The impact of β-blockers on the central and delta systolic pressures in a real-world population with treated hypertension: A cross-sectional study

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applanation tonometry, arterial stiffness, β-blockers, central blood pressure, diabetes, hypertension

1 | INTRODUCTION

1.1 | Background

In recent years, several studies have demonstrated that central blood pressure (BP) and central hemodynamic indexes appear to be better predictors of cardiovascular outcomes, end-organ damage, and mortality than peripheral BP, underlining the special importance of central aortic BP.1–7 Despite having a similar impact on the peripheral BP, various classes of antihypertensive medications have different effects on the central BP.2,8

Specifically, β-blockers are associated with more arterial stiffness and therefore, with a lesser reduction in systolic central BP.2,9–11 This raises the question of whether the effect of β-blockers on the central BP is maintained when part of a multidrug regimen. Few studies have examined the relationship between β-blockers and the central BP in a real-world population with treated hypertension.

Diabetes is associated with increased aortic wall stiffening, which in turn is intimately linked to central systolic and pulse pressures.10,12–16 To our knowledge, there are no studies evaluating the impact of diabetes on the relationship between β-blockers and the central systolic BP, and, by definition, the delta systolic pressure.

1.2 | Objectives

We aim to detect a difference in the delta systolic pressure, a differential between the peripheral and central systolic BP, in patients treated with and without β-blockers. We believe that amongst these patients, β-blocker-based treatments result in a higher systolic central BP and therefore, a reduction in the delta systolic pressure. Furthermore, we aim to assess the impact of diabetes on the delta systolic pressure amongst the subgroup of patients treated with β-blockers, as we believe that in these patients, the presence of diabetes is associated with a lower delta systolic pressure.
2 METHODS

2.1 Study design and setting

This cross-sectional observational study was performed at the Montreal Clinical Research Institute (IRCM) hypertension clinic. The study was approved by the IRCM ethics board. No funding was received to complete this research. We followed the STROBE statement in the reporting of this study.17

2.2 Patient recruitment

Adults with diagnosed hypertension who were treated with at least two antihypertensive agents were eligible. Exclusion criteria were: arrhythmia, kidney disease requiring dialysis regardless of their glomerular filtration rate, a change in treatment in the month preceding recruitment, and patients who were unable to complete the radial applanation tonometry assessment. Patients were excluded if the operator index, which is a composite quality control parameter, was less than 80, as this indicates high pulse wave variability and therefore, low-quality pulse wave measurement. All patients gave written consent to participate in the study.

2.3 Data collection

Patients were approached for recruitment by a nurse clinician during a follow-up visit at the IRCM hypertension clinic between 2014 and 2015. A written standardized questionnaire was administered to identify demographic information, as well as medical history. Antihypertensive medications and comorbidities were extracted from medical records. Using the standardized protocol in place, a nurse clinician systematically performed two blood pressure measurements, namely the peripheral BP with an in-office automatic sphygmomanometer, and subsequently, the central BP with radial applanation tonometry. Central aortic pressures and hemodynamic indexes were derived from radial applanation tonometry and pulse wave analysis.

2.4 Study outcomes

The primary outcome was the detection of a difference in the delta systolic pressure between patients treated with and without β-blockers. The delta systolic pressure is a differential between the peripheral and central systolic BP. The secondary outcome was to assess the impact of diabetes on delta systolic pressure amongst the subgroup of patients treated with β-blockers.

2.5 Statistical analysis

A sample of 200 patients provided 80% power to detect a group difference of the delta systolic pressure of 4 mmHg with a standard deviation of 10 mmHg. The data analysis was performed using Stata version 11. Group differences were compared using the Chi-square test or unpaired t-test, as indicated. The difference in the delta systolic pressure between the two groups was analyzed using univariate and multivariate linear regression to adjust for potential confounders. Variables were kept into the multivariable model if they were associated with the delta systolic pressure (with a p-value < 0.05), or if they confounded (change in point estimate of 10% or more) the association between β-blockers and the delta systolic pressure. Using an interaction term, we explored the effect of diabetes and β-blockers on the delta systolic pressure. Within the subgroup of patients treated with β-blockers, we ascertained the impact of diabetes on the delta systolic pressure using a mean group difference. A significance level of 0.05 was used for all statistical group differences.

3 RESULTS

Of the 251 consecutive patients approached, 43 patients were excluded: 15 were unable to complete the radial applanation tonometry assessment, 14 declined participation, 12 had a recent change in treatment, and 2 had a single antihypertensive medication. A total of 208 patients participated in the study. The main outcome was ascertained in all participants.

Patients were separated into two groups, those whose treatment included β-blockers (n = 92) and those without (n = 116). Most participants were Caucasian males with a median of three antihypertensive medications. The β-blocker group suffered from more comorbidities, such as coronary artery disease, dyslipidemia, and chronic kidney disease (Table 1).

As per the main outcome, β-blockers based treatments were associated with a higher central systolic BP as well as a lower delta systolic pressure (Table 1). This difference remained significant after adjustment for potential confounders (Table 2).

In addition, in patients whose treatment included β-blockers, the presence of diabetes was not associated with a significantly higher delta systolic pressure: 10.13 versus 9.83 in the diabetic and nondiabetic group respectively, with a mean group difference of −0.30 (95% CI, −2.40, 1.80). In our entire population, diabetes was independently associated with a mean increase in the delta systolic pressure of 1.49 mmHg, 95% CI (0.09–2.89) (Table 2).

4 DISCUSSION

Previous studies have compared β-blockers head-to-head with other antihypertensive treatments and found that β-blockers were associated with a higher central systolic BP. The CAFE study demonstrated...
that an atenolol-based treatment was less successful in diminishing the central systolic BP than non-β-blocker based treatments. To our knowledge, our study is the first to demonstrate that the effect of β-blockers on the central systolic pressure and the delta systolic pressure remains present even in real-world patients with chronically treated hypertension. This difference remained significant after adjustment for potential confounders. The real-life application of the findings obtained in carefully selected patients is a strength of this study.

The disparity in the central systolic BP and the delta systolic pressure may explain the worse clinical outcomes associated with β-blockers. While the less favorable hemodynamic profile of

### TABLE 1 Patient characteristics and mean blood pressure measurements

| Characteristics                                      | Patients treated with β-blockers (n = 92) | Patients treated without β-blockers (n = 116) | p-value |
|------------------------------------------------------|------------------------------------------|---------------------------------------------|---------|
| **Demographics and clinical characteristics**        |                                          |                                             |         |
| Age, mean ± SD                                       | 68 ± 1.22                                | 66 ± 1.14                                   | 0.17    |
| Men, n (%)                                           | 51 (55)                                  | 59 (51)                                     | 0.51    |
| Ethnicity, n (%)                                     |                                          |                                             | 0.19    |
| Caucasian                                            | 80 (87)                                  | 93 (80)                                     | -       |
| Other                                                | 12 (13)                                  | 23 (20)                                     | -       |
| BMI, mean ± SD                                       | 31 ± 6                                   | 29 ± 5                                      | 0.01    |
| Abdominal circumference (cm), mean ± SD              | 106 ± 14                                 | 100 ± 11                                    | 0.03    |
| **Comorbidities**                                    |                                          |                                             |         |
| History of diabetes, n (%)                           | 56 (61)                                  | 59 (51)                                     | 0.15    |
| Type 2 diabetes, n/total n (%)                       | 52/54 (96)                               | 55/59 (93)                                  | 0.90    |
| History of coronary artery disease, n (%)            | 24 (26)                                  | 8 (7)                                       | <0.001  |
| History of stroke or TIA, n (%)                      | 9 (10)                                   | 6 (5)                                       | 0.20    |
| History of kidney disease - eGFR <60 ml/min per 1.73 m², n (%) | 30 (33)                               | 15 (13)                                     | 0.001   |
| Treatment for dyslipidemia, n (%)                    | 65 (71)                                  | 64 (55)                                     | 0.02    |
| Active tobacco consumption, n (%)                    | 5 (5)                                    | 4 (3)                                       | 0.48    |
| Significant alcohol consumption*, n (%)              | 12 (13)                                  | 13 (11)                                     | 0.69    |
| Sedentarity, n (%)                                    | 65 (71)                                  | 52 (45)                                     | <0.001  |
| **Antihypertensive medication**                      |                                          |                                             |         |
| No. of BP-lowering drugs, median (range)             | 3 (2–7)                                  | 3 (2–5)                                     | <0.001  |
| Angiotensin-converting enzyme inhibitor, n (%)       | 25 (27)                                  | 29 (25)                                     | 0.72    |
| Angiotensin receptor blocker, n (%)                  | 49 (53)                                  | 80 (69)                                     | 0.02    |
| Calcium channel blocker, n (%)                       | 60 (65)                                  | 73 (63)                                     | 0.73    |
| Mineralocorticoid receptor antagonist, n (%)         | 8 (9)                                    | 2 (2)                                       | 0.71    |
| Thiazide or thiazide-like diuretics, n (%)           | 55 (60)                                  | 95 (82)                                     | <0.001  |
| Other†, n (%)                                        | 26 (28)                                  | 14 (12)                                     | 0.003   |
| **Treatment differences on the central, peripheral and delta systolic pressure** |                                          |                                             |         |
| Central systolic pressure, mean ± SD                 | -                                        | 128 ± 23                                    | 122 ± 21|
| Peripheral systolic pressure, mean ± SD              | 138 ± 20                                 | -                                           | 134 ± 21|
| Delta systolic pressure, mean ± SD                   | 10.01 ± 5                                | 11.50 ± 6                                   | -       |

Abbreviations: BMI, body mass index; BP, blood pressure; SD, standard deviation.

*Defined as more than 15 drinks per week for men and more than 10 drinks per week for women.

†Other include α-blockers and direct arterial vasodilators.
b-blockers might be explained by its negative chronotropic effect, recent data shows that the effect of b-blockers is both heart rate dependent and independent.\textsuperscript{2,19} Data regarding the interaction between diabetes and central systolic BP is sparse, however, diabetes seems to be associated with increased arterial stiffness.\textsuperscript{10,12-16} In type 2 diabetes, increased arterial stiffness is associated with cardiovascular risk, independently of glycemic control and ambulatory BP.\textsuperscript{13} We found that diabetes was associated with an increase in the delta systolic pressure, independently of b-blocker exposure. Amongst patients of the Framingham Heart Study, Cohen et al found evidence that arterial stiffness itself was associated with a higher risk of developing diabetes.\textsuperscript{20} Our study expands the available data on the relationship between diabetes, arterial stiffness, and antihypertensive treatments, but given their importance, these interactions warrant further studies.

### 4.1 Limitations

We acknowledge that due to the nature of this study, no causal association between b-blockers, diabetes, and delta systolic pressure can be inferred from our results. We strived to prevent measurement bias by performing calibration of the applanation tonometry device as specified and patients with unacceptable measures (operator index <80) were excluded; The mean operator index was 90%. Several selection biases could result in the underestimation of our primary outcome. Participants might have been subject to more incisive titration of treatment as they were recruited whilst visiting the IRCM specialized hypertension clinic. Additionally, patients were excluded if they had a recent change in medication which might have resulted in the selection of patients with satisfactory blood pressure control.

### 4.2 Conclusion

In conclusion, in real-world patients with treated hypertension, b-blocker-based treatments appear to be associated with a higher central systolic BP as well as a lower delta systolic pressure. Our results support current guidelines to treat hypertensive patients with b-blockers as part of a multidrug regimen and illustrate the need to further explore this association.

## AUTHOR CONTRIBUTIONS

Brigitte Bénard: Data curation; formal analysis; writing – original draft; writing – review & editing. Madeleine Durand: Conceptualization; formal analysis; writing – review & editing. Sylvie Berthoumieux: Conceptualization; investigation. Martine Gauthier: Investigation. Hélène L’Archeveque: Investigation. Maxime Lamarre-Cliche: Conceptualization. Michaél Laskine: Conceptualization; writing – review & editing. All authors have read and approved the final version of the manuscript.

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## CONFLICT OF INTEREST

The authors report no conflicts of interest.
DATA AVAILABILITY STATEMENT
The data that supports the findings in this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT STATEMENT
All patients gave written consent to participate in the study.

TRANSPARENCY STATEMENT
The lead author Brigitte Bénard affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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