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# Baroreflex sensitivity is higher during acute psychological stress in healthy subjects under $\beta$-adrenergic blockade

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## ABSTRACT

Acute psychological stress challenges the cardiovascular system with an increase in BP (blood pressure), HR (heart rate) and reduced BRS (baroreflex sensitivity). $\beta$-adrenergic blockade enhances BRS during rest, but its effect on BRS during acute psychological stress is unknown. This study tested the hypothesis that BRS is higher during acute psychological stress in healthy subjects under $\beta$-adrenergic blockade. Twenty healthy novice male bungee jumpers were randomized and studied with (PROP, $n = 10$) or without (CTRL, $n = 10$) propranolol. BP and HR responses and BRS [cross-correlation time-domain ($BRS_{TD}$) and cross-spectral frequency-domain ($BRS_{FD}$) analysis] were evaluated from 30 min prior up to 2 h after the jump. HR, cardiac output and pulse pressure were lower in the PROP group throughout the study. Prior to the bungee jump, BRS was higher in the PROP group compared with the CTRL group [$BRS_{TD}$: 28 (24–42) compared with 17 (16–28) ms · mmHg$^{-1}$, $P < 0.05$; $BRS_{FD}$: 27 (20–34) compared with 14 (9–19) ms · mmHg$^{-1}$, $P < 0.05$; values are medians (interquartile range)]. BP declined after the jump in both groups, and post-jump BRS did not differ between the groups. In conclusion, during acute psychological stress, BRS is higher in healthy subjects treated with non-selective $\beta$-adrenergic blockade with significantly lower HR but comparable BP.

## INTRODUCTION

Physiological adaptation to a potentially threatening situation involves a 'fight-or-flight' or stress response assumed to protect the individual [1]. Besides mental changes, the autonomic nervous system is also activated for fight or flight, in part, by promoting blood supply to skeletal muscles required to manage the threat. This reflex can be reproduced in animals by stimulation of the hypothalamic 'defence area', which relays descending neural traffic to the nuclei of the autonomic nervous system in the brain stem [2]. The stress-induced increase in

**Key words:** adrenergic $\beta$-antagonist, autonomic nervous system, baroreflex, haemodynamics, psychological stress.

**Abbreviations:** BP, blood pressure; $BP_o$, BP from oscillometric brachial pressure; BPV, BP variability; BRS, baroreflex sensitivity; $BRS_{TD}$, BRS determined by a cross-correlation time-domain method; $BRS_{FD}$, BRS determined by frequency-domain analysis; CO, cardiac output; CTRL, control; HF, high-frequency band; HR, heart rate; $HR_o$, HR from oscillometric brachial pressure HRV, HR variability; IBI, interbeat interval; IQR, interquartile range; LF, low-frequency band; $MAP_f$, finger mean arterial pressure; PP, pulse pressure; PROP, propranolol-treated; SBP, systolic BP; SV, stroke volume; SVR, systemic vascular resistance.

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HR (heart rate) by sympathetic stimulation of cardiac $\beta$-adrenergic receptors is accompanied by a rise in BP (blood pressure) primarily mediated by $\alpha$-adrenergic stimulation [3–5]. This concomitant increase in HR and BP implies modulation of baroreflex function. Specifically, during psychological stress, BRS (baroreflex sensitivity) was reported as being reduced [3,6], possibly by inhibitory inputs from the hypothalamus to the nucleus tractus solitarius as the origin of baroreceptor afferents [7].

The cardiovascular adaptation to psychological stress seems physiological, but the altered autonomic input may trigger ventricular arrhythmias in the presence of heart disease [8,9]. Both $\beta$-receptor blocking agents and an enhanced BRS have beneficial effects on outcome in patients with cardiovascular disease probably by preventing ventricular arrhythmias [10,11]. In an attempt to reduce the physical effects of acute psychological stress, $\beta$-adrenergic receptor blockade is widely used by performing artists and during public speaking [12,13]. With $\beta$-adrenergic receptor blockade, the HR response to acute psychological stress is reduced [14], and an increase in BRS during rest in healthy subjects has been reported [15,16]. Several studies have evaluated HRV (HR variability) during psychological stress with $\beta$-adrenergic receptor blockade, whereas the effect on BRS is unknown [17,18].

The present study tested the hypothesis that BRS is higher during acute psychological stress in healthy subjects with $\beta$-adrenergic blockade by determining BRS in healthy subjects using the lipophilic non-selective $\beta$-blocker propranolol prior to an imminent bungee jump. Healthy subjects without $\beta$-blockade served as reference in this model of acute psychological stress.

## MATERIALS AND METHODS

### Participants

Twenty healthy novice male bungee jumpers were randomized and studied with (PROP, $n = 10$) or without (CTRL, $n = 10$) propranolol (120 mg daily in three doses for the 3 days preceding the experiment and including the day of the jump), a non-selective lipophilic $\beta$-blocker commonly used to relieve symptoms of acute psychological stress [13]. Groups were comparable for height and weight, with slightly lower age in the PROP group (PROP: $26 \pm 4$ years, CTRL: $30 \pm 4$ years; $P < 0.05$). One week prior to the jump, health screening was performed by questionnaire and physical examination. Subjects with chronic use of medication, known cardiac arrhythmias or asthma were excluded. Each subject received verbal and written information about the study objectives, measurement techniques and the risks and benefits associated with the investigation. All subjects gave their written informed consent as approved by the AMC Medical Ethical Committee, and experiments were performed in accordance with the Declaration of Helsinki. Subjects performed their bungee jump in randomized order.

### Measurements

With the 60-m-high crane in full view, subjects witnessed their fellow subjects take their jump while measurements were performed on the hospital parking lot at an ambient temperature of 20 °C. Continuous finger BP and HR were recorded (Portapres; FMS) during 5 min in the supine position and another 5 min upright at stress, 30 min preceding ($t_{-30\ \mathrm{min}}$), and post-stress, 120 min following ($t_{+120\ \mathrm{min}}$) the jump (Figure 1). These time points were based on previous ratings of emotional states in bungee jumpers from 1 h prior to 1 h following the performance of a bungee jump [19]. The finger cuff was applied to the mid-phalanx of the left hand and placed in the midaxillary line at heart level. The continuous BP signal was converted into a digital signal at 100 Hz and stored on a hard disk for off-line analysis. Additionally, $BP_o$ and $HR_o$ (oscillometric BP and HR) (Omron M5-I; Omron Healthcare) were measured at $t_{-30\ \mathrm{min}}$ (supine and upright) before entering the elevator, on the platform when harnessed at $t_{-1\ \mathrm{min}}$ (upright), following the jump at $t_{+10\ \mathrm{min}}$ (upright) and $t_{+120\ \mathrm{min}}$ (supine and upright). $BP_o$ was used to calibrate the finger BP signal. SV (stroke volume) was estimated from the finger pulse pressure using the Modelflow method incorporating age, gender, height and weight (BeatScope 1.1 software; FMS) [20]. PP (pulse pressure) was the systolic–diastolic $BP_o$ difference, whereas PP divided by 3 and added with diastolic $BP_o$ gave $MAP_o$ (oscillometric mean arterial pressure). $MAP_f$ (finger mean arterial pressure) was the integral of the arterial pressure wave divided by the corresponding beat interval duration. After interpolation of the arterial pressure signal to 1 ms and detection of the 20% level of pressure pulse height for each heartbeat, the IBI (interbeat interval) was determined. HR (beats $\cdot$ min$^{-1}$) was the inverse of IBI. CO (cardiac output) was SV $\times$ HR and SVR (systemic vascular resistance) was the ratio of $MAP_f$ to CO.

Estimates of BRS were obtained in the frequency-domain ($BRS_{FD}$) by fast Fourier transform [21] and in the time-domain ($BRS_{TD}$) by the sequence method (cross-correlation BRS) [22]. For $BRS_{FD}$, beat-to-beat SBP (systolic BP) and IBI time series were detrended using a Hanning window. Power spectral density and cross-spectra of SBP variability [BPV (BP variability)] and IBI variability (HRV) were computed using discrete Fourier transform. The LF (low-frequency band; 0.06–0.15 Hz) and HF (high-frequency band; 0.15–0.4 Hz) [23] were selected, and $BPV_{LF}$-to-$HRV_{LF}$ transfer gain was computed for coherence >0.5. Estimates of $BRS_{TD}$ were obtained from beat-to-beat SBP and IBI data. The cross-correlation between a 10 s series of SBP and IBI samples was computed for delays $\tau$ in IBI of 0–5 s.

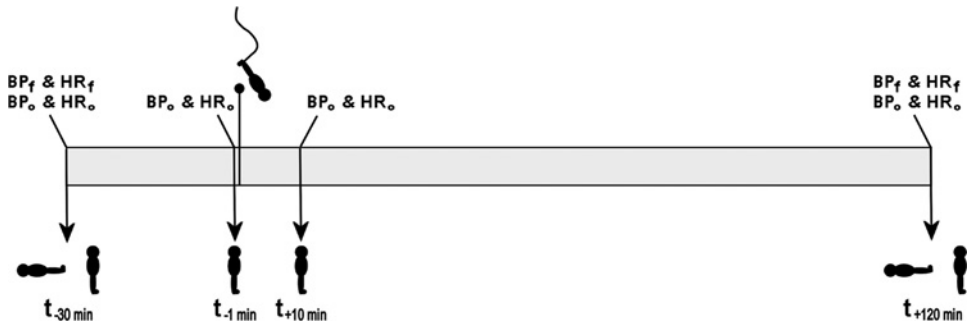


**Figure 1 Protocol**

Timing of the measurements at stress ($t_{-30\ min}$), and maximum stress ($t_{-1\ min}$) prior to the bungee jump and 10 min ($t_{+10\ min}$) and 120 min ($t_{+120\ min}$) post-stress following the bungee jump. $BP_f$, continuous finger BP; $HR_f$, HR from continuous finger BP.

The $\tau$ yielding the highest cross-correlation was selected if significant with $\alpha$ set at 0.05. The regression slope was recorded as one $BRS_{TD}$ value. Subsequently, the process was repeated for a series of SBP and IBI samples 1 s later. Distributions of individual $BRS_{TD}$ values are best described as log-normal [22]. Therefore geometric averages were used to obtain one value per subject at $t_{-30\ min}$ and $t_{+120\ min}$.

## Statistical analysis

Group data were expressed as means $\pm$ S.D. or medians and IQR (interquartile range). Differences between PROP and CTRL groups were identified using a Student's $t$ test when data were normally distributed; otherwise by using the Mann–Whitney rank sum test. Time series derived from the oscillometric data in the upright position were analysed by one-way repeated measures ANOVA. Supine oscillometric values and continuous arterial pressure data were compared using a paired Student's $t$ test or Wilcoxon signed rank test to detect time- and posture-dependent changes. The level of statistical significance was set at $P < 0.05$.

# RESULTS

Pre-jump data from two PROP subjects were excluded from BRS analysis due to insufficient quality of continuous arterial pressure recordings. Another two supine PROP recordings at $t_{-30\ min}$ were excluded from $BRS_{FD}$ analysis because of insufficient coherence between the SBP and IBI signals, whereas this was the case for one subject in the PROP group at $t_{+120\ min}$.

## Pre-jump

Prior to the bungee jump ($t_{-30\ min}$), $BRS_{FD}$ and $BRS_{TD}$ were higher with propranolol (Table 1 and Figure 2, left-hand panel) as was $HRV_{HF}$. HR and CO were lower, and with SVR tending to be higher, whereas BP was unaffected by propranolol (Table 2 and Figure 3). The HR increase upon standing was lower in the PROP than in the CTRL group ($P < 0.01$; Figure 4). From $t_{-30\ min}$ to $t_{-1\ min}$, BP increased to a similar extent in PROP and CTRL groups, whereas the rise in HR was less with propranolol ($P < 0.001$).

**Table 1 BRS, BP and HRV**

Values are medians (IQR). $^*P < 0.05$ and $^{**}P < 0.01$ compared with CTRL; $\dagger\dagger P < 0.01$ compared with $t_{-30\ min}$.

| Parameter | Group | $t_{-30\ min}$ | $t_{+120\ min}$ |
|---|---|---|---|
| $BRS_{TD}$ ($ms \cdot mmHg^{-1}$) | CTRL | 17 (16–28) | 24 (14–27) |
| | PROP | 28 (24–42)* | 27 (17–32) |
| $BRS_{FD}$ ($ms \cdot mmHg^{-1}$) | CTRL | 14 (9–19) | 19 (9–22) |
| | PROP | 27 (20–34)* | 18 (16–19) |
| $BPV_{LF}$ ($mmHg^2 \cdot Hz^{-1}$) | CTRL | 8 (4–15) | 5 (3–10) |
| | PROP | 4 (1–7) | 3 (2–7) |
| $HRV_{LF}$ ($ms^2 \cdot Hz^{-1}$) | CTRL | 1890 (698–2730) | 754 (472–1720) |
| | PROP | 3780 (1290–6360) | 1310 (702–1450) |
| $HRV_{HF}$ ($ms^2 \cdot Hz^{-1}$) | CTRL | 170 (66–186) | 653 (234–1300)†† |
| | PROP | 884 (506–2060)** | 1690 (340–2310) |

## Post-jump

Following the bungee jump, BP and HR had declined at $t_{+10\ min}$ to levels comparable with $t_{-30\ min}$, and BP decreased further in the PROP and CTRL groups (Table 2 and Figure 3). $HRV_{HF}$ at $t_{+120\ min}$ was higher than at $t_{-30\ min}$. No difference in BRS was observed between groups at $t_{+120\ min}$ (Table 1 and Figure 2, right-hand panel). The HR increase upon active standing at $t_{+120\ min}$ was lower in the PROP group compared with the CTRL group ($P < 0.05$; Figure 4). Moreover, in both groups, the orthostatic HR increases were larger compared with $t_{-30\ min}$ ($P < 0.05$).

# DISCUSSION

The present study addressed cardiac baroreflex function in humans under acute psychological stress. The new finding is that BRS is higher during acute psychological stress in healthy subjects under $\beta$-adrenergic blockade.

**Table 2 Cardiovascular variables**

Values are presented as means ± S.D. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with the CTRL group; †$P < 0.05$, ††$P < 0.01$ and †††$P < 0.001$ compared with $t_{-30\ min}$; ‡$P < 0.05$ and ‡‡$P < 0.01$ compared with supine. DBP, diastolic BP; o, oscillometric brachial pressure.

| | | Supine | | Upright | | | |
|---|---|---|---|---|---|---|---|
| Parameter | Group | $t_{-30\ min}$ | $t_{+120\ min}$ | $t_{-30\ min}$ | $t_{-1\ min}$ | $t_{+10\ min}$ | $t_{+120\ min}$ |
| $HR_o$ (beats · min$^{-1}$) | CTRL | 74 ± 14 | 67 ± 11 | 88 ± 17‡‡ | 114 ± 26††† | 92 ± 17 | 93 ± 17‡‡ |
| | PROP | 52 ± 8*** | 53 ± 7** | 58 ± 9***‡‡ | 65 ± 10***†† | 59 ± 10*** | 69 ± 10***†‡‡‡ |
| $SBP_o$ (mmHg) | CTRL | 146 ± 11 | 129 ± 9††† | 144 ± 14 | 160 ± 21†† | 151 ± 10 | 128 ± 13††† |
| | PROP | 134 ± 15 | 123 ± 12†† | 136 ± 16 | 155 ± 23†† | 139 ± 20 | 120 ± 11†† |
| $DBP_o$ (mmHg) | CTRL | 81 ± 10 | 72 ± 8††† | 92 ± 8‡‡ | 100 ± 11† | 88 ± 9 | 82 ± 7†††‡‡ |
| | PROP | 80 ± 12 | 65 ± 5†† | 92 ± 11‡‡ | 103 ± 12† | 88 ± 16 | 80 ± 6††‡‡ |
| $MAP_o$ (mmHg) | CTRL | 103 ± 10 | 91 ± 8††† | 110 ± 9‡‡ | 120 ± 12†† | 109 ± 8 | 97 ± 8†††‡ |
| | PROP | 98 ± 13 | 85 ± 6†† | 107 ± 11‡‡ | 120 ± 14†† | 105 ± 17 | 93 ± 8††‡‡ |
| $PP_o$ (mmHg) | CTRL | 65 ± 8 | 58 ± 4† | 52 ± 9‡‡ | 60 ± 19 | 63 ± 10† | 45 ± 9†††‡‡ |
| | PROP | 54 ± 9** | 57 ± 10 | 44 ± 11‡ | 52 ± 17 | 50 ± 9** | 40 ± 6‡‡ |
| CO (l · min$^{-1}$) | CTRL | 5.9 ± 0.8 | 5.0 ± 1.1 | 4.7 ± 0.6‡ | — | — | 4.5 ± 1.1 |
| | PROP | 4.2 ± 1.1*** | 3.8 ± 0.4** | 3.3 ± 0.9**‡‡ | — | — | 3.2 ± 0.5**‡‡ |
| SV (ml) | CTRL | 78 ± 10 | 74 ± 15 | 54 ± 16‡‡ | — | — | 47 ± 12‡‡ |
| | PROP | 81 ± 22 | 70 ± 7 | 55 ± 14‡‡ | — | — | 45 ± 4‡‡ |
| SVR (mmHg · s · ml$^{-1}$) | CTRL | 0.85 ± 0.18 | 0.92 ± 0.21 | 1.24 ± 0.28‡‡ | — | — | 1.24 ± 0.42‡‡ |
| | PROP | 1.05 ± 0.32 | 1.03 ± 0.12 | 1.69 ± 0.44*‡ | — | — | 1.47 ± 0.16‡‡ |

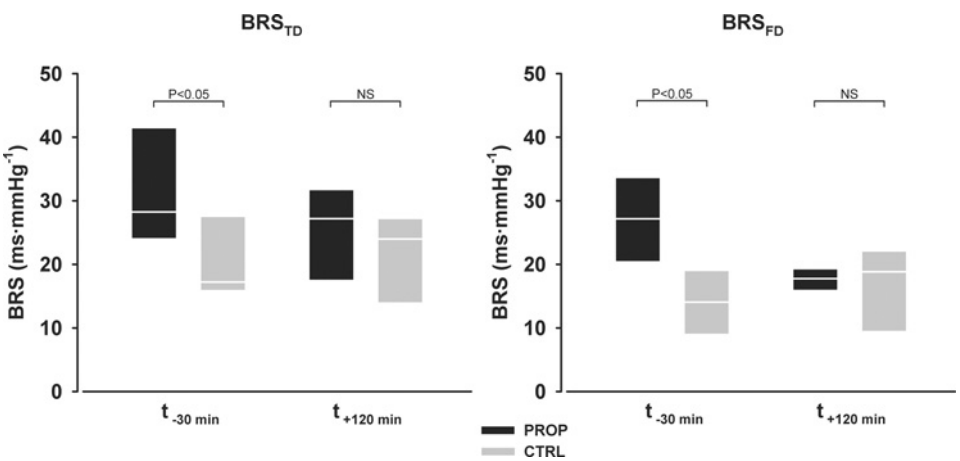


**Figure 2 BRS with compared with or without β-blockade**

BRS with (PROP; black bars) compared with without (CTRL; grey bars) propranolol pre-jump ($t_{-30\ min}$; left-hand panel) and post-jump ($t_{+120\ min}$; right-hand panel). Values are medians (IQR).

In healthy subjects, mental stress elicits sympathetic activation as reflected by an increase in muscle sympathetic nerve activity and plasma catecholamines with an elevated HR and BP [3–5,24]. In the present study, BP but not HR decreased after the bungee jump. Reported ratings on emotional states indicate that bungee jumpers are more anxious and wakeful in the hour before than in the hour after the bungee jump, and the post-jump decrease in BP conforms to this [19]. Co-activation of both the sympathetic and parasympathetic nervous system during psychological stress has been suggested [25] and may result in an elevated BP without an increase in HR. In animals under psychological stress, absence of a HR increase was attributed to increased parasympathetic activity, and these animals were revealed to be more vulnerable to ischaemia-induced fibrillation [26]. Active standing, like psychological stress, elicits sympathetic activation with an increase in HR and BP [27]. This study confirmed attenuation of the HR increase in response to active standing when under psychological stress [6]. This attenuation of the HR response was also observed with propranolol, which may suggest increased parasympathetic modulation of the orthostatic response during psychological stress. Consequently, upright HR

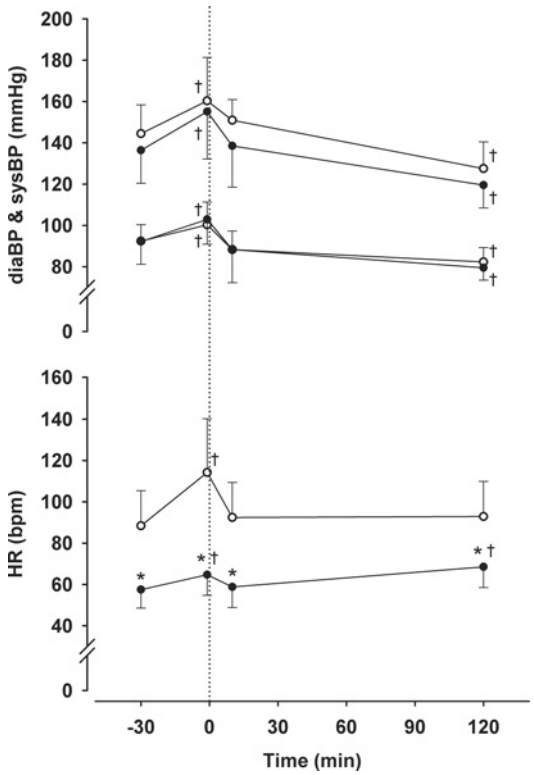


**Figure 3 BP and HR response to bungee jumping**

BP and HR in subjects treated with propranolol (PROP; ●) and in control subjects (CTRL; ○). The instant of the bungee jump is indicated by the dotted line. Values are mean ± S.D. $^*P < 0.001$ compared with the CTRL group; †$P < 0.05$ compared with $t_{-30\ min}$. bpm, beats · min$^{-1}$.

with propranolol was lower prior to compared with following the jump. This observation agrees with the results of Tulen et al. [28] who reported a psychological stress-mediated increase in SBP and diastolic BP, together with a slight reduction in upright HR, and attributed this to a reduced vagolytic effect of psychological stress.

The present study addressed BRS in healthy subjects under β-blockade during acute psychological stress. $BRS_{TD}$ and $BRS_{FD}$ were higher with β-adrenergic blockade during psychological stress. Quantitative differences between outcomes of $BRS_{TD}$ compared with $BRS_{FD}$ are likely related to methodological differences between time and frequency domain approaches [29]. For instance, in contrast with the cross-correlation BRS method used in the present study ($BRS_{TD}$), a threshold is applied in frequency domain analysis ($BRS_{FD}$), where sufficient coherence is required [22,29,30]. In addition, $BRS_{FD}$ produces one value over several minutes, whereas $BRS_{TD}$ is expressed as an average value comprising up to one value each second. Since pre-jump resting values were not determined, it remains unclear whether the differences in BRS were caused by an increase in or a preservation of BRS during stress. Evidence in both humans and experimental animal models support that enhanced sympathetic activity impairs cardiac baroreflex function [31,32], and several studies have examined β-adrenergic influence on HR control during psychological stress. Vaile et al. [18] reported an increase of vagal activity by β-adrenergic blockade during mental stress in healthy subjects, whereas Kardos et al. [17] investigated in heart failure patients the effects of lipophilic compared with hydrophilic β-blockade on BRS in rest and HRV during psychological stress. In heart failure, cardiac noradrenaline (norepinephrine) spillover and muscle sympathetic nerve activity are increased [33,34] together with a reduced BRS [35]. This impairment of arterial baroreflex circulatory control is implicated in an increased risk of sudden cardiac death and cardiovascular mortality [36,37]. Conversely, enhancement of BRS by training improves survival in postmyocardial infarction patients [11], effects shared by β-adrenergic blockade [10,15,16]. Adrenergic stimulation by psychological stress has arrhythmogenic effects in patients with ischaemic heart disease [8,9], and the finding that BRS during acute psychological stress is higher in healthy subjects with β-adrenergic blockade may, therefore, be of clinical relevance.

The mechanism of β-blockers in improving outcome in cardiovascular disease and enhancing BRS is ambiguous and has been attributed to an increase in vagal tone [38,39] and to anti-arrhythmogenic properties [40]. Furthermore, β-receptor blockade reduces cardiotoxic effects of endogenous-released catecholamines, inhibits renin release by blocking renal juxtaglomerular cell $\beta_1$-adrenoceptors, blocks presynaptic α-adrenoreceptor activity by limiting noradrenline release from sympathetic nerve terminals and reduces HR-related myocardial oxygen demand [41]. Throughout the present study, HR but not BP was lower with propranolol. In accordance with previous studies [4,42] propranolol tended to increase SVR, possibly due to blocking of $\beta_2$-receptor-mediated vasodilatation in skeletal muscles, leaving unopposed α-receptor activation. In addition to peripheral β-adrenergic receptors, the lipophilic β-blocker propranolol binds to receptors in the central nervous system. Indeed, animal studies have demonstrated central modulation of autonomic cardiac control after intracerebral injection of β-adrenergic blockers [43,44]. However, a central mechanism remains difficult to verify in humans and, thus, whether or not lipophilic and hydrophilic β-blockers have different autonomic cardiovascular effects remains debated [15,17,18].

In conclusion, the present study identified a higher BRS during acute psychological stress in healthy subjects with β-adrenergic blockade. In addition, the HR increase in response to active standing was lower during acute psychological stress, and this attenuated HR response was also seen with β-adrenergic blockade.

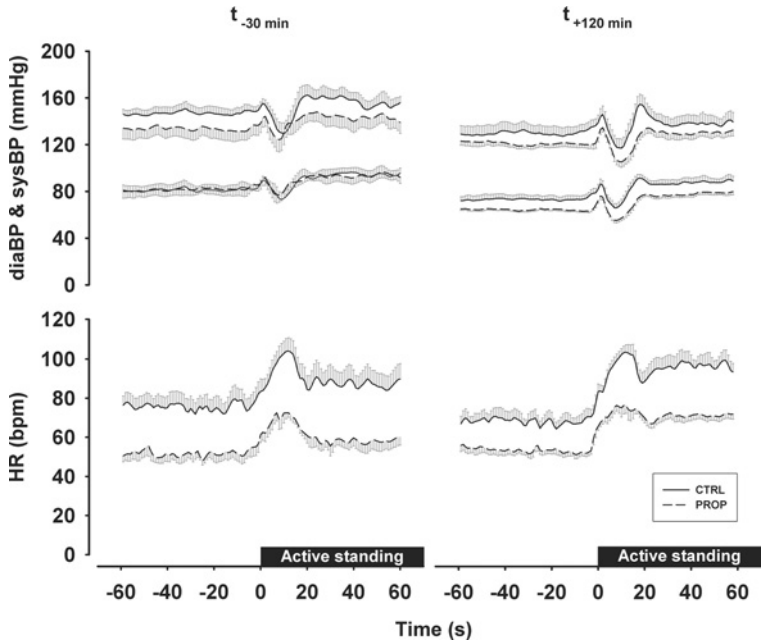


**Figure 4 BP and HR response to active standing**

BP and HR response to active standing with stress and post-stress before ($t_{-30\ min}$) and after ($t_{+120\ min}$) the jump with (PROP) and without propranolol (CTRL). Active standing was performed at 0 s. Values are means ± S.E.M.

## AUTHOR CONTRIBUTION

Jasper Truijen contributed to the experimental design, data acquisition, data analysis and writing of the manuscript. Shyrin Davis contributed to subjects handling and instrumentation and data acquisition. Wim Johan Stok contributed to data acquisition, data analysis and manuscript revision. Yu-Sok Kim contributed to the experimental design, data acquisition and manuscript revision. David van Westerloo, Marcel Levi and Tom van der Poll contributed to the experimental design, recruitment of volunteers and their medical examination, medical ethical committee review and manuscript revision. Berend Westerhof contributed to data analysis and manuscript revision. John Karemaker contributed to the experimental design, data acquisition, data analysis and manuscript writing. Johannes van Lieshout supervised the study, contributing to the experimental design, data analysis and writing of the manuscript.

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