BAROREFLEX SENSITIVITY IN TYPE 2 DIABETES MELLITUS AND END-STAGE LIVER DISEASE

Doctoral Thesis

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1. Introduction

Arterial baroreflex plays a dominant role in short term blood pressure regulation. The measurement of baroreflex sensitivity (BRS) is frequently used for the quantification of baroreflex function. It expresses the change in RR interval elicited by a unit change in blood pressure. It consists of two components: (I) the mechanical component (mechanical BRS or mBRS) represents the transduction of blood pressure change into baroreceptor vessel wall stretch; therefore, it is dependent on the elastic behaviour of the carotid sinus and the aortic arch; (II) the neural component (neural BRS or nBRS) provides information about the transduction of baroreceptor stretch into the change in cardiac sympatho-vagal balance and the responsiveness of the sinoatrial node.

BRS is decreased in type 2 diabetes mellitus (T2D). Furthermore, decreased BRS independently predicts major adverse cardiovascular events in this patient group. However, the underlying mechanisms behind the damaged baroreflex function in T2D are not well understood. While earlier results about the mechanical BRS are controversial, neural BRS have not yet been examined directly. Previous results about the components of BRS in different prediabetic states are also limited and controversial.

Cardiovascular autonomic neuropathy is a frequent complication in chronic liver disease independently from aetiology and accompanied by higher surgical risk during liver transplantation. BRS is decreased in cirrhotic patients and more severely damaged baroreflex function is associated with higher mortality. Based on earlier results, nitric oxide production increases in end-stage liver disease; furthermore, elevated level of nitric oxide could play a role in the attenuation of baroreflex function by acting in the nucleus tractus solitarius. However, the background of impaired baroreflex regulation is not clarified.

2. Objectives

Our first goal was the determination of the components of BRS in subjects with normal glucose metabolism (NGM), subjects with high metabolic risk (HMR) and patients with T2D in a cross-sectional population study. We hypothesized that there would be a stepwise deterioration from NGM towards T2D in both mechanical and neural BRS.

Our second goal was the determination of BRS and its components in patients with end-stage live disease (ESLD) within the confines of a cross-sectional case-control study. Based on previous results, we hypothesized that impaired neural integrative mechanisms (decreased neural BRS) would be responsible for damaged baroreflex regulation.

3. Methods

Paris Prospective Study III

Our final study population consisted of the following groups: 5857 subjects with NGM, 1450 subjects with HMR (metabolic syndrome [MetS] and/or impaired fasting glucose [IFG]), and 319 patients with T2D.

Determination of the Mechanical Component of BRS

Brachial systolic, diastolic and mean blood pressure values were determined using an oscillometric device. Then, end-diastolic diameter, intima-media thickness and pulsatile distension of the common carotid artery were measured with high-precision carotid echotracking. Afterwards, the recorded carotid distension curves were calibrated with brachial mean and diastolic pressure values to obtain carotid pulse pressure. Finally, our mBRS parameter ($mBRS_{PPS3}$), carotid pulse wave velocity was calculated using the Bramwell-Hill equation:

$mBRS_{PPS3} = \sqrt{1/(\rho \times DC)}$, where ρ is the density of blood and DC is the distensibility coefficient of the carotid artery. DC shows the relative change in cross-sectional area during systole elicited by a given pressure change. Higher $mBRS_{PPS3}$ represents stiffer arteries.

Determination of the Neural Component of BRS

Carotid distension curves were recorded for 5 minutes with high-precision carotid echotracking. RR interval and distension rate (ratio of pulsatile distension and the associated systolic rise time) time series were computed from the distension curves. Fast Fourier Transformation provided the power spectrum of distension rate and RR intervals. Mean cross-spectral transfer gain between distension rate and RR interval signals in the low-frequency band (0.04-0.15 Hz) represented the neural component of BRS ($nBRS_{PPS3}$).

Statistical Analysis

SAS software 9.4 was used to perform the statistical analyses. Variables with skewed distribution were logarithmically transformed. Unadjusted test for trend across the groups was employed using Armitage chi-square test or linear regression for categorical and continuous variables, respectively. Multivariable linear regression with Tukey's post hoc test was performed to quantify the associations between the subject groups and other parameters. The association of HMR or T2D with $nBRS_{PPS3}$ and $mBRS_{PPS3}$ was adjusted for potential confounders and suspected mediators identified from the literature. To separate the influence of IFG and other metabolic disturbances, we subdivided the HMR group into the following

subgroups: (I) IFG alone, no MetS; (II) MetS without IFG; (III) MetS with IFG. Then, we used these subgroups instead of the HMR group in the main analyses. Unstandardized regression coefficients (β) are presented with 95% confidence intervals (95% CI). The threshold for statistical significance was $P<0.05$

End-Stage Liver Disease Study

24 patients with ESLD were recruited from the Hungarian Transplant Waiting List. 23 healthy control subjects were also enrolled. The two groups were matched for age and sex.

Determination of BRS

Blood pressure and ECG were recorded simultaneously for 10 minutes. Systolic blood pressure and RR interval time series were computed from the recordings. Then, we identified the sequences in which systolic pressure and RR interval concurrently increased over 3 or more consecutive cycles. The slope of the RRI-systolic pressure relationship provided the BRS value of the sequence. Our BRS parameter (BRS_{ESLD}) was calculated as the mean value of the slopes of the sequences.

Determination of the Mechanical Component of BRS

Similarly to the previous study, brachial systolic, diastolic and mean blood pressure values were determined using an oscillometric device. Then, end-diastolic diameter, intima-

media thickness and pulsatile distension of the common carotid artery were measured with high-precision carotid echotracking. Afterwards, applanation tonometry was used for the determination of carotid pulse pressure. DC of the carotid artery represented the mechanical component in this study ($mBRS_{ESLD}$). Lower $mBRS_{PPS3}$ represents more rigid arteries.

Determination of the Neural Component of BRS

The neural component ($nBRS_{ESLD}$) was estimated as the ratio of BRS and its mechanical component.

Statistical Analysis

IBM SPSS v. 22 was used to perform the statistical analyses. Variables with skewed distribution underwent logarithmic transformation. Comparisons between groups were made by chi-square test and independent samples t-test for categorical and continuous variables, respectively. Data are presented as mean±SD or median (interquartile range). The threshold for statistical significance was $P<0.05$.

4. Results

Paris Prospective Study III

There was a decreasing trend in $nBRS_{PPS3}$ from NGM toT2D (p trend<0.0001). There was an increasing trend in $mBRS_{PPS3}$ from NGM to T2D (p trend<0.0001). Compared with the NGM group, $nBRS_{PPS3}$ was lower in the HMR group ($p<0.05$) and in the T2D group ($p<0.05$). Compared with the NGM group, $mBRS_{PPS3}$ was increased in the HMR group ($p<0.05$) and in the T2D group ($p<0.05$). There was no difference in $nBRS_{PPS3}$ and in $mBRS_{PPS3}$ between subjects with HMR and patients with T2D.

Multivariable Associations between T2D or HMR and the Components of BRS after Adjustment for Confounding and Mediating Factors as Compared with NGM

HMR was associated with decreased $nBRS_{PPS3}$ (β=-0.07 [95% CI, -0.12 to -0.01], p=0.029). T2D was also associated with decreased $nBRS_{PPS3}$ (β=-0.18 [95% CI, -0.29 to -0.07], p=0.002). The association between HMR or T2D and $mBRS_{PPS3}$ was not significant. Altered $mBRS_{PPS3}$ in the HMR and the T2D group was explained by blood pressure, heart rate and estimated glomerular filtration rate.

Multivariable Associations between the Subgroups of the HMR Group and the Components of BRS after Adjustment for Confounding and Mediating Factors as Compared with the NGM Group

There was no difference between subjects with IFG alone and subjects with NGM in $nBRS_{PPS3}$ and in $mBRS_{PPS3}$. Subjects with MetS without IFG had lower $nBRS_{PPS3}$ (β=-0.10 [95% CI, -0.18 to -0.02], p=0.019). There was no difference in $mBRS_{PPS3}$ between subjects with MetS without IFG and subjects with NGM. Both $nBRS_{PPS3}$ and $mBRS_{PPS3}$ was altered in subjects with MetS with IFG (β=-0.15 [95% CI, -0.25 to -0.05], p=0.004, and β=0.14 [95% CI, 0.05 to 0.24], p=0.002, respectively).

End-Stage Liver Disease Study

BRS_{ESLD} was decreased in patients compared with controls (7.00 [5.80, 9.25] vs. 11.1 [8.50, 14.80] ms/mmHg, p<0.01). While $mBRS_{ESLD}$ showed no difference between the two groups, $nBRS_{ESLD}$ was decreased in the patient group (3.54±1.20 vs. 4.48±1.43 ms/10^{-3}, p<0.05).

5. Conclusions

- T2D is associated with decreased neural BRS independently from confounding factors (age, sex, body mass index, smoking, alcohol consumption and physical activity score) and mediating factors (mean blood pressure, statin use, estimated glomerular filtration rate, and additionally, $mBRS_{PPS3}$ in the case of $nBRS_{PPS3}$, heart rate in the case of $mBRS_{PPS3}$).
- The altered mechanical BRS is explained by mediating factors (blood pressure, heart rate, estimated glomerular filtration rate) in T2D.
- IFG per se is not independently associated with decreased neural BRS or altered mechanical BRS.
- In line with earlier findings, we can conclude that patients with MetS have decreased neural BRS.
- Patients with MetS with IFG have altered mechanical BRS independently from confounders and mediators.
- In accordance with previous results, we can conclude that patients with ESLD have decreased BRS.
- The mechanical BRS of ESLD patients is comparable with healthy control subjects.
- The neural BRS of ESLD patients is decreased.

6. Bibliography of the Candidate's Publications

Publications Related to the Thesis

Cseh D[*], Climie RE[*], Offredo L, Guibout C, Thomas F, Zanoli L, Danchin N, Sharman JE, Laurent S, Jouven X, Boutouyrie P, Empana JP. (2020) Type 2 Diabetes Mellitus Is Independently Associated With Decreased Neural Baroreflex Sensitivity: The Paris Prospective Study III. Arterioscler Thromb Vasc Biol, 40: 1420-1428.

[*]These authors contributed equally to this article.

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Other Publications

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