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**Dissection of carotid sinus hypersensitivity: the timing of vagal and vasodepressor effects and the effect of body position**

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## Abstract

*Background* We assessed the timing of vagal and sympathetic factors that mediate hypotension during carotid sinus massage (CSM) in patients with carotid sinus hypersensitivity. We hypothesised that a fall in cardiac output would precede vasodepression, and that vasodepression would be exaggerated by head-up tilt. *Methods and results* We performed pulse contour analyses on blood pressure recordings during CSM in syncope patients during supine rest and head-up tilt. In a subset we simultaneously recorded muscle sympathetic nerve activity supine. During supine rest, systolic blood pressure decreased from  $150\pm 7$  mmHg to  $107\pm 7$  mmHg ( $p<.001$ ) and heart rate from  $64\pm 2$  to  $39\pm 3$  beats/minute ( $p<.01$ ). Cardiac output decreased with heart rate to nadir ( $66\pm 6\%$  of baseline),  $3.1\pm 0.4$ s after onset of bradycardia. By contrast, total peripheral resistance reached nadir ( $77\pm 3\%$  of baseline) after  $11\pm 1$ s. During head-up-tilt, systolic blood pressure fell from  $149\pm 10$  mmHg to  $90\pm 11$  mmHg and heart rate decreased from  $73\pm 4$  to  $60\pm 7$  beats/minute. Compared to supine rest, cardiac output nadir was lower ( $60\pm 8$  vs  $83\pm 4\%$ ,  $p<0.05$ ), whereas total peripheral resistance nadir was similar ( $81\pm 6$  vs  $80\pm 3\%$ ). The time to nadir from onset of bradycardia did not differ from supine rest. At the onset of bradycardia there was an immediate withdrawal of muscle-sympathetic nerve activity while total peripheral resistance decay occurred much later (6-8s). *Conclusion* The hemodynamic changes following CSM have a distinct temporal pattern that is characterised by an initial fall in cardiac output (driven by heart rate), followed by a later fall in total peripheral resistance even though sympathetic withdrawal is immediate. This pattern is independent of body position.

Key words: reflex, physiology, syncope, vagus nerve, vasodilation

## Introduction

In the 2009 European Society of Cardiology (ESC) guidelines on the diagnosis and treatment of syncope, carotid sinus hypersensitivity is diagnosed when carotid sinus massage (CSM) elicits  $\geq 3$  seconds asystole (cardio-inhibitory type), a fall in systolic blood pressure of  $\geq 50$ mmHg (vasodepressor type) or both (mixed type) [12]. The ESC guidelines state that “the diagnosis of [carotid sinus hypersensitivity] requires the reproduction of spontaneous symptoms during (i.e. syncope) CSM performed supine and erect (...)”. Performing CSM while upright has been shown to provide a higher sensitivity of the test [13]. The underlying mechanism has not been elucidated, although augmented vasodepression has been suggested [13].

When CSM triggers hypotension, loss of consciousness is not immediate [22]. The time span from the start of critical systemic hypotension to loss of consciousness (i.e. “cerebral ischemic anoxia reserve time” [22]) may vary from 5 - 8 s. When the duration of cerebral hypoperfusion is shorter than 5 - 8 s, the event may go unnoticed. It may be accompanied by only non-specific cerebral complaints (e.g., “light-headedness”). In this light it is crucial to have an in-depth understanding of the temporal sequence of vagal and sympathetic factors that affect blood pressure during episodes of hypotension in carotid sinus hypersensitivity. The prevailing view is that cardio- and vasodepression occur simultaneously [12]. However, if the time course for vasodilation is shown to be much longer, this provides a strong indication for withholding medications that are known to interfere with vasomotor control in patients with carotid sinus hypersensitivity. It may also explain why pacemaker therapy may not be effective in all patients [14].

With this background, we set out to assess the exact sequence of vagal and sympathetic factors that affect blood pressure during episodes of hypotension in carotid sinus hypersensitivity. Based on current knowledge of baroreflex function, we hypothesised that patterns of changes in cardiac output would be rapid secondary to vagal excitation (whether with asystole or only bradycardia), whereas the fall in vascular resistance would be slower depending on sympathetic neuro-vascular conducting lag time [8]. We also hypothesized that the total peripheral resistance decrease during CSM would be more profound in the upright than the supine position, resulting in more severe hypotension..

We tested these hypotheses by performing a retrospective pulse contour analysis of continuous arterial blood pressure records obtained during carotid sinus massage in patients with unexplained syncope. In a subset of seven patients we present simultaneous microneurographic recordings of muscle-nerve vasoconstrictor activity which support the hypothesis that while sympathetic nerve inhibition during CSM is almost immediate, the ensuing vasodilatation is delayed. Contrary to our hypothesis the exaggerated effects of CSM during head-up tilt be cardiac output dependent, while total peripheral resistance nadir after CSM is not affected by body position. We conclude that the response to CSM is biphasic, which may yield new therapeutic options targeting vasodilation in carotid sinus hypersensitivity. Furthermore, contrary to the prevailing view, the vasodepressor response does not appear to be augmented during head up tilted CSM.

## Methods

### *Patient selection*

We retrospectively selected patients from our clinical files from Christchurch hospital (ranging from 2000 to 2009) and the Academic Medical Center at the University of Amsterdam (ranging from 2004 to 2009). All selected patients were diagnosed with carotid sinus hypersensitivity and had undergone carotid sinus massage (CSM) as part of the diagnostic work-up for unexplained transient loss of consciousness. Because we used pulse contour analysis to estimate the second-to-second changes in cardiac output and peripheral resistance (see below) we excluded blood pressure recordings with artefacts that would interfere with the analysis.

### *Protocol*

CSM was performed in accordance to the prevailing ESC guidelines on syncope [3; 4; 12]. The differences between the versions 2001, 2004 and 2009 are not relevant to the methods of this study. In summary, before starting the test, the absence of contra-indications (e.g. presence of carotid bruits, recent myocardial infarction or CVA) was verified. CSM of 5-10 seconds to each carotid sinus consecutively was executed while supine. If this did not result in an asystole  $>3$  s or a fall in systolic blood pressure  $> 50$  mmHg, CSM was repeated  $\sim 5$  minutes after the patient had been head up tilted at an angle of 60 degrees.

### *Measurements*

Blood pressure was continuously measured using either Finapres technology [7; 9] (Amsterdam) or direct from the brachial artery (Christchurch). Heart rate was measured using a lead-II ECG in all patients. Muscle sympathetic nerve activity was measured in a subset of patients (Christchurch) using the standard microneurography multi-unit peroneal nerve technique as described in detail earlier [10]. All data were stored on a personal computer for analysis. Patients gave written informed consent for the microneurography studies and the procedure was approved by the local medical ethics committee.

### *Analysis*

Off-line, beat-to-beat cardiac output and total peripheral resistance were calculated using Modelflow (Beatscope 1.1a, TNO-BMI, The Netherlands) and re-sampled to 1 Hz. This method tracks rapid changes in stroke volume accurately, both supine and during orthostatic stress [18; 19]. Mean arterial pressure was the integral over one heart beat and heart rate was the inverse of the pulse interval. Cardiac output was stroke volume times heart rate. Total peripheral resistance was mean arterial pressure divided by cardiac output. Cardiac output, and Total peripheral resistance are expressed relative to the interval 15 to 5 seconds before supine CSM. In all patients systolic blood pressure, heart rate, cardiac output and total peripheral resistance nadir values were determined (Figure 1). Because in some patients there was uncertainty about the exact timing of the start of CSM the first decrease of heart rate beyond the variation of the baseline measurement was considered to represent the start of CSM. This moment was identified by visual inspection of the recording by a single observer. For all parameters the interval (seconds) from start of CSM to nadir were determined (Figure 1).

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### *Patient groups*

The patients were divided into three groups. In group I (n = 11) we assessed the temporal relationship between changes in cardiac output and total peripheral resistance in vasodepressor-type carotid sinus hypersensitivity. Patients in group I had a fall in systolic blood pressure  $> 20$  mmHg during supine CSM in the absence of asystole  $> 3$  s. We used a two tailed t-test (significance level: .05) to assess the difference between nadir timing of cardiac output and total peripheral resistance. Data in group I fitted a normal distribution, and are presented as mean  $\pm$  SEM.

In group II (n = 4) we assessed the temporal relationship between changes in systolic blood pressure, heart rate, cardiac output and total peripheral resistance in patients with asystole  $> 3$  s triggered by

supine CSM (cardio-inhibitory type carotid sinus hypersensitivity ). Because of the small sample number we choose to present the data from this group as individual records. From 4 patients in group I and from 2 patients in group II, records of peroneal microneurography during CSM were available. They are also presented as individual records.

Group III (n = 9) consisted of patients who underwent CSM both during supine rest and head-up tilt. In this group we tested the effect of body position on the hemodynamic changes induced by CSM. Patients who had been tilted to horizontal on occurrence of syncope after CSM were not included, since the change in body position would interact with the pulse contour analysis. Therefore this group consisted predominantly of vasodepressor type carotid sinus hypersensitivity patients. In group III nadir values of systolic blood pressure, heart rate, cardiac output and total peripheral resistance during supine and head up tilted CSM were compared using a two tailed t-test (significance level: .05). Data in group III fitted a normal distribution, and are presented as mean  $\pm$  SEM. Patient characteristics are given in Table 1.

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## Results

During supine CSM in group I (>20 mmHg fall in systolic blood pressure without asystole), systolic blood pressure fell from  $150 \pm 7$  to  $107 \pm 7$  mmHg ( $p < .001$ ). See Figure 2. Heart rate decreased from  $64 \pm 2$  to  $39 \pm 3$  beats  $\cdot$  min<sup>-1</sup> ( $p < .001$ ). Cardiac output decreased synchronous to heart rate to  $66 \pm 6$  % of baseline value, and reached its nadir value (i.e.  $66 \pm 6$  % baseline value)  $3.1 \pm 0.4$  s after start of heart rate decrease. By contrast total peripheral resistance reached its lowest value ( $77 \pm 3$  % of baseline value) after  $11 \pm 1$  s. See Figure 3.

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Inter-individually total peripheral resistance nadir and cardiac output nadir were positively correlated ( $R = .62$ ,  $p = .05$ ) suggesting intact coupling of reflex-mediated control of vagal and sympathetic outflow. Heart rate nadir and cardiac output nadir were also closely correlated ( $R = .90$ ,  $p = .001$ ). In four patients from group I recordings of muscle sympathetic nerve activity during CSM were available. See Figure 4. At the start of heart rate decrease there was an immediate withdrawal of sympathetic activity in all, while total peripheral resistance decrease only set in 6-8 s later.

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Group II (supine CSM resulting in asystole >3 s) consisted of only four patients and their individual recordings are given in Figures 5 and 6. In all four total peripheral resistance remained below baseline values in 5-10 s after resumption of cardiac contractions, whereas cardiac output rose to or above baseline values within 1-2 s. In two patients simultaneous recording of muscle sympathetic nerve activity showed latencies of 8-10 s between resumption of sympathetic activity and an increase in total peripheral resistance. In one of those patients CSM was repeated with a cardiac pacemaker stand by. Also without asystole (or bradycardia) this pattern was present (Figure 6).

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During CSM while head up tilted (Group III) systolic blood pressure fell from  $149 \pm 10$  mmHg to  $90 \pm 11$  mmHg. Heart rate decreased from  $73 \pm 4$  beats  $\cdot$  minute<sup>-1</sup> to  $60 \pm 7$  beats  $\cdot$  minute<sup>-1</sup>. Compared to supine CSM, cardiac output nadir was lower ( $60 \pm 8$  vs  $83 \pm 4$  % baseline values), whereas total peripheral resistance nadir was similar ( $81 \pm 6$  vs  $80 \pm 3$  % baseline values). See Figure 7. The timing of nadirs did not differ from those after supine CSM (data not shown).

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## Discussion

The main findings of this study are: 1) Hypotension induced by CSM has underlying vagal and sympathetic mechanisms that have a distinct temporal pattern of onset. The fall in cardiac output is mediated by heart rate (i.e. under vagal control) and occurs within ~2 seconds after the start of CSM. The nadir of total peripheral resistance (i.e. sympathetically-mediated) is only reached after ~10 s, at which point cardiac output has already returned to baseline values. The withdrawal of sympathetic activity is almost synchronous with the fall in heart rate (see below). The delay in total peripheral resistance decrease is therefore likely to be determined by the sympathetic neuro-vascular conducting lag time. 2) Contrary to the widely adopted view that upright CSM has a higher diagnostic yield because it enhances the vasodepressor response, our study suggests that there is a nuance to this view. The nadir total peripheral resistance level after supine and head-up tilted CSM appears to be equal. However, during supine CSM the total peripheral resistance fall can be overcome by an increase in cardiac output, whereas during tilt this is not the case because the upright position limits venous return. So the exaggerated hypotension during head-up tilted CSM relates more to a lower cardiac output than total peripheral resistance.

The sequential changes in heart rate and blood pressure during CSM have been studied before. The early occurrence of heart rate nadir, and the later-occurring blood pressure nadir that we found are in agreement with the values reported by Brown et al. [5]. They studied the heart rate and blood pressure response in 66 patients undergoing coronary angiography (i.e. while supine) and found an onset of cardiac slowing within 2 cardiac cycles from start of CSM. The time to maximum RR-interval prolongation was  $4.6 \pm 1.9$  s while systolic blood pressure nadir was reached after  $8.9 \pm 3.2$  s [5]. A later study by Almquist et al (8 patients) found latency for RR-interval nadir of 2.4 s and 14 s for systolic blood pressure nadir [1]. These studies had a limited methodological power to differentiate decreased heart rate, decreases cardiac contractility, and changes in vascular resistance to explain CSM induced hypotension. Ours is the first study that documents the beat-to-beat changes in directly assessed total peripheral resistance following CSM.

The latencies that we found are also in agreement with insight in normal arterial baroreflex function as for example elegantly studied by Wallin and Eckberg using neck suction challenges [20]. They showed that releasing the pressure of the neck chamber (which in the context of our study could be considered to be the equivalent of CSM), caused an increase of the RR-interval within 1 s, with a simultaneous pause in the muscle sympathetic neurogram after a latency of 1.5-2 s. Similar simultaneous changes have been documented during phase 4 of the Valsalva's manoeuvre [16; 21]. Vagal cardiac postganglionic fibers are short and the heart responds rapidly to changes of nerve activity [2]. In contrast, sympathetic postganglionic nerve fibers are long and, moreover, an increase in total peripheral resistance occurs more slowly because neural activation of vascular smooth muscle contraction is a relatively slow process [8]. Vice versa, withdrawal of vasoconstrictor tone will only lead to vasodilation after a lag time such as is apparent in Figures 4-6.

Several studies have documented that the sensitivity of CSM can be enhanced by performing the test both supine and upright [13; 15]. Smith et al have hypothesized that the fall in blood pressure during head-up tilt CSM would be augmented because of a higher dependency on vascular resistance as compared to supine [13; 17], and this reasoning is also taken into the current ESC guidelines [12]. Other explanations include increased heart rate baroreflex sensitivity when upright, and an increase in the stimulus [13]. Our data show that the view that upright CSM augments the vasodepressor response has a nuance. Total peripheral resistance nadir itself is unchanged by body position. However, because cardiac output is lower while upright (due to a gravitational limitation to venous return) the combined effect translates to a lower blood pressure.

To our knowledge there are only six recordings in the literature of muscle sympathetic nerve activity during CSM in syncope patients [6; 11; 17]. The seven recordings that we add, clearly demonstrate that withdrawal of sympathetic activity is only followed by a decrease of total peripheral resistance after a latency of ~6 seconds.



There are some methodological limitations to this study. First of all, this was a retrospective study based on clinically obtained data. Some patients were using medications interfering with blood pressure control. The precise level of pressure applied to the carotid sinus and its timing are lacking (see method section). We did also not calibrate the computed cardiac output and total peripheral resistance against a gold standard. This has however been overcome by expressing the changes in cardiac output and total peripheral resistance relative to baseline. Second, to be able to reliably use the pulse contour analysis method, only a selection of patients were included. We excluded patients who were tilted back shortly after up-right CSM. Therefore our results are typically applicable to patients with mixed (or pure vasodepressor) response, and may have limited application to patients with severe cardio-inhibitory responses. Finally, due to the technically demanding nature of microneurography we have not been able to assess MSNA during head-up tilted CSM and this should be part of future work.

How do the results of this study benefit carotid sinus hypersensitivity patients? Knowing that the vasodepressor component of carotid sinus hypersensitivity is asynchronous to cardio-inhibition may be an incentive to withhold medications that interfere with vasoconstriction (e.g. ACE-inhibitors, calcium antagonists) in syncope patients with carotid sinus hypersensitivity. Whether this indeed is beneficial needs further study. Furthermore, the fact that cardiac output seems the major determinant of hypotension when up-right, could imply that carotid sinus hypersensitivity patients who remain symptomatic after pacemaker implantation would benefit from volume expansion measures and withholding diuretics. This should also be tested prospectively.

We conclude that the hemodynamic changes following carotid sinus massage have a distinct temporal pattern wherein the first phase is characterised by a fall in cardiac output secondary to bradycardia,, followed by a delayed decrease of total peripheral resistance even though sympathetic withdrawal is immediate. This pattern is independent of body position. The augmented hypotensive responses following head-up tilted carotid sinus massage is explained by a lower cardiac output, while total peripheral resistance nadir is unaffected by body position.

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**Author Contribution**

CTPK: study design, analysis, manuscript draft

DLJ: study design, data acquisition, analysis

WW: study design, data acquisition, analysis

**Conflict of interest**

The authors have no conflict of interest in relation to this paper.

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**Figure 1: Representative example and measurement of nadir delays**

Example of hemodynamic changes following right sided carotid sinus massage (indicated by black bar) in a 64-year old female syncope patient. BP: continuous blood pressure (filled dot is nadir) ; HR: heart rate (filled square is nadir); CO: cardiac output in arbitrary units (open dot is nadir); TPR: total peripheral resistance in arbitrary units (open square is nadir). Grey bar indicates baseline interval. Arrows indicate calculation of intervals to respective nadirs of systolic blood pressure (SBP), HR, CO and TPR. (start of HR decline is  $t = 0$ ).

**Figure 2: Group I: Group mean of hemodynamic changes during supine CSM**

Group I mean ( $n=11$ , error bars depict SEM) of systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and cardiac output and total peripheral resistance estimation during supine carotid sinus massage. Black bar estimates timing and duration of carotid sinus massage. Note the instantaneous decrease of heart rate and cardiac output, while the decrease in total peripheral resistance is delayed.

**Figure 3: Group I, temporal differentiation of cardio- and vasodepressor response**

Nadir values and their timing relative to start of change of heart rate ( $n=11$ , mean, error bars depict SEM). SBP: systolic blood pressure, HR: heart rate, CO: cardiac output; TPR: total peripheral resistance.

**Figure 4: Sympathetic activity during CSM in patients with vasodepressor response and no asystole (group I)**

Records from four syncope patients during supine right sided carotid sinus massage. BP: blood pressure, MSNA: muscle sympathetic nerve activity; HR: heart rate; TPR: total peripheral resistance expressed as %-baseline. Left upper: 64-year old female; right upper: 65-year old female; 70-year old female; 61-year old male. Black bars estimate timing and duration of carotid sinus massage. Note the simultaneous decrease of MSNA and HR, while TPR decrease has a delay of ~10 s.

**Figure 5: Group II, vasodepressor response lasts beyond asystole**

Original blood pressure records in three patients with asystole > 3 s during supine carotid sinus massage. Black bars estimate timing and duration of carotid sinus massage. Cardiac output (CO) expressed as %-baseline: grey line; Total peripheral resistance (TPR) expressed as %-baseline: black line; Upper panel denotes female aged 71, middle panel male aged 52, lower panel female aged 61. In the latter the MSNA is added. Note the absence of MSNA during the asystole, the increase of cardiac output at the resumption of cardiac action while TPR is still falling.

**Figure 6: Temporal differentiation of cardiac output (CO) and total peripheral resistance (TPR) changes is unaffected by cardiac pacing**

Records from a male patient aged 81 from group II, during supine carotid sinus massage (upper panel). MSNA: muscle sympathetic nerve activity. CO: cardiac output, grey line; TPR: total peripheral resistance, black line; HR: heart rate, dotted line. Note the absence of MSNA during the asystole. CSM was repeated with cardiac pacemaker on stand by (lower panel). Black bars estimate timing and duration of carotid sinus massage. Note that at resumption of cardiac contraction TPR remains below baseline values. This is unaffected by cardiac pacing.

**Figure 7: Group III: effects of body position on hemodynamic response to carotid sinus massage**

Systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR) and estimations of cardiac output (CO) and total peripheral resistance (TPR) during supine carotid sinus massage. Black bar estimates timing and duration of carotid sinus massage. Group mean ( $n=9$ , error bars depict SEM). n.s.: non-significant difference; \*\*:  $p < .01$ ; \*\*\*:  $p < .001$

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Table 1 Patient Characteristics

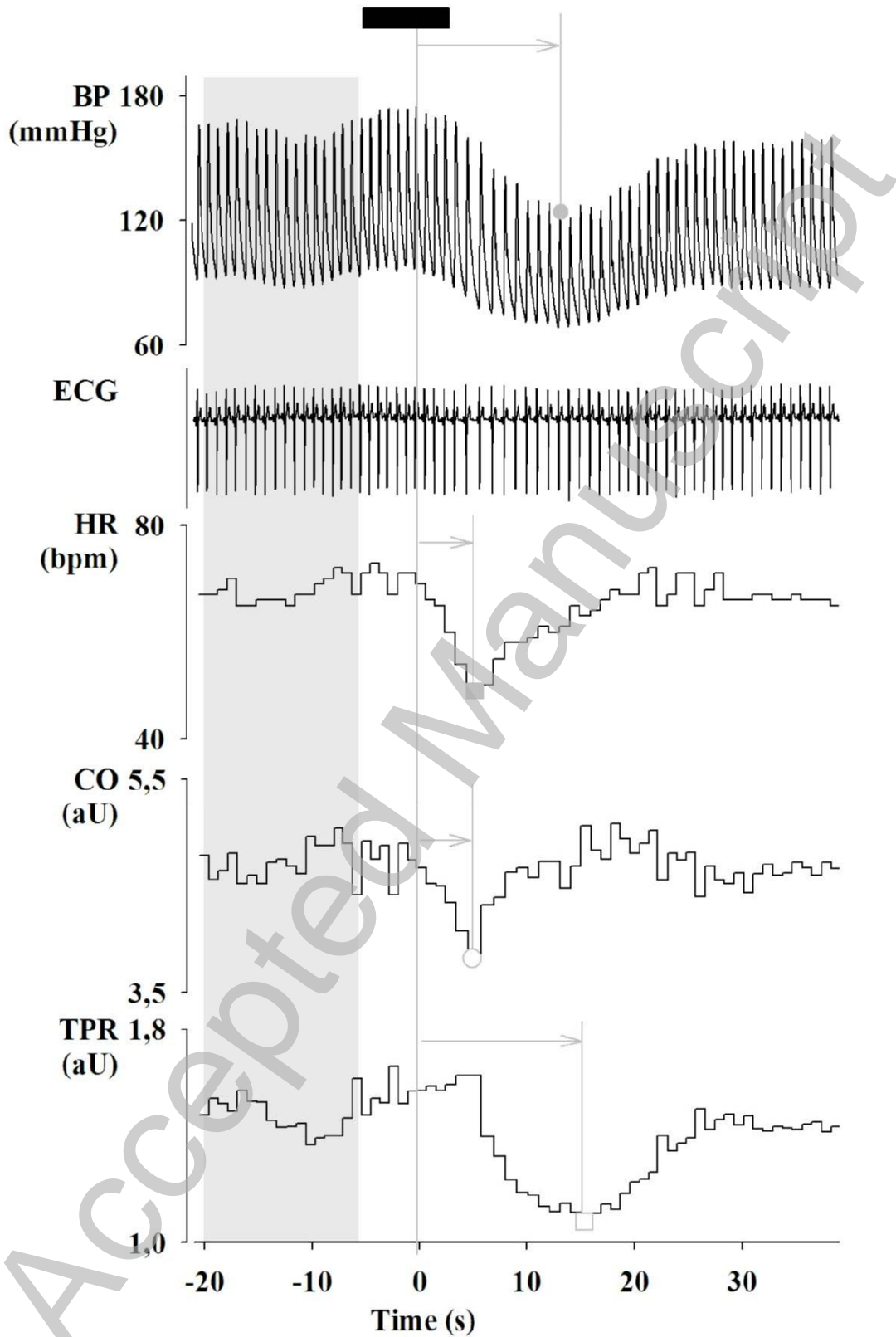
	<b>Group I</b> Vasodepressor type CSH, supine	<b>Group II</b> Cardio-inhibitory type CSH, supine	<b>Group III</b> Vasodepressor type CSH, supine vs head-up-tilted
<b>Number and sex</b>	11 (8 males)	4 (2 males)	9 (6 males)
<b>Age (years, median, range)</b>	66 (55-86)	66 (52-81)	68 (52-81)
<b>Body mass index (kg/m<sup>2</sup>, median, range)</b>	24 (23-28)	25 (23-27)	27 (24-28)
<b>Medical history:</b>			
<b>Hypertension</b>	5	2	4
<b>Coronary/ peripheral artery disease</b>	3	2	4
<b>Diabetes Mellitus type 2</b>	1	1	2
<b>Chronic Obstructive Lung Disease</b>	2	1	1
<b>Medications</b>			
<b>Beta-blockers</b>	4	2	4
<b>ACE-inhibitors / ATII-antagonists</b>	4	2	2
<b>Calcium-channel-blockers</b>	1	1	2
<b>Diuretics</b>	2	1	2

CSH: carotid sinus hypersensitivity

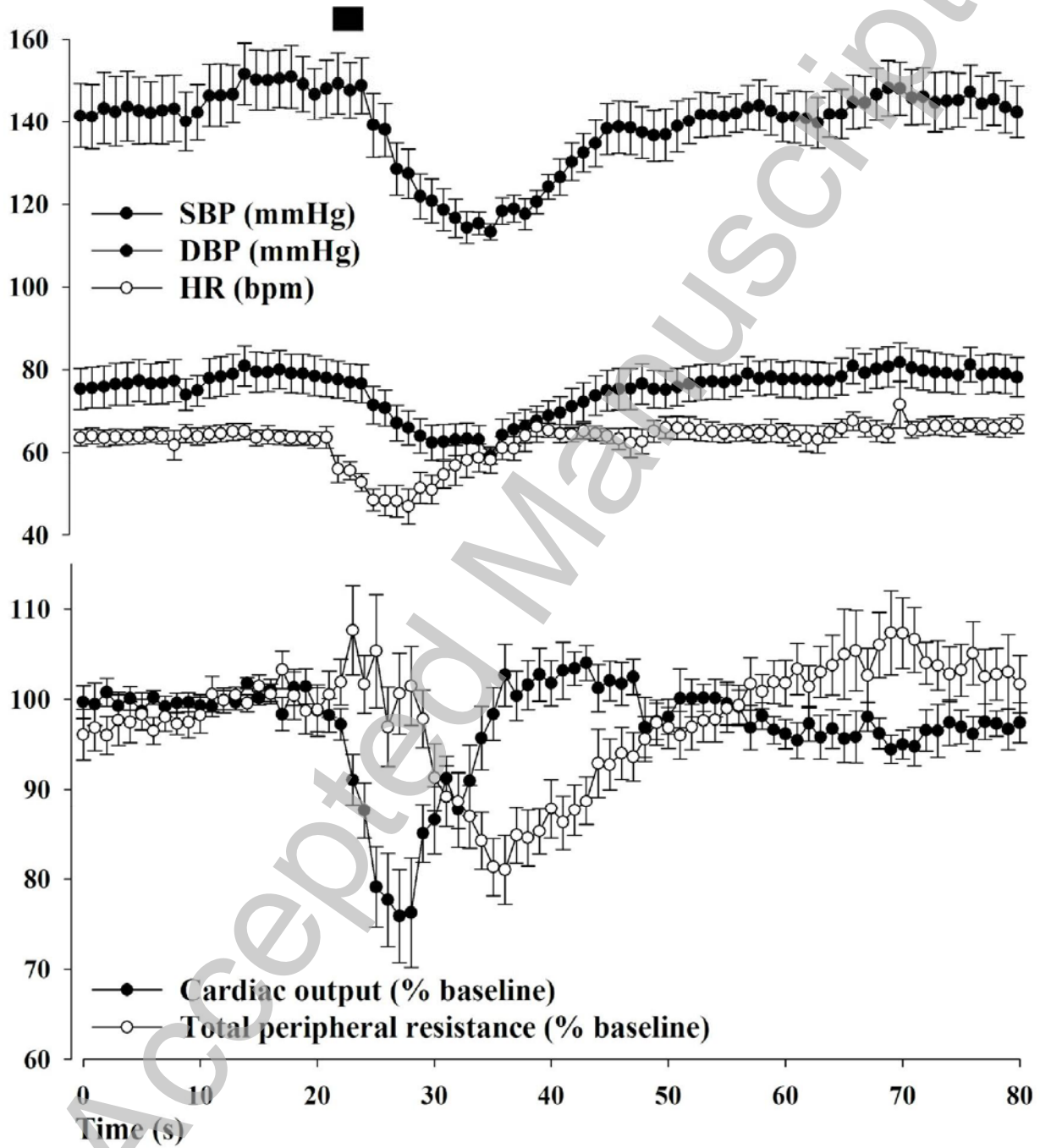
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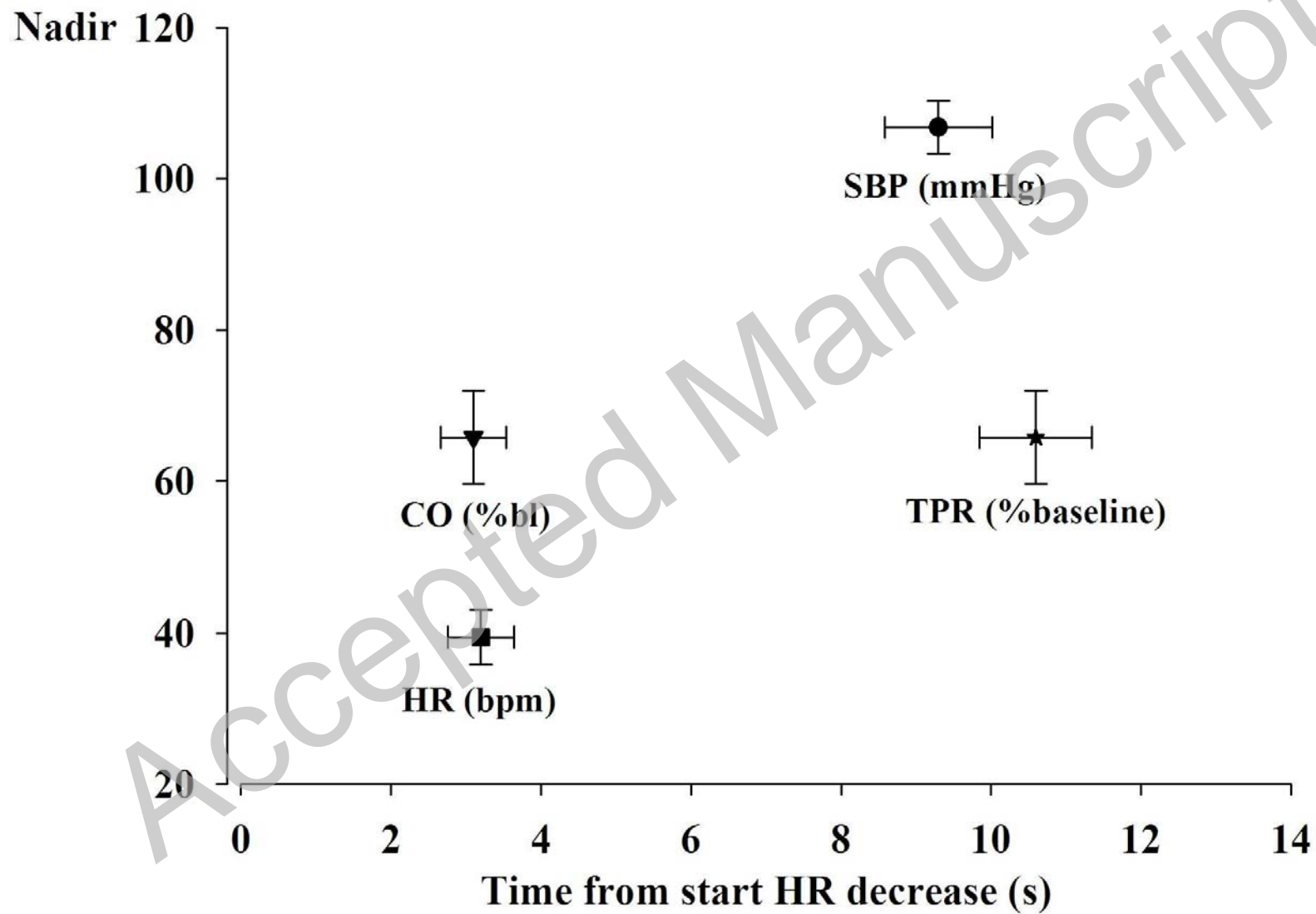
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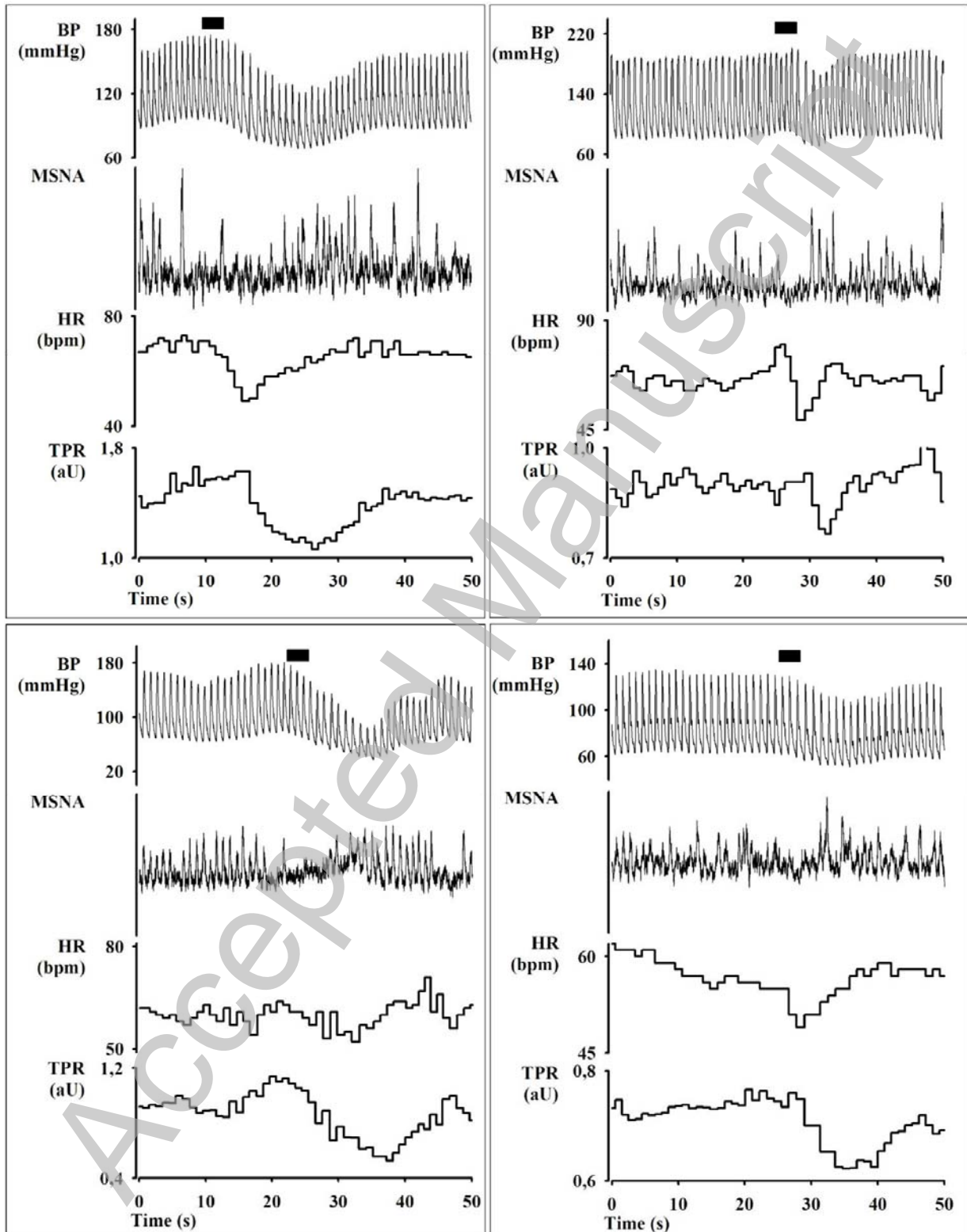




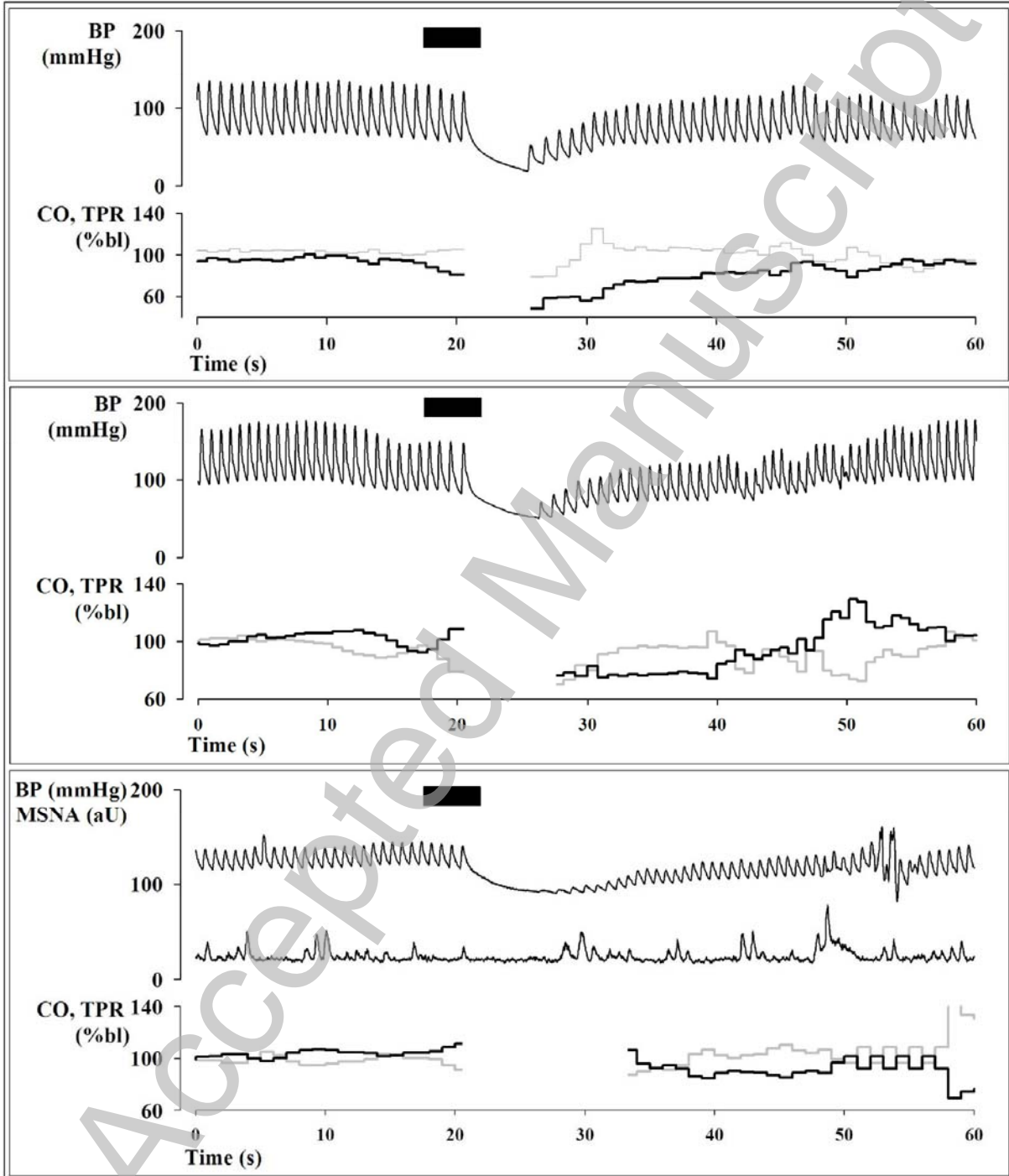
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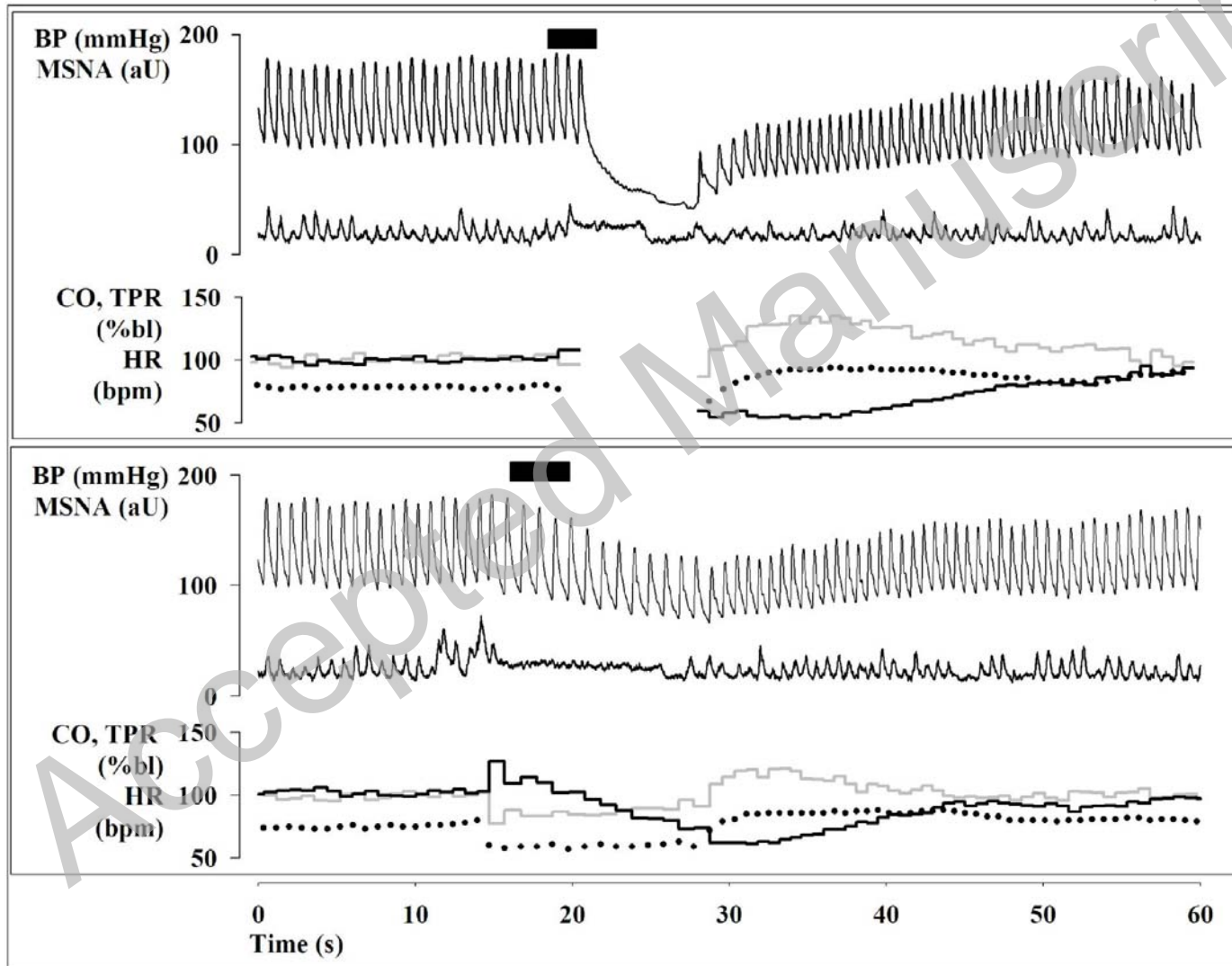


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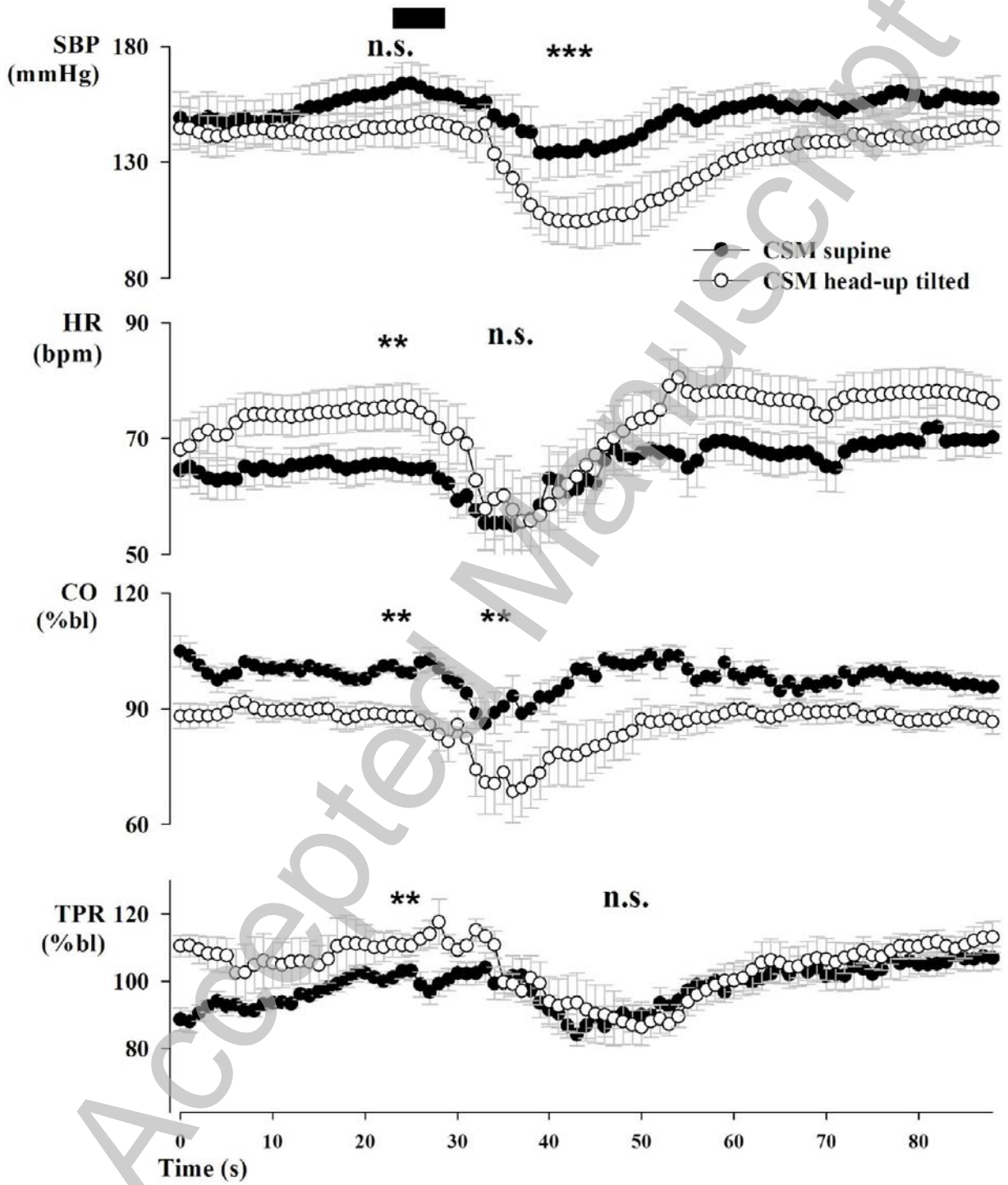


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