distensibility coefficient was calculated as radial wall strain/PP, where radial wall strain=(internal $\text{Diameter}_{\text{systole}}$ –

$Diameter_{diastole}$)/$Diameter_{diastole}$ and PP was carotid pulse pressure obtained by integration of the carotid distension waveform. Carotid stiffness (m/s) was derived from distensibility coefficient using the Bramwell and Hill equation.

Statistical analysis. Analyses were conducted separately in those who were working and those who were not. This was due to the non-working participants by definition having no data for OPA (i.e. accumulated at work), while those working did have data for OPA. This could have also resulted in the non-working group having more time for PA in other domains. All data are expressed as mean ± standard deviation for continuous variables and n (%) for categorical variables. Data that were not normally distributed (fasting glucose and nBRS) were log transformed. Due to the skewed distribution of perceived stress and in the absence of validated cut-off values, quartiles were used. Comparisons between groups were performed using ANOVA for continuous data and Cochran-Armitage test for categorical data where appropriate. Linear regression analyses were performed to quantify the separate associations between nBRS or mBRS (outcomes) and PA (main exposure). The linearity assumption of the associations between PA and nBRS or mBRS were ensured by comparing Akaike information criterion (AIC) values of linear models with models with quadratic or cubic terms on PA. Models were first adjusted for age and sex and then for variables known or suspected to contribute the variance in nBRS or mBRS from the literature and included mean BP, body mass index (BMI), total cholesterol, antihypertensive medication, personal history of CVD, smoking, alcohol, education, perceived stress, and resting heart rate. When investigating nBRS, adjustment was made on mBRS (to account for the mechanical component of BRS) but not heart rate due to potential collinearity. To assess whether SPA may compensate for the

anticipated deleterious association between high OPA and nBRS or mBRS, we further adjusted for SPA. Based on our previously reported findings of impaired nBRS in those with an exaggerated BP response to exercise (25), we further adjusted regression analysis for exercise BP. Finally, to account for the harmful effect of shift work on the autonomic nervous system, we also adjusted the analysis for shift work. All analyses were two-sided and $p<0.05$ was considered statistically significant. All data were analyzed using SAS 9.4 (Statistical Analysis System, Cary, NC, USA).

Results

Participant characteristics.

Excluded participants. Of the initial 10,157 recruited participants**,** a total of 1508 had missing data on carotid echo-tracking parameters (due to technical issues) and covariates leaving a final study population of 8649 participants (Figure 1). The characteristics of those excluded from the current analysis are presented in Table S1.

Included participants. The baseline characteristics of those working (n=5039) compared to those who were not working (n=3610) are shown in Table 1. There was on average 8 years of age difference between the working and non-working groups (56±4 and 64±6 years). SPA and LPA were significantly higher in the non-working compared to the working population ($p<0.0001$ for both); however working adults engaged in higher intensity SPA compared to non-working adults, even after accounting for differences in age (1.51, 95% confidence intervals [CI] 1.49, 1.52 MJ/h vs 1.47 95%CI 1.46, 1.49 MJ/h, $p=0.002$). TPA was significantly higher in the working compared to the non-working population ($p<0.0001$). The distribution of nBRS and mBRS across age in the working and non-working populations are shown in Figure 2.

Associations between the domain of PA, nBRS and mBRS.

Working population

Occupational PA. The characteristics of the working population by tertiles of OPA are reported in Table 2. Those most likely to engage in high levels of OPA were younger, had higher BMI and lower education and occupational level. Table S2 displays the associations between PA and nBRS and mBRS adjusted for age and sex and Table 3 displays the fully adjusted models. In multivariate analysis (Table 3), higher OPA was associated with significantly lower nBRS and borderline significant higher mBRS. Table S3 shows the β coefficients for all variables included in the multivariate models for nBRS and mBRS. The association between OPA and nBRS remained independent after additionally adjusting for SPA (β=-0.02 95% CI-0.04, -0.003, p=0.028), exaggerated BP response to exercise (β=-0.03, 95% CI -0.05, -0.01, p=0.005) and for shift work (β=-0.02 95% CI-0.04, -0.003, p=0.026). When examining the type of OPA separately (i.e. lifting heavy loads, standing or walking at work) lifting heavy loads was associated significantly with impairment in both nBRS and mBRS (Table 3).

Sport PA. Higher levels of SPA were significantly related to higher nBRS and lower mBRS (Table 3). When examining the intensity of sport, compared to no sport, adults who engaged in high intensity but not light-moderate intensity sport had significantly better (i.e. higher) nBRS function, whereas those who engaged in light-moderate, but not high intensity SPA, had better (i.e. lower) mBRS. The frequency of SPA (<1, 1-2, 2-3, 3-4, >4 hours/week) was borderline related to nBRS (β=0.01 95% CI -0.003, 0.03, p=0.099) and inversely related to mBRS (β=-0.4 95% CI -0.08, -0.01, p=0.009). Table S4 shows the β coefficients for all variables included in the models for nBRS

and mBRS. The associations between SPA and nBRS and mBRS remained significant after further adjusting for an exaggerated BP response to exercise (β=0.05, 95% CI 0.03, 0.08, p<0.001 and -0.05 95% CI -0.10, -0.003, p=0.037 respectively). Of note, while an analysis by type of sports was not possible, walking, jogging, swimming, cycling and tennis were the most commonly reported sports with 68% of the working population and 78% of the non-working population who participated in sport engaging in one of these activities most frequently.

Leisure time PA. LPA was borderline related to higher nBRS and lower mBRS, after adjusting for age and sex (Table S4). However, after adjusting for all confounders, LPA was no longer related to nBRS or mBRS (Table 3).

Total PA. No associations were observed between TPA and nBRS or mBRS.

Non-working population

Sport PA. Higher levels of SPA were significantly related to better (i.e. lower) mBRS after adjusting for age and sex (table S5) and after adjusting for all confounders (Table 4). Table S6 displays the β coefficients for all variables included in the models for nBRS and mBRS. Similar to the working population, those who engaged in light-moderate, but not high intensity SPA, had better (i.e. lower) mBRS. There was no association with nBRS. Frequency of SPA was not related to nBRS or mBRS.

Leisure time PA. LPA was related to better mBRS, independently of age and sex (Table S5), but not after adjusting for all confounders (Table 4).

Total PA. Higher levels of TPA were significantly associated with better mBRS after adjusting for all confounders. There was no significant association with nBRS.

Discussion

The main findings of this large study of community dwelling healthy adults were: I) in working adults OPA was associated with impaired nBRS even after accounting for SPA and other known CVD risk factors and SPA (in particular high intensity) was associated with better nBRS; II) both in working and non-working adults, SPA (in particular light to moderate intensity) was related to lower mBRS, independently of confounders.

Recent work has shown that OPA was associated with higher daily systolic BP (26), accelerated progression of carotid intima media thickness (27), aortic stiffness (10), increased CVD risk (4-9) and mortality (11). We add to these earlier findings by investigating the association of OPA, in comparison with SPA and LPA, with the neural and mechanical components of the BRS pathway. The association between higher OPA and lower nBRS (and higher mBRS) reported in the present study does not imply that movement at work is harmful for health, but suggests that the chronic cardiovascular loading that occurs daily at work may be. Importantly, the associations between OPA and poorer nBRS remained even after adjusting for SPA (which was favorably associated with nBRS).

The associations between OPA and nBRS (and mBRS) may be explained via the chronic exposure to high BP induced by a physically demanding workload (26). Exposure to high BP daily during normal activity may create a 'resetting' of the baroreflex so that BP is regulated at a higher set point (28, 29). Further, OPA is likely to be more akin to resistance, rather than aerobic, activity and consequently may cause an increase in BP with little increase in blood flow or shear stress induced nitric

oxide release. Indeed, when examining the different types of OPA associated with nBRS and mBRS, *lifting heavy loads* (i.e. resistance activity) was associated with an impairment in both components. Furthermore, OPA may be a marker of poor psychosocial conditions, however, the association between OPA and nBRS remained after adjustment for education and perceived stress. Work stressors such as effort-reward imbalance or demand-control imbalance could also be involved but were not measured in the current study (30, 31).

Only a few prior studies have examined the association of SPA with the neural and mechanical component of the BRS. They were of small sample size and used invasive methods to measure BRS (infusion of vasoactive drugs). In two studies conducted in older adults, the positive relationship between PA and higher BRS was primarily driven by an increase in the neural component of the BRS arc (18, 32). We add to these earlier findings by examining a large and community based population, using non-invasive method (high precision carotid echotracking) suited to large observational studies. Furthermore, we compared different intensities of SPA and showed that those who engaged in high, but not light-moderate intensity SPA had better nBRS function compared to no SPA. This may explain why we did not see an association in the non-working population as they typically engaged in lower intensity SPA (even after accounting for age difference, 1.47 95%CI 1.46, 1.49 MJ/h vs 1.51, 95% CI 1.49, 1.52 MJ/h, p=0.002).

On the other hand, light to moderate SPA, but not high intensity SPA was associated with better (i.e. lower) mBRS in both the working and non-working populations. While a number of previous studies have shown that recreational PA or short term

exercise interventions are beneficially related to mBRS (i.e. arterial stiffness) (33, 34), to our knowledge, this is the first, large study in older adults to compare different intensities of habitual SPA in relation to mBRS. Speculatively and among other mechanisms, long term vigorous intensity SPA may chronically expose the vasculature to increased stress placed on the load-bearing elastin fibers of the arterial wall, causing them to fatigue (35) and ultimately resulting in an increase in stiffness of the artery (36).

LPA was not related to nBRS or mBRS in either population. This may be because the data obtained for LPA using the Baecke questionnaire is limited with regards to intensity or duration compared to SPA, thus these components are not considered in the estimation of the LPA. Alternatively or in conjunction, LPA is typically performed at lighter intensity compared to that required to participate in structured sport and may not have been intense enough to elicit an effect on nBRS or mBRS. Finally, TPA was only beneficially associated with mBRS in non-working adults. As TPA is a combination of OPA, SPA and LPA, the relationship between TPA and mBRS in non-working adults was predominantly driven by the inverse association between SPA and mBRS in this population.

This study has potentially important public health and clinical implications. Firstly and from a public health perspective, given that both impaired BRS and arterial stiffness are predictors of mortality (12, 37), identifying modifiable and non-pharmacological risk factors such as PA that may affect these two vascular parameters is of paramount importance. Secondly and from a clinical perspective, when assessing baroreflex function in a given patient, it is crucial to understand what

is related to mechanical and neural baroreflex, thereby discriminating between inadequate treatment, central failure or severe arterial stiffening. Understanding how PA differently affects the neural and mechanical components of BRS, may enable more targeted exercise prescription in conditions where either component is predominantly affected. Finally, while increasing engagement in regular PA is a necessary and ongoing concern worldwide and should not be discouraged, our findings add to existing literature suggesting that high levels of OPA may be harmful for (vascular) health. Indeed, a recent systematic review and meta-analysis showed that men with high OPA had an 18% increased risk of early mortality, compared to those engaging in lower levels of OPA (11). Our findings provide a potential underlying mechanism linking high levels of OPA and mortality, which may be explained by an impairment in nBRS. Although these findings need to be confirmed in future work, together they provide evidence for participation in both high (if tolerable) and moderate intensity aerobic activity while minimizing chronic, isometric activity for vascular health.

There are some limitations to our study that should be considered. We acknowledge the weak effect size for the association between PA and nBRS and mBRS. However, given our relatively healthy cohort, it would be expected that greater effects would be observed in those with established disease. Secondly, we relied on self-report questionnaire data to assess PA. Furthermore, data on cardiorespiratory fitness were not available and although we could have estimated fitness level via the NET-F algorithm (38), this would require an estimate of PA which may have resulted in collinearity within our models. We used carotid PP in the calculation of carotid stiffness instead of central BP. However, this approach has been recently validated in

comparison with tonometry (39). Additionally, the cross-sectional nature of the study limits inference regarding causality, and whether a change in PA is related to a change in nBRS or mBRS could not be studied. Finally, this study was conducted in a mostly Caucasian population and our results should be confirmed in more ethnically diverse populations.

Conclusions. This study has shown for the first time, that higher amounts of OPA is associated with impaired nBRS (and borderline mBRS) independent of known CVD risk factors, while higher amounts of SPA are associated with better nBRS and mBRS. These findings have implications for occupations involving a high level of OPA.

Perspectives. By demonstrating an association between higher amounts of OPA and nBRS impairment on one hand, and higher amounts of SPA and better nBRS on the other, the current study suggests that nBRS might be one disease pathway linking PA with CVD and mortality. This should be investigated prospectively in future studies and the ongoing follow-up of events in the PPS3 will enable this hypothesis to be tested. Furthermore, the results of the present study have implications for the dissemination of non-invasive evaluation of BRS in clinical practice.

Acknowledgments. We thank N Estrugo, S Yanes, JF Pruny and J Lacet Machado for performing the study recruitment of PPS3 study participants, Dr. MF Eprinchard, Dr. JM Kirzin and all the medical and technical staff of the IPC Center, the Centre de Ressources Biologiques de l'Hôpital European Georges Pompidou staff (C. de Toma, B. Vedie), and the Platform for Biological Resources (PRB) of the Hôpital Européen

Georges Pompidou for the management of the biobank. The PPS3 is organized under an agreement between INSERM and the IPC Center, and between INSERM and the Ressources Biologiques de l'Hôpital European Georges Pompidou, Paris, France. We also thank the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAM-TS, France) and the Caisse Primaire d'Assurance Maladie de Paris (CPAM-P, France) for helping make this study possible. Work on this manuscript was made possible for REC by a Prestige and Marie Curie Fellowship, a Lefoulon Delalande Fellowship, a High Blood Pressure Research Council of Australia Franco-Aus exchange grant and L'Institute Servier research grant. TVS is supported by a grant from the ANR (National Agency for Research).

Sources of Funding. Work on this manuscript was made possible for REC by a Prestige and Marie Curie Fellowship, a Lefoulon Delalande Fellowship, a High Blood Pressure Research Council of Australia Franco-Aus exchange grant and L'Institute Servier grant. TVS is supported by a grant from the ANR (National Agency for Research).

Disclosures. None.

References.

1. Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity–a systematic review of longitudinal studies. *BMC Public Health.* 2013;13(1):813.

2. World Health Organization. Global recommendations on physical activity for health. Geneva, Switzerland; 2010.

3. Krause N. Physical activity and cardiovascular mortality-disentangling the roles of work, fitness, and leisure. *Scand J Work Environ Health*. 2010:349-55.

4. Cheng X, Li W, Guo J, Wang Y, Gu H, Teo K, et al. Physical activity levels, sport activities, and risk of acute myocardial infarction: results of the INTERHEART study in China. *Angiology*. 2014;65(2):113-21.

5. Moe B, Mork PJ, Holtermann A, Nilsen TIL. Occupational physical activity, metabolic syndrome and risk of death from all causes and cardiovascular disease in the HUNT 2 cohort study. *Occup Environ Med.* 2013;70(2):86-90.

6. Krause N, Brand RJ, Arah OA, Kauhanen J. Occupational physical activity and 20-year incidence of acute myocardial infarction: results from the Kuopio Ischemic Heart Disease Risk Factor Study. *Scand J Work Environ Health*. 2015:124-39.

7. Clays E, Lidegaard M, De Bacquer D, Van Herck K, De Backer G, Kittel F, et al. The combined relationship of occupational and leisure-time physical activity with all-cause mortality among men, accounting for physical fitness. *Am J Epidemiol*. 2013;179(5):559-66.

8. Holtermann A, Marott JL, Gyntelberg F, Søgaard K, Suadicani P, Mortensen OS, et al. Occupational and leisure time physical activity: risk of all-cause mortality

and myocardial infarction in the Copenhagen City Heart Study. A prospective cohort study. *BMJ Open*. 2012;2(1):e000556.

9. Stender M, Hense H, Döring A, Keil U. Physical activity at work and cardiovascular disease risk: results from the MONICA Augsburg study. *International Journal of Epidemiology.* 1993;22(4):644-50.

10. Ujka K, Bruno RM, Bastiani L, Bernardi E, Sdringola P, Dikic N, et al. Relationship between occupational physical activity and subclinical vascular damage in moderate-altitude dwellers. *High Alt Med Biol*. 2017;18(3):249-57.

11. Coenen P, Huysmans MA, Holtermann A, Krause N, Van Mechelen W, Straker LM, et al. Do highly physically active workers die early? A systematic review with meta-analysis of data from 193 696 participants. *Br J Sports Med.* 2018;52(20):1320-6.

12. La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation*. 1988;78(4):816-24.

13. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *Am J Epidemiol*. 2003;158(2):135-43.

14. Soares-Miranda L, Sattelmair J, Chaves P, Duncan G, Siscovick DS, Stein PK, et al. Physical activity and heart rate variability in older adults: the Cardiovascular Health Study. *Circulation*. 2014;129(21):2100-10.

15. Dietrich DF, Ackermann-Liebrich U, Schindler C, Barthélémy J-C, Brändli O, Gold DR, et al. Effect of physical activity on heart rate variability in normal weight, overweight and obese subjects: results from the SAPALDIA study. *Eur J Appl Physiol.* 2008;104(3):557-65.

16. Garet M, Degache F, Pichot V, Duverney D, Costes F, Da Costa A, et al. Relationship between daily physical activity and ANS activity in patients with CHF. *Med Sci Sports Exerc*. 2005;37(8):1257-63.

17. Kiviniemi AM, Perkiömäu N, Auvinen J, Herrala S, Hautala AJ, Ahola R, et al. Lifelong physical activity and cardiovascular autonomic function in midlife. *Med Sci Sports Exerc.* 2016;48(8)1506-13.

18. Hunt BE, Farquhar WB, Taylor JA. Does reduced vascular stiffening fully explain preserved cardiovagal baroreflex function in older, physically active men? *Circulation*. 2001;103(20):2424-7.

19. Monahan KD, Tanaka H, Dinenno FA, Seals DR. Central arterial compliance is associated with age-and habitual exercise–related differences in cardiovagal baroreflex sensitivity. *Circulation*. 2001;104(14):1627-32.

20. Empana J-P, Bean K, Guibout C, Thomas F, Bingham A, Pannier B, et al. Paris Prospective Study III: a study of novel heart rate parameters, baroreflex sensitivity and risk of sudden death. *Eur J Epidemiol.* 2011;26(11):887-92.

21. Zanoli L, Empana J-P, Estrugo N, Escriou G, Ketthab H, Pruny J-F, et al. The Neural Baroreflex Pathway in Subjects With Metabolic Syndrome: A Sub-Study of the Paris Prospective Study III. *Medicine*. 2016;95(2).

22. Baecke JA, Burema J, Frijters J. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr.* 1982;36(5):936-42.

23. Ono R, Hirata S, Yamada M, Nishiyama T, Kurosaka M, Tamura Y. Reliability and validity of the Baecke physical activity questionnaire in adult women with hip disorders. *BMC Muscloskelet Disord*. 2007;8(1):61.

24. Kornet L, Hoeks AP, Janssen BJ, Willigers JM, Reneman RS. Carotid diameter variations as a non-invasive tool to examine cardiac baroreceptor sensitivity. *J Hypertens.* 2002;20(6):1165-73.

25. Sharman JE, Boutouyrie P, Perier M-C, Thomas F, Guibout C, Khettab H, et al. Impaired baroreflex sensitivity, carotid stiffness, and exaggerated exercise blood pressure: a community-based analysis from the Paris Prospective Study III. *EHJ*. 2018;39(7):599-606.

26. Clays E, De Bacquer D, Van Herck K, De Backer G, Kittel F, Holtermann A. Occupational and leisure time physical activity in contrasting relation to ambulatory blood pressure. *BMC Public Health.* 2012;12(1):1002.

27. Krause N, Brand RJ, Kaplan GA, Kauhanen J, Malla S, Tuomainen T-P, et al. Occupational physical activity, energy expenditure and 11-year progression of carotid atherosclerosis. *Scand J Work Environ Health.* 2007:405-24.

28. Joyner MJ. Baroreceptor function during exercise: resetting the record. *Exp Physiol*. 2006;91(1):27-36.

29. Raven PB, Fadel PJ, Ogoh S. Arterial baroreflex resetting during exercise: a current perspective. *Exp Physiol*. 2006;91(1):37-49.

30. Trudel X, Brisson C, Milot A, Masse B, Vézina M. Psychosocial work environment and ambulatory blood pressure: independent and combined effect of demand-control and effort-reward imbalance models. *Occup Environ Med.* 2013:oemed-2013-101416.

31. Kaewboonchoo O, Sembajwe G, Li J. Associations between Job Strain and Arterial Stiffness: A Large Survey among Enterprise Employees from Thailand. *Int J Environ Res Public Health*. 2018;15(4):659.

32. Deley G, Picard G, Taylor JA. Arterial baroreflex control of cardiac vagal outflow in older individuals can be enhanced by aerobic exercise training. *Hypertension*. 2009;53(5):826-32.

33. Li Y, Hanssen H, Cordes M, Rossmeissl A, Endes S, Schmidt-Trucksäss A. Aerobic, resistance and combined exercise training on arterial stiffness in normotensive and hypertensive adults: a review. *Eur J Sport Sci.* 2015;15(5):443-57.

34. Tanaka H, Safar ME. Influence of lifestyle modification on arterial stiffness and wave reflections. Oxford University Press; 2005.

35. WW N, MF OR. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. London: Hodder Arnold Publishing; 2005.

36. Vlachopoulos C, Kardara D, Anastasakis A, Baou K, Terentes-Printzios D, Tousoulis D, et al. Arterial stiffness and wave reflections in marathon runners. *Am J Hypertens.* 2010;23(9):974-9.

37. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *JACC*. 2010;55(13):1318-27.

38. Stamatakis E, Hamer M, O'donovan G, Batty GD, Kivimaki M. A non-exercise testing method for estimating cardiorespiratory fitness: associations with all-cause and cardiovascular mortality in a pooled analysis of eight population-based cohorts. *EHJ* 2012;34(10):750-8.

39. Kozakova M, Boutouyrie P, Morizzo C, Della Latta D, Jamagidze G, Chiappino D, et al. Radiofrequency-based wall tracking for noninvasive assessment of local carotid pulse pressure: comparison with applanation tonometry and association with organ damage. *J Hypertens*. 2018;36(12):2362-8.

Novelty and Significance.

What is new?

- In this study, we determined the association between different domains of physical activity with baroreflex sensitivity, distinguishing between the neural and mechanical components of the baroreflex arc.
- We showed that occupational physical activity was inversely related to neural baroreflex function, while sport related activity was positively associated with neural baroreflex function.

What is relevant?

- Baroreflex sensitivity is a marker of autonomic function and reduced baroreflex function is related to higher risk of cardiac mortality and sudden death.
- Previous studies have shown that total (or habitual) physical activity is associated with better autonomic function, however, little consideration is given as to whether different domains of physical activity are differently associated with baroreflex sensitivity.

Summary.

- This study provides evidence of differential associations between domains of physical activity and baroreflex sensitivity.

Figure legends.

Figure 1. Flowchart describing the selection process of the participants included in the study.

Figure 2. The relationship between the neural (upper panel) and mechanical (bottome panel) components of baroreflex and age in the working (black bars) and non-working (grey bars) populations.

Table 1. Characteristics of working and non-working study participants.

Characteristics	Working (n=5039)	Non-working (n=3610)	P value
Age (years)	56±4	64±6	<0.0001
Male, n (%)	3341 (66)	1969 (55)	<0.0001
Body mass index (kg/m^2)	25.12±3.54	25.06±3.69	0.46
Smoking status, n (%)			
Non-smoker	2581 (51)	1928 (53)	0.045
Ex-smoker	1585 (31)	1221 (34)	0.020
Cessation less than 1 year ago	59 (1)	30 (1)	0.12
Current smoker	814 (16)	431 (12)	<0.0001
Alcohol consumption, n (%)			
Non-drinker	606 (12)	414 (11)	0.43
Rarely	1723 (34)	1168 (32)	0.074
Certain days of the week	1628 (32)	964 (27)	<0.0001
Almost every day	1080 (21)	1062 (29)	<0.0001
History of cardiovascular disease, n (%)	69 (1)	102 (3)	<0.0001
Tertiary education, n (%)	2142 (43)	1269 (35)	<0.0001
Professional occupation category, n (%)			
High	2661 (55)	912 (25)	<0.0001
Medium	1762 (35)	1726 (48)	<0.0001
Low	432 (9)	56 (2)	<0.0001
No activity	-	275 (8)	-
Unemployed	-	634 (18)	-
Shift work, n (%)	80 (1)	-	-
Systolic blood pressure (mmHg)	129±16	133±17	<0.0001
Resting heart rate (bpm)	61±9	62±9	0.001
BP lowering medication, n (%)	516 (10)	799 (22)	<0.0001
Lipid lowering medication, n (%)	386 (8)	652 (18)	<0.0001
Glucose lowering medication, n (%)	76 (2)	112 (3)	<0.0001
Fasting glucose (mg/dL)*	4.6±0.1	4.6±0.1	0.006
Total cholesterol (mg/dL)	221±36	221±36	0.60
High density lipoprotein (mg/dL)	57±15	60±15	<0.0001
Occupational PA score†	2.2±0.9	-	-

Sport PA score	2.7±2.7	2.8±2.8	<0.0001
Intensity (MJ/h)	1.52±0.28	1.45±0.27	<0.0001
Leisure PA score†	2.8±0.6	3.0±0.5	<0.0001
Total PA score†	7.7±1.4	5.7±1.0	<0.0001
Neural baroreflex sensitivity* ($ms^2/mm)2x10^8$	2.99±0.61	2.86±0.65	<0.0001
Mechanical baroreflex sensitivity (m/s)	6.93±1.29	7.37±1.47	<0.0001

Data are mean ± SD unless otherwise stated. *Data are log transformed, †Physical activity scores were derived from the Baecke physical activity questionnaire (23).
PA, physical activity.

Table 2. Participant characteristics by level of occupation-related physical activity (OPA) in working participants (n=5039).

Characteristics	Low OPA (n=1625)	Moderate OPA (n=1729)	High OPA (n=1685)	P for trend
Age (years)	57.5±5.3	56.0±3.9	55.6±3.7	<0.0001
Male, n (%)	1078 (66)	1136 (66)	1127 (67)	0.76
Body mass index (kg/m^2)	24.86±3.39	24.98±3.4	25.51±3.77	<0.0001
Smoking status, n (%)				
Non-smoker	855 (53)	889 (51)	837 (50)	0.23
Ex-smoker	522 (32)	541 (31)	522 (31)	0.77
Cessation less than 1 year ago	21 (1)	23 (1)	15 (1)	0.42
Current smoker	227 (14)	276 (16)	311 (18)	0.002
Alcohol consumption, n (%)				
Non-drinker	176 (11)	151 (9)	279 (17)	<0.0001
Rarely	537 (33)	615 (36)	571 (34)	0.29
Certain days of the week	530 (33)	596 (34)	502 (30)	0.013
Almost every day	381 (23)	366 (21)	333 (20)	0.034
History of cardiovascular disease, n (%)	31 (2)	11 (1)	27 (2)	0.004
Tertiary education, n (%)	888 (55)	855 (49)	399 (24)	<0.0001
Professional occupation category, n (%)				
High	994 (61)	1116 (65)	551 (33)	<0.0001
Intermediate	438 (27)	578 (33)	746 (44)	<0.0001
Low	10 (1)	34 (2)	388 (23)	<0.0001
No activity	-	-	-	-
Unemployed	-	-	-	-
Shift work, n (%)	11 (1)	19 (1)	50 (3)	<0.0001
Systolic blood pressure (mmHg)	129±16	129±15	130±16	0.008
Resting heart rate (bpm)	61±9	61±9	62±9	0.004
BP lowering medication, n (%)	171 (11)	168 (10)	177 (11)	0.67
Lipid lowering medication, n (%)	139 (10)	127 (8)	120 (8)	0.32
Glucose lowering medication, n (%)	22 (1)	20 (1)	34 (2)	0.097

Fasting glucose (mg/dL)*	4.60±0.1	4.60±0.1	4.61±0.1	0.01
Total cholesterol (mg/dL)	220.4±36	221.4±35.0	220.8±36.8	0.81
High density lipoprotein (mg/dL)	57.5±14.8	57.7±15.2	57.0±14.9	0.31
Occupational PA score†	1.26±0.77	2.19±0.14	2.99±0.47	<0.0001
Stand at work	2.44±0.83	2.89±0.67	3.97±0.83	<0.0001
Walk at work	2.56±0.84	3.11±0.7	3.99±0.82	<0.0001
Lift heavy loads at work	1.26±0.64	1.5±0.74	2.64±1.09	<0.0001
Sport PA score†	2.70±0.75	2.71±0.71	2.65±0.70	0.026
Intensity (MJ/h)	1.53±0.28	1.52±0.828	1.52±0.27	0.39
Leisure PA score†	2.77±0.59	2.79±0.54	2.92±0.59	<0.0001
Neural baroreflex sensitivity* $(ms^2/mm)2x10^8$	3.01±0.6	3.00±0.6	2.96±0.63	0.023
Mechanical baroreflex sensitivity (m/s)	6.91±1.28	6.85±1.21	7.02±1.37	0.014

Data are mean ± SD unless otherwise stated. *Data are log transformed, †Physical activity scores were derived from the Baecke physical activity questionnaire (23).

PA, physical activity.

Table 3. Association between domains of physical activity (PA), neural and mechanical baroreflex sensitivity in working participants (n=5039), multivariate analysis.

PA domain	Neural baroreflex sensitivity β (95%CI)	Mechanical baroreflex sensitivity β (95%CI)
Occupational PA score†	-0.02 (-0.04, -0.003), p=0.022	0.04 (-0.004, 0.08), p=0.074
*Lifting heavy loads**	-0.02 (-0.04, -0.002), p=0.033	0.05 (0.02, 0.09), p=0.004
*Walking**	-0.02 (-0.04, 0.005), p=0.056	0.03 (-0.002, 0.07), p=0.064
*Standing**	-0.02 (-0.04, 0.00001), p=0.050	0.06 (0.02, 0.09), p=0.003
Sport PA score†	0.04 (0.02, 0.07), p=0.003	-0.05 (-0.09, -0.00001), p=0.049
Light to moderate intensity	0.02 (-0.02, 0.06), p=0.36	-0.11 (-0.19, -0.02), p=0.011
High intensity	0.05 (0.01, 0.09), p=0.018	-0.06 (-0.13, 0.02), p=0.16
Leisure time PA score†	0.02 (-0.005, 0.05), p=0.10	-0.02 (-0.08, 0.03), p=0.42
Total PA score	0.008 (-0.005, 0.02), p=0.23	-0.003 (-0.03, 0.02), p=0.78

Unstandardized regression coefficients (per one point increase in score) and 95% confidence intervals (CI) were estimated from linear regression analyses. Model adjusted for age, sex, mean blood pressure, body mass index, total cholesterol, antihypertensive medication, history of cardiovascular disease, smoking, alcohol, education, perceived stress, and resting heart rate; for the neural baroreflex sensitivity analysis, model is not adjusted for resting heart rate but for carotid stiffness. *The regression coefficients are given per level (n=5 levels) of each variable, †Physical activity was derived from the Baecke questionnaire of physical activity (23).

Neural baroreflex sensitivity is log transformed.

Table 4. Association between domains of physical activity (PA), neural and mechanical baroreflex sensitivity in non-working participants (n=3610), multivariate analysis.

PA domain	Neural baroreflex sensitivity β (95%CI)	Mechanical baroreflex sensitivity β (95%CI)
Sport PA†	0.01 (-0.02, 0.04), p=0.51	-0.08 (-0.15, 0.02), p=0.012
Light to moderate intensity	0.02 (-0.03, 0.07), p=0.47	-0.11 (-0.21, -0.004), p=0.042
High intensity	0.04 (-0.02, 0.09), p=0.16	-0.05 (-0.17, 0.06), p=0.36
Leisure time PA†	0.02 (-0.02, 0.05), p=0.404	-0.05 (-0.14, 0.03), p=0.18
Total PA†	0.01 (-0.01, 0.03), p=0.38	-0.05 (-0.10, -0.009), p=0.018

Unstandardized regression coefficients (per one point increase in score) and 95% confidence intervals (CI) were estimated from linear regression analyses. Model adjusted for age, sex, mean blood pressure, body mass index, total cholesterol, antihypertensive medication, history of cardiovascular disease, smoking, alcohol, education, perceived stress, and resting heart rate; for the neural baroreflex sensitivity analysis, model is not adjusted for resting heart rate but for carotid stiffness. †Physical activity was derived from the Baecke questionnaire of physical activity (23). Neural baroreflex sensitivity is log transformed.