The International Journal of Cardiovascular Imaging (2019) 35:927–936
https://doi.org/10.1007/s10554-018-01523-3

ORIGINAL PAPER

Association between beta-adrenoceptor antagonist-induced sympathicolysis and severity of coronary artery disease as assessed by coronary computed tomography angiography (CCTA)

Michael Messerli[1] · Monika Maredziak[1,2] · Susan Bengs[1,2] · Ahmed Haider[1,2] · Andreas A. Giannopoulos[1] · Moritz Schwyzer[1] · Dominik C. Benz[1] · Elia von Felten[1] · Ken Kudura[1] · Valerie Treyer[1] · Michael Fiechter[1] · Christoph Gräni[1] · Tobias A. Fuchs[1] · Aju P. Pazhenkottil[1] · Ronny R. Buechel[1] · Philipp A. Kaufmann[1] · Catherine Gebhard[1,2,3]

Received: 26 September 2018 / Accepted: 24 December 2018 / Published online: 8 January 2019

Abstract

Enhanced sympathetic nervous system activity is associated with increased mortality in many cardiac conditions including heart failure and coronary artery disease (CAD). To ensure adequate image quality of coronary CT angiography (CCTA), pre-scan β-adrenergic blockers (BB) are routinely administered. It is currently unknown whether sensitivity to sympathicolytic compounds is associated with severity of CAD. A total of 2633 consecutive patients (1733 [65.8%] men and 900 [34.2%] women, mean age 56.7 ± 11.5 years) undergoing CCTA for exclusion of significant CAD at our department between 06/2013 and 12/2016 were evaluated. Acute heart rate (HR) responses to BB administration were recorded in all patients. Coronary plaque burden as indicated by segment severity score (SSS), segment involvement score (SIS), and significant CAD (i.e. > 50% luminal narrowing) was higher in weak responders to BB as compared to strong responders to BB ($p = 0.001$ for SSS and SIS, and $p = 0.021$ for significant CAD). Accordingly, in a multiple linear regression model adjusted for known risk factors of CAD such as smoking, hypertension, diabetes and dyslipidaemia, as well as age, sex, body mass index (BMI), glomerular filtration rate, and HR during CCTA scan, a strong response to BB was selected as a significant independent negative predictor of coronary plaque burden (beta coefficient − 0.08, $p = 0.001$). We demonstrate that individuals with a weak acute response to BB administration encounter an increased risk of severe CAD. Taking into account sensitivity to sympatho-inhibition may add complementary information in patients undergoing CCTA for evaluation of CAD.

Keywords Cardiac sympathetic activity · Cardiovascular risk · Coronary computed tomography angiography

Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in the western world. According to WHO data, 17.7 million patients died from CVD in 2015, thereby accounting for 31% of all global deaths [1]. It is estimated that by 2020 CAD will become the largest cause of disease burden worldwide [2]. Hence, improved risk prediction tools are urgently needed. Coronary CT angiography (CCTA) provides the opportunity to non-invasively evaluate coronary anatomy and assess the extent and severity of coronary atherosclerosis [3].

The introduction of prospective ECG-triggering [4] has, among other factors, led to a tremendous radiation dose reduction from initially over 20 millisievert (mSv) [5] to approximately 3 mSv in current clinical routine [6], or

Michael Messerli and Monika Maredziak share first authorship.

✉ Catherine Gebhard
catherine.gebhard@usz.ch

[1] Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland

[2] Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland

[3] Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Ramistrasse 100, Zurich, Switzerland

less in specialized centers [7]. However, in order to ensure adequate image quality for diagnosis, prospectively ECG-triggered CCTA is restricted to patients with low and regular heart rate (HR) during the scan with target HRs ideally less than 65 bpm and a variability of less than ± 5 bpm [4, 8]. To ensure this, a medically induced sympathicolysis prior to the exam using β-adrenergic blockers (BBs) is widely applied in CCTA studies, as administration of these agents allow HR reduction to below 65–70 bpm [9].

Sympathetic nervous system activation plays a key regulatory role in cardiovascular system functions as an increase in cardioactive neurotransmitters provides the heart with inotropic stimulation and adapts cardiac performance to increased workload [10]. However, persistent efferent sympathetic activity has been shown to increase mortality in patients with heart failure [11]. Further, increased sympathetic tone is associated with both, initiation and progression of atherosclerotic disease by promoting vascular endothelial dysfunction, platelet activation and platelet-derived growth factor secretion [12]. In addition, enhanced sympathetic outflow favors the rupture of vulnerable plaques by enhancing platelet activation, hypercoagulability and microvascular constriction [13].

Thus, given (1) the association of sympathetic activity and atherosclerotic disease and (2) the routine use of sympathicolytic drugs during CCTA, the aim of this study was to assess whether the magnitude of pre-scan BB induced sympathicolysis correlates with severity of CAD in patients undergoing clinically indicated CCTA.

Methods

Study population

Between June 2013 and December 2016, a total of 2633 consecutive patients (of whom 65.8% were men) with a mean age of 56.7 ± 11.5 years and a mean body mass index (BMI) of 27.1 ± 11.7 kg/m^2 referred for CCTA at the University Hospital Zurich were retrospectively included in this study. Repeated CCTA examinations and patients who did not receive intravenous BB prior to CCTA were excluded. Our study was conducted in compliance with ICH-GCP-rules and the declaration of Helsinki and was evaluated and approved by the local ethics committee (BASEC No. 2017-1112). The need for written informed consent was waived by the ethics committee due to the retrospective nature of the study.

Heart rate control prior to CCTA

To achieve a low HR for the CCTA examination a calm and quiet atmosphere was created before patient preparation. Patients were informed about the course of events during the examination and baseline HR was recorded. Patients were then asked to breathe in deeply and hold their breath for 15 s (according to the maximum duration of scanning). If HR was > 65 bpm during breath-hold at full inspiration depth, intravenous metoprolol (Beloc®, AstraZeneca, London, UK) was administered up to a maximum of 35 mg (range 1–35 mg, mean 14.2 ± 9.0 mg). The mean metoprolol dose per kg body weight was 0.18 ± 0.12 mg/kg (range 0.01–0.76 mg/kg). The breathing commands were repeated until the target HR of < 65 bpm was reached. A single dose of 2.5 mg of sublingual isosorbide dinitrate (Isoket, Schwarz Pharma, Monheim, Germany) was administered 2 min prior to the scan in all patients.

CCTA scanning technique and image evaluation

CCTA was performed on a 64-slice CT scanner (Discovery HD 750, GE Healthcare, Waukesha, WI, USA) from 06/2013 to 11/2014 and on a 256-slice scanner (Revolution CT, GE Healthcare) from 12/2014 to 12/2016 as previously described in detail [14–16]. The following scanning parameters were applied: standard Kernel, slice thickness 0.625 mm, and increment 0 mm. The images were analysed by consensus of two experienced readers according to Society of Cardiovascular Computed Tomography guidelines [17]. Luminal diameter stenosis severity was scored as 0% (normal), 1–49% (mild CAD), 50–69% (moderate CAD) and ≥ 70% (severe CAD). CAD was defined as any narrowing of the luminal diameter. Non-evaluable coronary segments were excluded from the analysis. For the assessment of CAD severity, coronary artery plaque scores were calculated using a segment stenosis score (SSS) and a segment-involvement score (SIS). SSS was used as a measure of coronary plaque burden. Each individual segment was scored from 0 to 3 (normal to severe) luminal obstruction. Subsequently, scores of all 15 individual segments were summed to a total score ranging from 0 to 45. SIS was calculated based on the presence of plaque within a segment, irrespective of the degree of luminal stenosis within each segment and was also summed to a total score ranging from 0 to 15 [18]. Patients routinely obtained a non-contrast CT exam at our institution for coronary calcium scoring (CACS). The latter was performed on a 64-slice CT scanner (LightSpeed VCT, GE Healthcare) with the following scanning parameters: 64 × 2.5 mm collimation, rotation time of 0.35 s, tube voltage of 120 kV and a tube current of 200 mA. The semi-automatic software SmartScore (GE Healthcare) was used for quantification of CACS (Agatston units, AU). Segments with prior coronary artery stent implantation or bypass-vessels were not included in the CACS analysis and non-evaluable coronary segments were excluded from the analysis.

Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Prior to analyses, basic assumptions were checked. Student's *t*-test, Mann–Whitney test, analysis of variance (ANOVA) or Kruskal–Wallis test were used for group comparisons of continuous variables. For categorical variables, Chi square tests were used. Summed SSS (range 0–45) and summed SIS (range 0–15) were each categorized into three strata (SSS = 0, SSS > 0 ≤ 4 as well as SSS > 4 and SIS = 0, SIS > 0 ≤ 4, and SIS > 4) before further analysis. For presentation of patient's baseline characteristics the study cohort was stratified according to the median split-dichotomized variable 'HR response to BB' (median: 85.2 bpm/mg/kg metoprolol). This variable was computed by dividing the HR decrease (bpm) following metoprolol administration (calculated as HR baseline—HR during scan) by the total amount of injected metoprolol (in mg/kg body weight in order to account for a potentially confounding effect of body weight on metoprolol metabolism). Relationships between BB-dependent HR changes and CCTA outcomes were evaluated using Pearson and Spearman's correlation coefficient, as appropriate. A multivariate stepwise linear regression model taking into account known risk factors of CAD, glomerular filtration rate (GFR), body mass index (BMI), HR during scan, age and sex was applied to assess the association of HR response (as continuous variable) with severity of CAD and Agatston calcium score. Predictors of a weak response to BB administration were assessed in a stepwise logistic regression model. All tests were two-sided, and *p*-values below 0.05 were considered significant. The data were analysed by two senior researchers (MM and CG) and were reviewed and validated by the Biostatistics Department of the Epidemiology, Biostatistics and Prevention Institute at the University of Zurich. Statistical analyses were performed with IBM SPSS statistics v24.0 (IBM Corp., Armonk, N.Y.) and GraphPad Prism (v4.0, GraphPad Software, San Diego, CA).

Results

Patient characteristics

A total of 2633 subjects (1733 [65.8%] men and 900 [34.2%] women) with a mean age of 56.7 ± 11.5 years were analysed. Of the entire population, 15.8% of patients were on BB therapy at the time of their CCTA (Table 1). The median HR decrease following BB was 85.2 bpm/mg/kg metoprolol (range − 401.5 to 833.0 bpm/mg/kg). For comparison of baseline demographics, the study population was stratified in strong and weak responders to BB administration according to the median split-dichotomized variable. There was no difference in baseline characteristics between strong and weak responders to BB administration, except that a weaker HR response to BB injection was more often observed in women as compared to men ($p = 0.04$, Table 1; Fig. 1a) and that weak responders were slightly older than strong responders (57.3 ± 11.6 vs. 56.2 ± 11.5 years, $p = 0.017$, Table 1). Patient characteristics stratified by response to BB prior to CCTA are depicted in Table 1.

Association of β-sympathicolysis and severity of CAD

On average, HR decreased by 171 bpm/mg/kg metoprolol in strong responders and by 46 bpm/mg/kg metoprolol in weak responders (Table 2). Patients with a weak response to BB administration had a higher baseline HR as compared to strong responders (73.7 ± 10.3 vs. 72.4 ± 9.5, $p = 0.001$, Table 2). Heart rate during scan was significantly lower in strong responders as compared to weak responders (55.5 ± 5.7 bpm vs. 62.2 ± 7.9 bpm in weak responders, $p = 0.001$, Table 2). Accordingly, the target heart rate of ≤ 65 bpm was not reached in 270 patients (10.3%) of whom 168 (12.8%) were weak responders and 102 (7.7%) were strong responders. The radiation dose values in mSv did not differ between strong and weak responders ($p = 0.18$, Table 2), while mean arterial pressure (MAP) was slightly higher in strong responders ($p = 0.018$, Table 2).

Coronary plaque burden as indicated by segment severity score (SSS), segment involvement score (SIS), and significant CAD (i.e. > 50% luminal narrowing) was higher in weak responders as compared to strong responders ($p = 0.001$ for SSS and SIS, Fig. 1b, c, $p = 0.021$ for significant CAD, Table 2). Similarly, CACS, as indicated by Agatston score, was higher in weak as compared to strong responders ($p = 0.013$, Table 2; Fig. 1d). While baseline HR did not differ between SSS or CACS strata (Fig. 2a, b, $p = 0.3$ and $p = 0.9$, respectively), an increased plaque or calcium burden was detected in patients with a higher HR during scan (Fig. 2c, d).

HR response to BB is a significant predictor of coronary plaque burden in CCTA

In a multiple stepwise linear regression model adjusted for known risk factors of CAD including age, sex, BMI, GFR, smoking, hypertension, diabetes, dyslipidemia, and HR during scan, a strong HR response to BB (continuous variable) was selected as a significant negative predictor of SIS (beta coefficient − 0.08, $p = 0.001$, Table 3). Similarly, a strong HR response to BB administration was selected as a significant negative predictor of SSS in a multiple stepwise linear regression adjusted for the above variables

Table 1 Baseline demographics of the study population stratified by strong and weak responders to β-blocker (BB) administration according to the median split-dichotomized variable

	Total (n = 2633)	Strong response to BB (n = 1318)[a]	Weak response to BB (n = 1315)	*p*-value
Age (years)	56.7 ± 11.5	56.2 ± 11.5	57.3 ± 11.6	0.017
Male sex, n (%)	1733 (65.8%)	889 (67.5%)	844 (64.2%)	0.04
BMI kg/m^2	27.1 ± 11.7	26.8 ± 10.2	27.4 ± 13.1	0.07
GFR (ml/min)	107.1 ± 36.5	108.3 ± 37.5	105.7 ± 35.0	0.05
Hypertension, n (%)	904 (34.3%)	452 (34.3%)	452 (34.4%)	0.95
Smoking, n (%)	632 (24%)	307 (23.3%)	325 (24.7%)	0.38
Diabetes, n (%)	190 (7.2%)	98 (7.4%)	92 (7.0%)	0.66
Dyslipidemia, n (%)	873 (33.2%)	427 (32.4%)	446 (33.9%)	0.40
Family history of CAD	591 (22.4%)	304 (23.1%)	286 (21.8%)	0.42
Previous MI, n (%)	56 (2.1%)	27 (2.0%)	29 (2.2%)	0.78
Previous CABG, n (%)	45 (1.7%)	17 (1.3%)	28 (2.1%)	0.10
Previous PCI, n (%)	84 (3.2%)	38 (2.9%)	46 (3.5%)	0.37
Angina symptoms[b]	228 (8.7%)	106 (8.0%)	122 (9.3%)	0.26
Dyspnea[c]	235 (8.9%)	121 (9.2%)	114 (8.7%)	0.65
Medication				
Platelet inhibitor	483 (18.4%)	239 (18.1%)	244 (18.6%)	0.77
Beta-blocker	417 (15.8%)	199 (15.1%)	218 (16.6%)	0.29
ACE inhibitor	636 (24.2%)	328 (24.9%)	308 (23.4%)	0.38
Lipid lowering agents	538 (20.4%)	262 (19.9%)	276 (21.0%)	0.47

Values are given as mean ± standard deviation or as n (%)

ACE angiotensin-converting enzyme, *BMI* body mass index, *CABG* coronary artery bypass grafting, *CAC* coronary artery calcium, *CAD* coronary artery disease, *GFR* glomerular filtration rate, *MI* myocardial infarction, *PCI* percutaneous coronary intervention

[a]Defined as a heart rate decrease of more than 85.2 bpm/mg/kg metoprolol

[b]CCS class ≥ 2

[c]NYHA functional class ≥ 2

(beta coefficient − 0.08, $p = 0.001$, Table 3). In contrast, HR response to BB administration was not selected as a significant predictor of coronary calcium as indicated by Agatston score (p = NS, data not shown).

A stronger HR response to BB administration was observed in men as compared to women ($p = 0.011$, Fig. 1a). Hence, when the study population was stratified by sex, HR response to BB was predictive of coronary plaque burden (SSS) only in men (β coefficient − 0.05, $p = 0.027$, n = 1733), but not in women (β coefficient − 0.003, $p = 0.921$, n = 900). Accordingly, a significant interaction between sex and HR response to BB was observed when an interaction term consisting of sex and HR response to BB was entered in the above models ($p < 0.05$, data not shown), indicating that the association between HR and coronary plaque burden is sex-dependent.

Predictors of HR responses to BB

Amongst all independent variables (age, sex, body mass index, baseline heart rate, cardiovascular risk factors including smoking status, hypertension, diabetes, dyslipidemia, and positive family history of coronary artery disease, known coronary artery disease including previous myocardial infarction and/or revascularization, medication, and glomerular filtration rate) female sex (OR 1.29, 95% CI 1.1–1.5, $p = 0.003$), age (OR 1.02, 95% CI 1.01–1.03, $p < 0.001$), and baseline HR (OR 1.01, 95% CI 1.00–1.02, $p = 0.007$) were selected as significant predictors of a blunted response to BB administration in a stepwise logistic regression model (Table 4).

Discussion

In this retrospective analysis we assessed the acute HR response to BB administration as a potential surrogate marker of sympathetic tone in patients undergoing CCTA and describe its association with the severity and extent of CAD. We observed that both, a stronger sympatholytic response to BB administration and a lower HR during CCTA, were associated with reduced coronary plaque burden. Accordingly, a strong HR response to BB administration was identified as a significant and negative predictor of coronary plaque burden in a stepwise linear regression model.

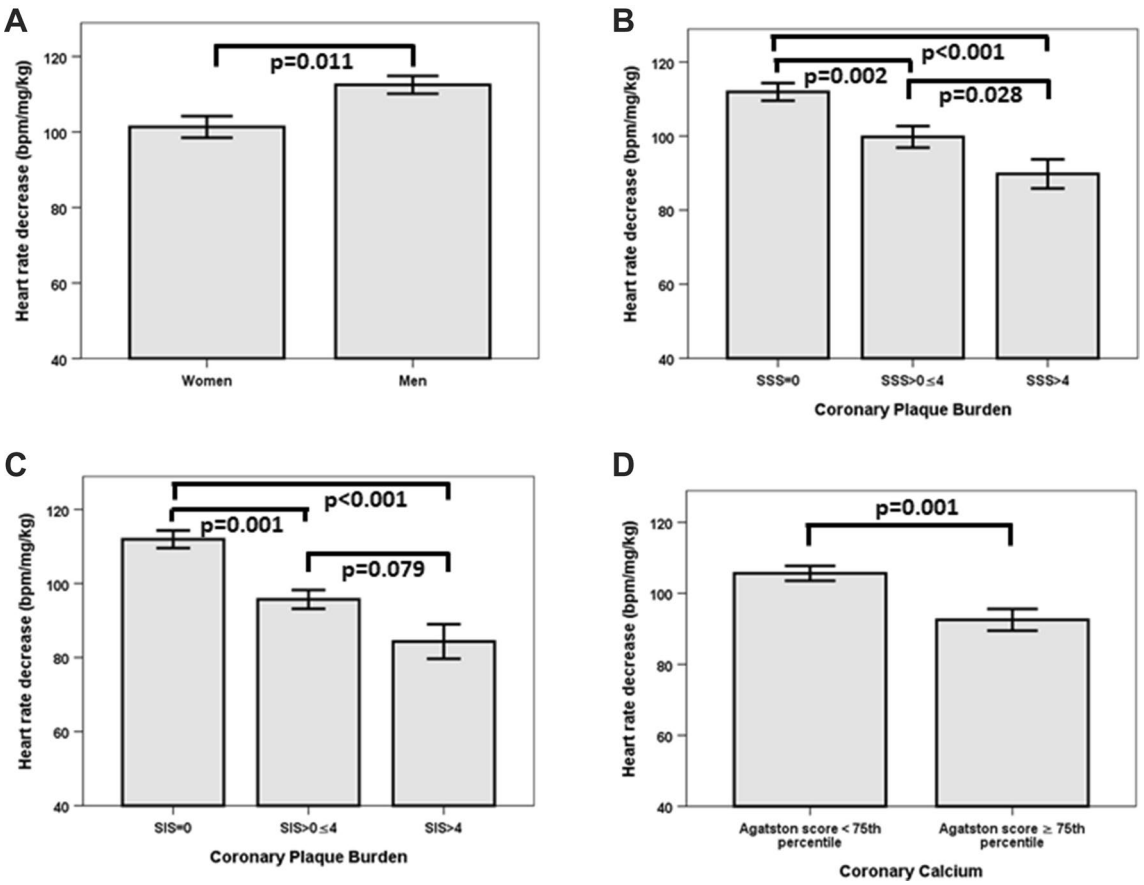

Fig. 1 Women reacted significantly stronger to metoprolol administration as compared to men (**a**). Higher coronary plaque burden as indicated by segment severity score (SSS) stratified by tertiles was observed in weak responders (**b**). Coronary plaque burden as indicated by segment involvement score (SIS), stratified by tertiles was higher in patients with weak response to BB (**c**). Patients with weak responses to metoprolol had a higher coronary calcium load (**d**). Data are presented as mean ± SEM

The extent of cardiac sympathetic activation can be estimated from physiological parameters, blood biomarkers, and imaging findings. These parameters comprise heart to mediastinum (H/M) ratio of iodine-123-labelled *meta*-iodobenzylguanidine (^{123}I-*m*IBG) uptake, plasma norepinephrine levels, and beat-to-beat HR variability, all of which have been shown to add incremental prognostic value in different cardiac conditions associated with chronically enhanced sympathetic outflow [19, 20]. Increased neuronal release of norepinephrine is usually accompanied by an increase in norepinephrine concentration in the sympathetic synaptic cleft, which, in turn, leads to desensitization of myocardial β-adrenoceptors. β-blockers inhibit catecholamine interactions with β-adrenoceptors, thus preventing G_s protein activation, formation of cAMP, and subsequent activation of protein kinase A [21]. This protects the myocardium from catecholamine toxicity leading to a reduction of their proarrhythmic effect as well as to anti-ischemic effects via increased coronary blood flow during diastole and reduced myocardial oxygen demand [22]. Accordingly, the amount of administered BBs has been shown to be related to plasma norepinephrine levels in patients with heart failure and a relationship between HR achieved with BBs and hard outcomes has previously been demonstrated [23–25]. Thus, given the positive associations between coronary stenosis severity and a blunted β-adrenoceptor antagonist-mediated effect in our study, it is tempting to hypothesize that the weak HR response to BB administration in patients with increased plaque burden might be related to chronic sympathetic hyperactivity in this population resulting in reduced β-adrenoceptor density and, thus, less immediate sensitivity to BB bolus injection. However, although the negative chronotropic response on HR is considered the gold standard for assessing the degree of β-adrenergic–receptor blockade [26], HR responsiveness to BB therapy is not a variable routinely measured to assess sympathetic activity, and no data exist directly relating a blunted HR responsiveness to BB administration to increased sympathetic activity. Nevertheless, several previous studies support the concept that altered β-adrenergic receptor sensitivity may mirror

Table 2 Angiographic and hemodynamic parameters of the study population stratified by strong and weak responders to β-blocker (BB) administration according to the median split-dichotomized variable

	Total (n = 2633)	Strong response to BB (n = 1318)[a]	Weak response to BB (n = 1315)	*p*-value
HR decrease in bpm[b]	108.7 ± 94.3	171.1 ± 94.3	46.0 ± 32.6	< 0.001
HR variability during scan	5.8 ± 6.6	5.8 ± 6.2	6.0 ± 6.9	0.7
HR baseline (bpm)	73.0 ± 9.9	72.4 ± 9.5	73.7 ± 10.3	0.001
HR rate during scan (bpm)	58.8 ± 7.6	55.5 ± 5.7	62.2 ± 7.9	0.001
HR rate during scan > 65 bpm	270 (10.3%)	102 (7.7)	168 (12.8)	0.01
MAP baseline (mmHg)	99.1 ± 11.2	100.3 ± 11.3	98.1 ± 11.0	0.02
Effective dose (mSv)	1.8 ± 1.1	1.8 ± 1.1	1.8 ± 1.0	0.18
SSS	1.9 ± 3.7	1.7 ± 3.4	2.2 ± 4.0	0.001
SIS	1.3 ± 2.1	1.1 ± 2.0	1.4 ± 2.2	0.001
Significant CAD[c]	595 (22.6%)	277 (21.3%)	318 (25.2%)	0.021
Agatston calcium score	184.1 ± 454.3	159.8 ± 413.2	208.3 ± 491.0	0.013
High agatston score[d]	508 (23.2%)	229 (20.9%)	279 (25.6%)	0.010

Values are given as mean ± standard deviation or as n (%)

CAD coronary artery disease, *HR* heart rate, *MAP* mean arterial blood pressure, *SIS* segment involvement score, *SSS* segment severity score

[a]Defined as a heart rate decrease of more than 85.2 bpm/mg/kg metoprolol

[b]HR decrease in bpm per mg/kg metoprolol

[c]> 50% luminal narrowing

[d]Agatston score > 75th percentile

baseline autonomic tone and may carry prognostic information. Indeed, Charkoudian et al. have shown that chronic elevations in muscle sympathetic nerve activity result in an apparent downregulation of adrenergic receptor responsiveness [27]. Similarly, Bell et al. report a smaller reduction in resting energy expenditure following adrenergic receptor blockade with propranolol in individuals with high resting sympathetic nervous system activity determined by plasma norepinephrine levels [28] and enhanced release of norepinephrine from cardiac adrenergic nerves has been demonstrated to downregulate myocardial β-adrenoceptor density [29]. Further, it is established that persistent sympathetic firing is associated with an increased risk of mortality, sudden cardiac death, heart failure, and fatal myocardial infarction [30–32]. Accordingly, long-term BB therapy has been a cornerstone of secondary prevention therapy for patients with CAD, as large-scale clinical trials demonstrated their treatment effects on mortality [33].

Consistent with our data, two studies have reported a relation between autonomic dysfunction, as assessed by HR variability, and coronary atherosclerosis [34, 35]. Indeed, these two studies found a positive association between increased sympathetic tone, as indicated by low heart rate variability, and angiographic severity or rapid progression of CAD [34, 35]. Thus, taken together with these previous data, our findings indicate that the HR responsiveness to BB administration—a simple and easily obtainable parameter—might provide additional information in patients with suspected CAD. Notably, while these former reports were based on angiographic assessment of CAD, we used CCTA based severity scores in our study. CCTA enables direct visualization of coronary stenosis severity, extent and distribution and has been shown to have a prognostic value in a wide variety of patient's settings [36]. Accordingly, SSS and SIS have been validated as a robust method to effectively stratify patients risk with CAD [18].

Although an elevated resting HR has been suggested as a simple and prognostic surrogate of sympathetic activity [19, 25], and an association between HR and atherosclerotic plaque burden has previously been reported [37], we did not observe a relation between baseline HR and severity of CAD in our study. The latter might be related to the fact that only patients with an increased baseline HR > 65 who received BBs prior to CCTA were included in our study. Notably, while baseline HR was not associated with CAD severity, a logistic regression analysis identified baseline HR, together with female sex and increasing age, as significant predictors of a blunted HR responsiveness to BB administration in our study. Accordingly, resting HR was significantly higher in weak responders to BB administration. Given the known association between resting HR and sympathetic tone [19, 25], these data further support the concept that an increased resting level of sympathetic nervous system activation might account for the observed reduced sensitivity to acute BB injection in patients with severe CAD. Similarly, cardiac sympathetic activity as assessed by myocardial fluorine-18 (^{18}F)-dihydroxyphenylalanine (DOPA) uptake has recently been shown to be significantly enhanced in aged women,

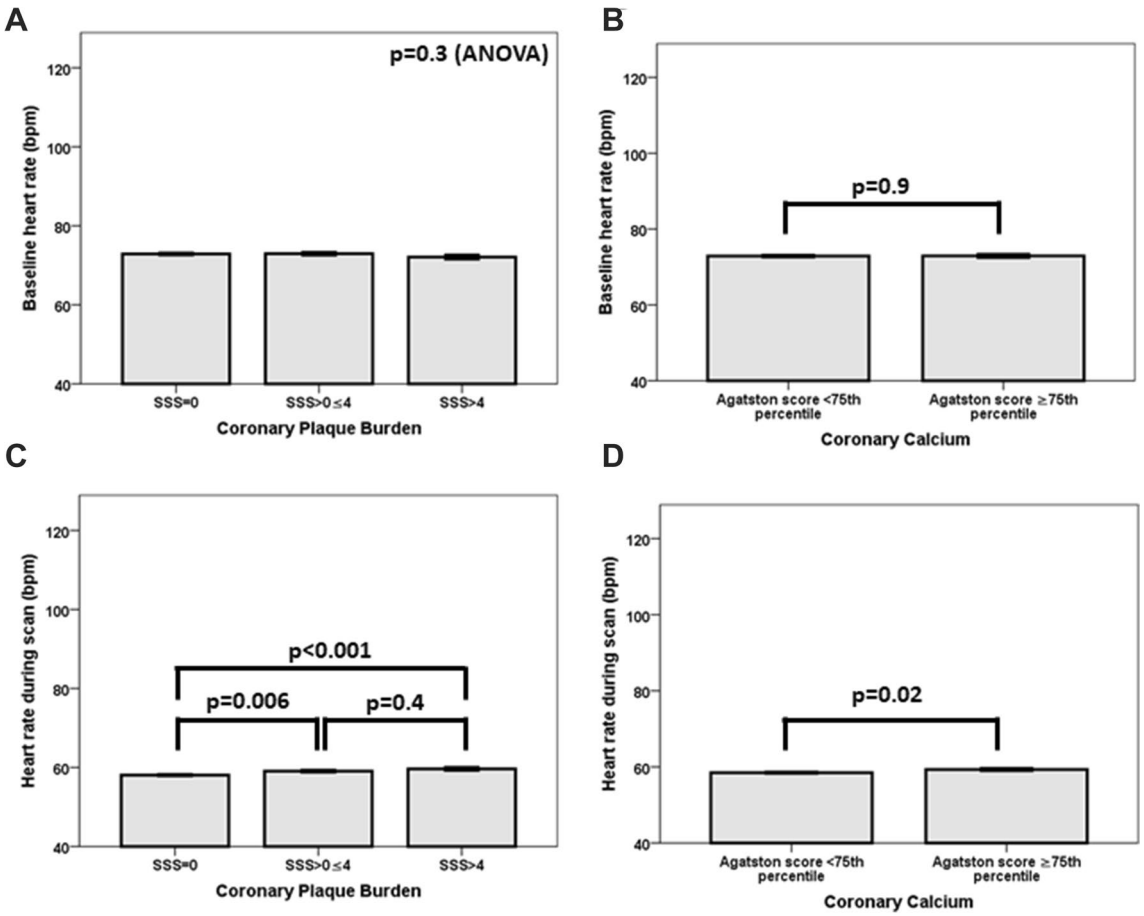

Fig. 2 Baseline heart rate was not associated with coronary plaque burden (**a**) or coronary calcium burden (**b**). A higher heart rate during the scan was associated with increased plaque burden (**c**). A higher heart rate during the scan was associated with higher coronary calcium burden (**d**). Data are presented as mean ± SEM

indicating that sex and age might be important determinants of autonomic nervous system activity [38]. Consistent with this assumption, a weaker HR response to BB administration was observed in women as compared to men in our study and both, female sex and age, were selected as significant predictors of a blunted HR response to BB. Finally, multiple regression analysis revealed a significant interaction between sex and HR response to BB, indicating that the association between BB sensitivity and coronary plaque burden is sex-dependent.

As with any study, certain design limitations are inherent. First, responses to BBs have been shown to vary among different ethnic groups [39]. Thus, given that our study is a retrospective analysis in mainly Caucasian patients, the generalizability of our findings is limited. Second, our study is observational and does not provide information on the underling mechanism. Third, although a comprehensive group of adjustment variables was employed, unmeasured variables not incorporated into the regression analysis may have affected the results. Notably, an increase in false positive findings due to increased motion susceptibility at a heart rate > 75 bpm has recently been reported in patients undergoing native CT imaging for quantification of CACS [40]. Thus, an effect of the increased HR during scan on image quality in weak responders to BB injection in our study cannot completely be ruled out. However, only 1.9% of patients in our study cohort had a scanning HR exceeding 75 bpm. In addition, our regression models were adjusted for HR during scan in order to account for a potentially confounding effect of an increased HR on image quality, and coronary segments that were non-evaluable due to artefacts/low image quality were excluded from our analysis. Fourth, the injected amount of BB was titrated until a target HR of < 65 was reached in each patient. Thus, no pre-specified treatment scheme was applied in our study and the amount of administered BB was left to the discretion of the treating physician. Nevertheless, in order to account for this potential treatment bias, we calculated the individual HR response per mg/kg of injected BB in our study. Finally, although patients were asked to suspend their regular medications 24 h prior to

Table 3 Stepwise linear regression models for coronary segment involvement score (SIS) and segment severity score (SSS). Only variables staying in the final model are presented

Independent variable	Standardized coefficient β	*p*-value
Stepwise linear regression model for segment involvement score (SIS, continuous variable) in patients undergoing CCTA for suspected coronary artery disease (n = 2633)		
Age	0.29	< 0.001
Male sex	0.18	< 0.001
Hypertension	0.10	< 0.001
Dyslipidemia	0.09	< 0.001
Diabetes	0.08	< 0.001
HR response to BB	− 0.08	< 0.001
Stepwise linear regression model for segment severity score (SSS, continuous variable) in patients undergoing CCTA for suspected coronary artery disease (*n* = 2633)		
Age	0.26	< 0.001
Male sex	0.16	< 0.001
Hypertension	0.09	0.001
Diabetes	0.09	0.001
Dyslipidemia	0.08	0.001
HR response to BB	− 0.08	0.001
Smoking	0.04	0.03

Regression analysis was performed among age, sex, body mass index (BMI), heart rate during scan (HR, continuous variable), HR response to BB (β-blocker) administration (bpm/mg/kg, continuous variable), cardiovascular risk factors including smoking status, hypertension, diabetes, dyslipidemia, and positive family history of coronary artery disease, and glomerular filtration rate (GFR). CCTA coronary CT angiography

Table 4 Stepwise logistic regression model for weak response to β-blocker (BB) administration

Independent variable	OR (95% CI)	*p*-value
Female sex	1.29 (1.10–1.51)	0.003
Baseline HR	1.02 (1.01–1.03)	< 0.001
Age	1.01 (1.00–1.02)	0.007

Only variables staying in the final model are presented (n = 2633)

Regression analysis was performed among age, sex, body mass index (BMI), baseline heart rate (HR), cardiovascular risk factors including smoking status, hypertension, diabetes, dyslipidemia, and positive family history of coronary artery disease, known coronary artery disease including previous myocardial infarction and/or revascularization, medication, and glomerular filtration rate

CI confidence interval, *OR* odds ratio

CCTA, we cannot exclude an effect of individual treatment regimen, in particular of BBs, on our endpoints. However, no difference was found in the HR response to BB injection in patients on BB medication as compared to patients who were not on BBs indicating that treatment with long-acting BBs did not interfere with the acute HR increment following BB injection prior to CCTA scan.

In conclusion, our retrospective analysis demonstrates that individuals with a weak acute response to BB administration have an increased risk of CAD as compared to individuals encountering a strong HR decrease following BB injection. Our study is the first to show an association between this routinely obtained parameter and CAD severity and supports the hypothesis that cardiac autonomic dysfunction might be operative in patients with severe CAD. Our data underline the value of understanding sympathetic nervous system activity in CAD and indicate that understanding the nature of cardiac autonomic modulation may provide pathophysiologic and therapeutic insights in cardiovascular disease management. Further larger-scale investigations across different age- and risk-groups will have to delineate the prognostic significance and underlying mechanisms of our findings.

Acknowledgements This study was supported by grants from the Iten-Kohaut Foundation, Switzerland (MM), the Swiss National Science Foundation (SNSF), the Olga Mayenfisch Foundation, Switzerland, the OPO Foundation, Switzerland, the Novartis Foundation, Switzerland, the Helmut Horten Foundation, Switzerland, and the Swissheart Foundation (CG).

Compliance with ethical standards

Conflict of interest Michael Messerli received a research grant from the Iten-Kohaut Foundation, Switzerland. Catherine Gebhard received research grants from the Novartis Foundation, Switzerland. The University Hospital of Zurich holds a research contract with GE Healthcare. No further specific grants from funding agencies in the public, commercial, or not-for-profit sectors were received for this study.

Research involving human participants The study was conducted in compliance with ICH-GCP-rules and the declaration of Helsinki and was evaluated and approved by the local ethics committee (BASEC No. 2017-01112).

Informed consent The need for written informed consent was waived by the ethics committee due to the retrospective nature of the study.

References

1. World Health Organisation (2017) Cardiovascular disease statistic. WHO. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed 06 Sept 2018
2. Beaglehole R (1999) International trends in coronary heart disease mortality and incidence rates. J Cardiovasc Risk 6(2):63–68
3. American College of Cardiology Foundation Task Force on Expert Consensus D, Mark DB, Berman DS, Budoff MJ, Carr

JJ, Gerber TC et al ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on expert consensus documents. J Am Coll Cardiol. 2010;55(23):2663–2699
4. Husmann L, Valenta I, Gaemperli O, Adda O, Treyer V, Wyss CA et al (2008) Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. Eur Heart J 29(2):191–197
5. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC et al (2009) Estimated radiation dose associated with cardiac CT angiography. JAMA 301(5):500–507
6. Stocker TJ, Deseive S, Leipsic J, Hadamitzky M, Chen MY, Rubinshtein R et al (2018) Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the PROspective multicenter registry on radiation dose estimates of cardiac CT angiography in daily practice in 2017 (PROTECTION VI). Eur Heart J 39(41):3715–3723
7. Stehli J, Fuchs TA, Bull S, Clerc OF, Possner M, Buechel RR et al (2014) Accuracy of coronary CT angiography using a submillisievert fraction of radiation exposure: comparison with invasive coronary angiography. J Am Coll Cardiol 64(8):772–780
8. Maeda E, Tomizawa N, Yamamoto K, Kanno S, Akahane M, Ino K et al (2015) Optimized heart rate for 320-row cardiac CT can be feasibly predicted from prescan parameters. Springerplus 4:697
9. Herzog BA, Husmann L, Burkhard N, Gaemperli O, Valenta I, Tatsugami F et al (2008) Accuracy of low-dose computed tomography coronary angiography using prospective electrocardiogram-triggering: first clinical experience. Eur Heart J 29(24):3037–3042
10. Middlekauff HR (1997) Mechanisms and implications of autonomic nervous system dysfunction in heart failure. Curr Opin Cardiol 12(3):265–275
11. Florea VG, Cohn JN (2014) The autonomic nervous system and heart failure. Circ Res 114(11):1815–1826
12. Remme WJ (1998) The sympathetic nervous system and ischaemic heart disease. Eur Heart J 19:F62–F71
13. Thrall G, Lane D, Carroll D, Lip GY (2007) A systematic review of the effects of acute psychological stress and physical activity on haemorheology, coagulation, fibrinolysis and platelet reactivity: implications for the pathogenesis of acute coronary syndromes. Thromb Res 120(6):819–847
14. Benz DC, Grani C, Hirt Moch B, Mikulicic F, Vontobel J, Fuchs TA et al (2016) Minimized radiation and contrast agent exposure for coronary computed tomography angiography: first clinical experience on a latest generation 256-slice scanner. Acad Radiol 23(8):1008–1014
15. Benz DC, Fuchs TA, Grani C, Bruengger AAS, Clerc OF, Mikulicic F et al (2018) Head-to-head comparison of adaptive statistical and model-based iterative reconstruction algorithms for submillisievert coronary CT angiography. Eur Heart J Cardiovasc Imaging 19(2):193–198
16. Gaemperli O, Husmann L, Schepis T, Koepfli P, Valenta I, Jenni W et al (2009) Coronary CT angiography and myocardial perfusion imaging to detect flow-limiting stenoses: a potential gatekeeper for coronary revascularization? Eur Heart J 30(23):2921–2929
17. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ et al (2009) SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 3(2):122–136
18. Al-Mallah MH, Qureshi W, Lin FY, Achenbach S, Berman DS, Budoff MJ et al (2014) Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international confirm registry. Eur Heart J Cardiovasc Imaging 15(3):267–274
19. Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L et al (2012) Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (systolic heart failure treatment with the I(f) inhibitor ivabradine trial) study. J Am Coll Cardiol 59(22):1938–1945
20. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA et al (2000) Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis risk in communities. Circulation 102(11):1239–1244
21. Freedman NJ, Lefkowitz RJ (2004) Anti-beta(1)-adrenergic receptor antibodies and heart failure: causation, not just correlation. J Clin Invest 113(10):1379–1382
22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al (2016) 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18(8):891–975
23. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW (2009) Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. Ann Intern Med 150(11):784–794
24. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE et al (1996) Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 94(11):2807–2816
25. Cohen-Solal A, Jacobson AF, Pina IL (2017) Beta blocker dose and markers of sympathetic activation in heart failure patients: interrelationships and prognostic significance. ESC Heart Fail 4(4):499–506
26. Shin J, Johnson JA (2007) Pharmacogenetics of beta-blockers. Pharmacotherapy 27(6):874–887
27. Charkoudian N, Joyner MJ, Sokolnicki LA, Johnson CP, Eisenach JH, Dietz NM et al (2006) Vascular adrenergic responsiveness is inversely related to tonic activity of sympathetic vasoconstrictor nerves in humans. J Physiol 572(Pt 3):821–827
28. Bell C, Seals DR, Monroe MB, Day DS, Shapiro LF, Johnson DG et al (2001) Tonic sympathetic support of metabolic rate is attenuated with age, sedentary lifestyle, and female sex in healthy adults. J Clin Endocrinol Metab 86(9):4440–4444
29. Haeusler G (1990) Pharmacology of beta-blockers: classical aspects and recent developments. J Cardiovasc Pharmacol 16(Suppl 5):S1–S9
30. Camm AJ, Pratt CM, Schwartz PJ, Al-Khalidi HR, Spyt MJ, Holroyde MJ et al (2004) Mortality in patients after a recent myocardial infarction—a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 109(8):990–996
31. Manfrini O, Pizzi C, Trere D, Fontana F, Bugiardini R (2003) Parasympathetic failure and risk of subsequent coronary events in unstable angina and non-ST-segment elevation myocardial infarction. Eur Heart J 24(17):1560–1566
32. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P (2005) Heart-rate profile during exercise as a predictor of sudden death. New Engl J Med 352(19):1951–1958
33. Brugts JJ, Bertrand M, Remme W, Ferrari R, Fox K, MacMahon S et al (2017) The treatment effect of an ACE-inhibitor based regimen with perindopril in relation to beta-blocker use in 29,463 patients with vascular disease: a combined analysis of individual data of ADVANCE, EUROPA and PROGRESS trials. Cardiovasc Drugs Ther 31(4):391–400

34. Huikuri HV, Jokinen V, Syvanne M, Nieminen MS, Airaksinen KE, Ikaheimo MJ et al (1999) Heart rate variability and progression of coronary atherosclerosis. Arterioscler Thromb Vasc Biol 19(8):1979–1985
35. Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama K et al (1990) Decreased magnitude of heart rate spectral components in coronary artery disease. Its relation to angiographic severity. Circulation 81(4):1217–1224
36. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ et al (2011) Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 58(8):849–860
37. Perski A, Olsson G, Landou C, Defaire U, Theorell T, Hamsten A (1992) Minimum heart-rate and coronary atherosclerosis—Independent relations to global severity and rate of progression of angiographic lesions in men with myocardial-infarction at a young age. Am Heart J 123(3):609–616
38. Burger IA, Lohmann C, Messerli M, Bengs S, Becker A, Maredziak M et al (2018) Age- and sex-dependent changes in sympathetic activity of the left ventricular apex assessed by 18F-DOPA PET imaging. PloS ONE 13(8):e0202302
39. Hu H, Jui HY, Hu FC, Chen YH, Lai LP, Lee CM (2007) Predictors of therapeutic response to beta-blockers in patients with heart failure in Taiwan. J Formos Med Assoc 106(8):641–648
40. van der Werf NR, Willemink MJ, Willems TP, Vliegenthart R, Greuter MJW, Leiner T (2018) Influence of heart rate on coronary calcium scores: a multi-manufacturer phantom study. Int J Cardiovasc Imaging 34(6):959–966