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CLINICAL RESEARCH

# Pathophysiological aspects of carotid sinus massage

## Cardioinhibition and vasodepression occur independent, respond differently to massage duration, and evoke corrective blood pressure responses

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**Aims** We studied the blood pressure (BP) decrease after carotid sinus massage to study cardioinhibition (CI) and arterial vasodepression (aVD), whether CI and aVD occur independent of one another, and how the BP decrease ends.

**Methods and results** We measured BP, heart rate (HR), stroke volume, and total peripheral resistance (TPR) retrospectively in carotid sinus massage cohorts in two Dutch syncope centres. Cardioinhibition and aVD were defined as HR and TPR decreasing below 3 SD under pre-massage baseline means. We used the logratio method to analyse changes relative to baseline and tested whether CI and aVD occurred together more often than through chance and whether the responses depended on massage duration and on corrective BP increases. Cardioinhibition occurred in 48% and aVD in 30% of 244 massages of 90 persons. Cardioinhibition and aVD did not occur together more often than randomly. Compared with aVD, CI occurred more often, earlier, faster, and shorter with a larger maximal but similar overall BP-decreasing effect. Longer massage duration yielded a larger BP decrease through stronger aVD. The BP decrease evoked corrective increases of HR and TPR.

**Conclusion** Cardioinhibition appears as a phasic response to the onset of massage, independent of aVD, which is a more latent response sensitive to ongoing massage. Blood pressure corrections probably depend on the contralateral carotid sinus and aortic baroreceptors. The BP decrease after sinus massage may in part depend on the efficacy of corrective responses.

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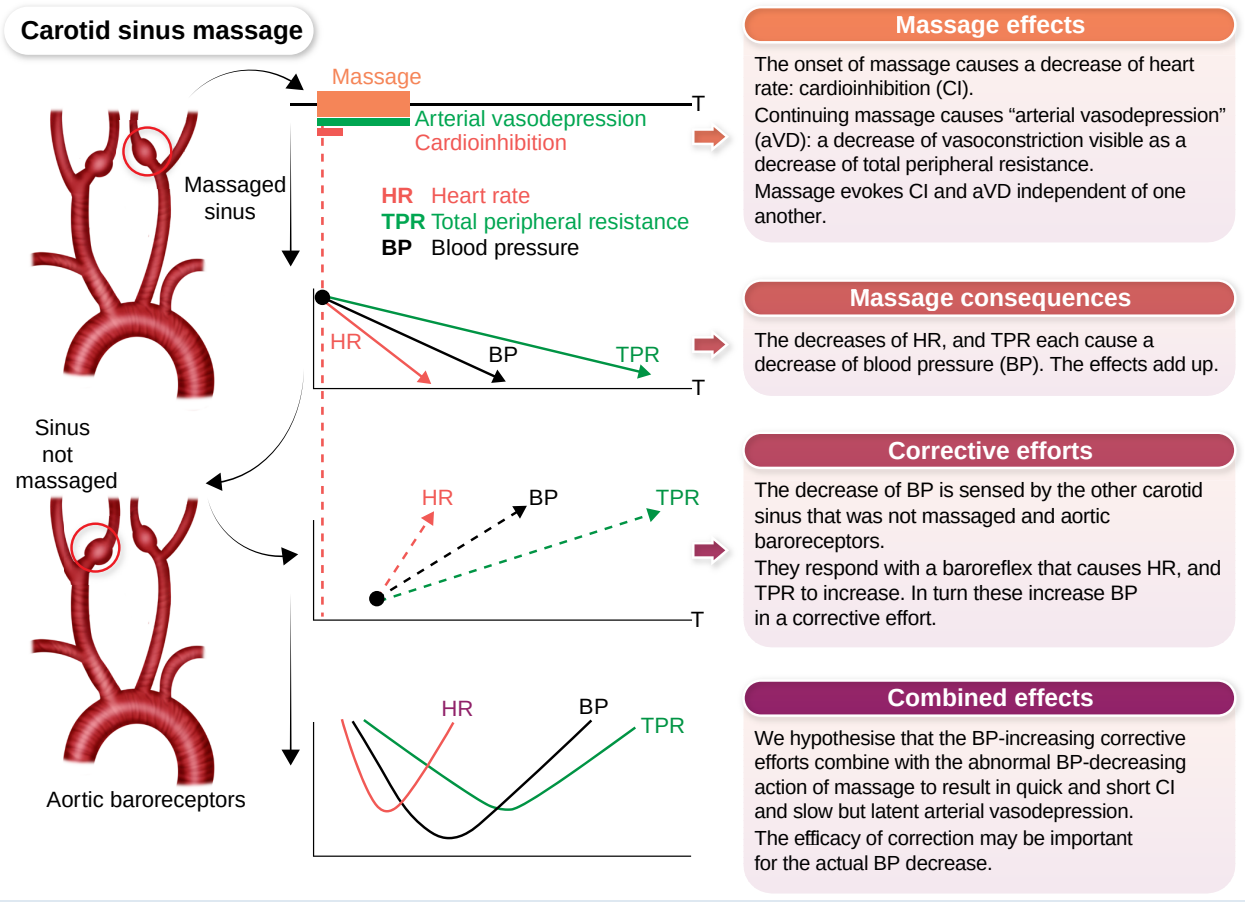
## Graphical Abstract




**Keywords** Carotid sinus massage • Syncope • Baroreflex • Cardioinhibition • Vasodepression

## What's new?

- Carotid sinus massage evokes cardioinhibition and arterial vasodepression independent of one another.
- Compared with vasodepression, cardioinhibition after carotid sinus massage occurs more often, earlier, and faster; cardioinhibition has a larger maximal blood pressure (BP)-decreasing effect but lasts shorter than arterial vasodepression, so they have similar overall BP-decreasing effects.
- Longer massage duration caused a larger BP decrease through stronger vasodepression.
- The BP decrease following carotid sinus massage elicits a corrective BP-increasing response.
- Even when blood pressure has returned to baseline 90 s after onset of massage, that blood pressure may have a different haemodynamic make-up.
- The results suggest a need for fresh research into the execution and pathophysiology of carotid sinus massage.

# Introduction

Carotid sinus syncope is a common cause of syncope and falls among the elderly, making carotid sinus massage (CSM) important for diagnosis.[1] Various aspects of pathophysiology and of massage execution remain unclear, such as massage duration.[2] These uncertainties may underlie large differences in diagnostic yield of CSM.[3,4]

Current standards define carotid sinus hypersensitivity following CSM as a drop of systolic blood pressure (SBP) over 50 mmHg or an asystolic pause over 3 s.[1] Smaller responses may have less clinical relevance but reflect the same pathophysiology. Because we aimed to study CSM regardless of response magnitude, we used 'CSM response' (CSMR) to avoid confusion with 'carotid sinus hypersensitivity'.

External pressure on carotid baroreceptors evokes a response similar to the baroreflex elicited by elevated blood pressure (BP), consisting of a decrease of sympathetic activity that lowers total peripheral resistance (TPR) and may also lower heart rate (HR), as well as increased vagal cardiac tone decreasing HR and probably cardiac contractility, which by itself can lower stroke volume (SV). The CSMR may thus involve all three haemodynamic parameters of mean arterial pressure (MAP): for each heartbeat, MAP is the product of HR, TPR, and SV.[5]

In reflex syncope, three processes vary in importance: 'cardioinhibition' (CI) is a vagal decrease of HR and of cardiac contractility; 'arterial vasodepression' (aVD) is a decrease of sympathetic peripheral vasoconstriction causing a decrease of TPR; 'venous vasodepression', due to venous pooling, appears as a decrease of SV in vasovagal syncope.[5–7] The literature on carotid sinus hypersensitivity emphasizes aVD and CI,[1,8] with CI reaching its maximal effect before aVD.[8–11]

We studied three pathophysiological questions using retrospective CSM cohorts from two Dutch university syncope departments. First, we quantitated *the relative contributions of CI and aVD* irrespective of predefined abnormality criteria. We assessed CI and aVD using individual signal-to-noise comparisons and used the logratio method to compare contributions of HR, SV, and TPR to MAP.[5–7] Second, we studied whether *CI and aVD in CSMR occur independent of one another*, suggested by rat studies showing that sympathetic baroreflex responses were triggered at a lower BP range than cardiac parasympathetic responses.[12] Moreover, in rats, CI depended more on aortic than on carotid baroreflex activation, while sympathetic withdrawal could be evoked by carotid as well as aortic baroreceptor afferents.[13] Third, we investigated explanations for *the transient nature of CSMR:* massage duration,[14] and the likelihood that massage-related hypotension evokes corrective baroreflexes.

# Methods

## Patient recruitment

Carotid sinus massage was performed as part of extended tilt tests,[15] in the syncope units of the Leiden and Amsterdam University Medical Centres (LUMC and AUMC). Cohort data containing all CSM procedures were gathered from January 2017 to September 2020 for Leiden and from January 2016 to December 2017 for Amsterdam. Additional tests containing abnormal CSM results according to European Society of Cardiology (ESC) criteria (i.e. BP fall ≥ 50 mmHg or asystole ≥ 3 s) were added from the periods January 2018 to December 2020 for the AUMC and from July 2010 to December 2017 (records of 18 persons) for the LUMC.

## Massage procedures

In Leiden, CSM was mostly performed in patients with suspected spontaneous carotid sinus syncope, almost exclusively in the upright position because of higher chances of CSMR[16] and to further reduce complication risks.[1,17] Massages were almost always carried out by one examiner (J.G.v.D.) without measuring massage pressure. Both sides were massaged irrespective of the response to the first side. After palpation to find the spot of major pulsation,[2] the examiner massaged around that spot vertically during at least 10 s, while indicating start and finish to a technician marking the event in the video-electroencephalogram (EEG) as standard protocol.

In Amsterdam, CSM was conducted as part of the diagnostic protocol for reflex syncope in patients over 40 years of age.[1] Massage technique was similar to that in Leiden with massages carried out by one examiner (F.J.d.L.) without measuring massage pressure. Massage in principle comprised two supine and two upright massages, but massages were stopped once a massage fulfilled ESC abnormality criteria.[1] The start and end of massage were noted on the continuous BP machine.

## Time series analysis

Haemodynamic data were acquired either as continuous BP waveforms stored on an EEG database for part of Leiden data and later converted to beat-to-beat data with Modelflow (TNO, the Netherlands) or as Finometer beat-to-beat data (remaining Leiden data, all Amsterdam data), using the same Modelflow algorithms.

Modelflow yielded beat-to-beat values of SBP, diastolic BP (DBP), MAP, HR, SV, and TPR, interpolated linearly at 2 Hz to simplify temporal analysis.[5–7] A period of 180 s before to 240 s after onset of massage was extracted. Periods in which patients were tilted back or another massage was started were deleted. Records were inspected for artefacts and extraneous beats using interactive software. Artefact periods of short duration flanked by stable similar amplitudes could be replaced by linear interpolation but were deleted otherwise.

The logratio analysis rests on the multiplicative relation $MAP = HR{\cdot}SV{\cdot}TPR$.[5] For each massage, we defined baseline values as the mean of MAP, HR, SV, and TPR over a period of 170 s ending 10 s before massage. Each time series was divided by the mean baseline value to result in ratios. Logarithms (Base 10) of ratios were taken ('$_{LR}$'). The relation between logratio parameters is additive, so for each point in time, $MAP_{LR} = HR_{LR} + SV_{LR} + TPR_{LR}$. The method reflects physiological relations between parameters, allowing comparisons across groups, parameters, or periods.[5,6]

## First aim: relative contributions of cardioinhibition and arterial vasodepression

We determined the presence or absence of CI (HR decrease) and aVD (TPR decrease) for each massage. As the CSMR was largely over within 45 s after onset of massage, we performed an automated search in this period for minimum peaks of SBP, MAP, HR, and TPR and for a maximum peak for SV (*Figure 1*). If necessary, peak latency and amplitude were interactively corrected. Artefacts resulted in missing data.

We calculated the mean and standard deviation (SD) per massage and parameter over the 45 s *before* onset of massage and used these to calculate a 3 SD detection threshold (below the mean for HR and TPR and above the mean for SV) (*Figure 1*). This threshold was applied to already identified peaks. Peak amplitudes exceeding the threshold were considered 'overt' and others 'obscure'. Each trace thus contained an overt peak, an obscure peak or missing data. Overt HR decreases represented the presence of CI, while obscure HR peaks represented absent CI. Similarly, overt and obscure TPR represented the presence and absence of aVD. Hence, the presence or absence of CI and aVD depended on individual signal-to-noise comparisons.

The magnitude of CI and aVD was quantified first as absolute peak amplitudes and second as differences between peak and baseline amplitudes ('delta'). The third method aimed to capture sustained effects on BP. We calculated the 'sustained magnitude' as the average of all valid values per massage of the logratio time series of $MAP_{LR}$, $HR_{LR}$, $SV_{LR}$, and $TPR_{LR}$ (*Figure 1*). We did so for the 'early period' (first 45 s after onset of massage) and the 'late period' (45–90 s after onset of massage).

## Second aim: co-occurrence of cardioinhibition and arterial vasodepression

We investigated whether CI and aVD were associated with age, sex, and number of syncopal events in the year before testing. To assess whether CI and aVD preferentially occurred together, we counted the numbers of overt and obscure HR and TPR responses, excluding massages with missing HR or TPR data. We formed four groups: 'pure CI' consisted of overt HR and obscure TPR; 'pure aVD' was overt TPR with obscure HR; 'CI-and-aVD' required both responses to be overt; and 'neither-CI-nor-aVD' required that both be obscure. A tendency for CI and aVD to occur coupled should result in high numbers of massages in which CI and aVD were either both present or both absent, called 'concordant' responses. That tendency should also result in few massages with only one overt response (either HR or TPR), labelled 'discordant' responses. We counted actual concordant and discordant responses and calculated the expected numbers, i.e. how often combinations would occur based on the overall proportions of overt and obscure HR and TPR responses. We compared real and expected proportions using the $\chi^2$ test, with a statistical difference indicating coupling of CI and aVD.

## Third aim: the transient nature of carotid sinus massage response

We split massages into 'shorter' and 'longer' groups based on median massage duration and evaluated whether longer massages exerted a stronger BP-decreasing effect of HR and TPR, apparent through a lower minimum, longer peak latencies, larger delta peak amplitudes, and larger sustained magnitude in the early period.

We investigated whether the low BP caused by CSMR evoked corrective BP-increasing responses. As HR and TPR can contribute to the abnormal BP decrease as well as to the subsequent BP correction, an HR increase after an HR minimum could be due to the end of the abnormal HR decrease or to an HR-increasing correction. We assumed that BP corrections could appear as increases of both HR and TPR. If so, massages showing pure CI, i.e. with an abnormal HR decrease but without an abnormal TPR decrease, might exhibit a corrective TPR increase. Likewise, pure aVD might allow recognition of a corrective HR increase. We therefore took the four aVD/CI groups and compared sustained magnitudes of $HR_{LR}$, $SV_{LR}$, and $TPR_{LR}$ of the late period within each group.

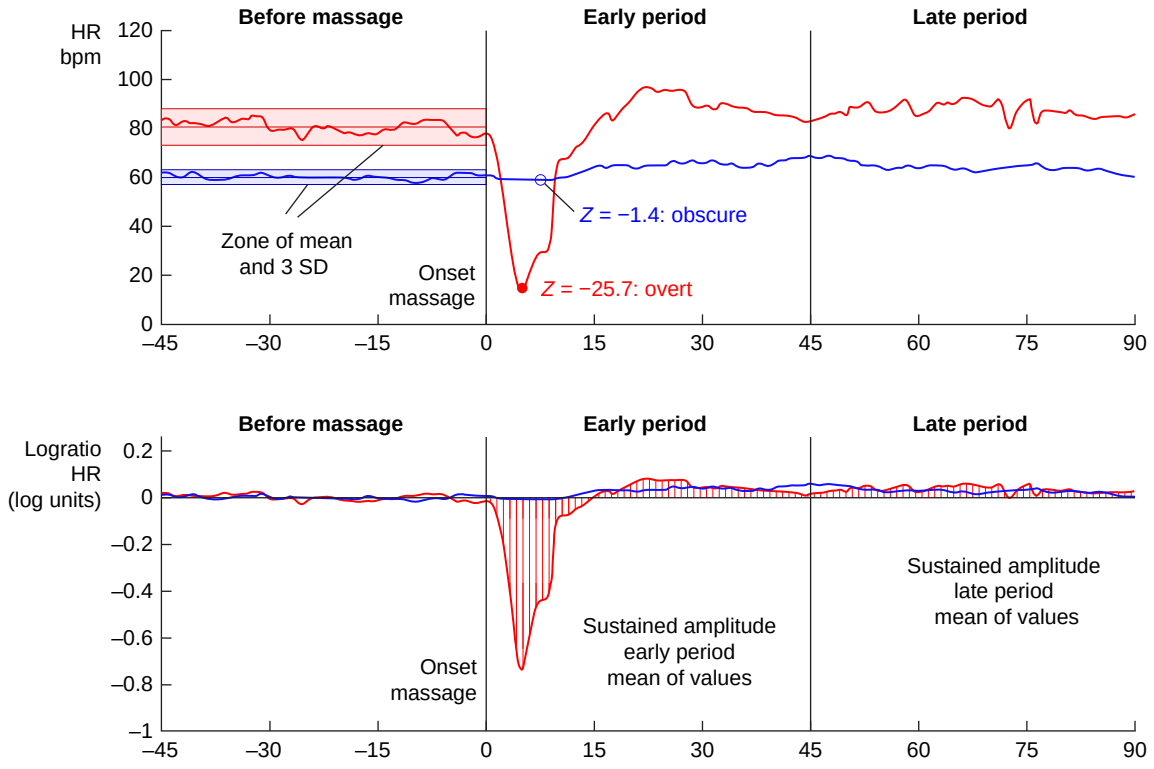



**Figure 1** Analysis scheme. Example HR data are shown for two individual massages, in red (the one with the large decrease) and blue. The top panel shows HR in beats per minute, and the bottom panel shows corresponding logratio values. The top panel shows the 45-s pre-massage period used to calculate the mean and SD of individual HR data. The figure shows a 3 SD zone above and below mean HR. The 45 s after onset of massage form the 'early period', in which points of minimum HR were identified. The amplitude of HR at the minima was expressed as the difference from baseline divided by SD, i.e. a *Z*-score. *Z*-scores larger than −3 were regarded as 'obscure' peaks (example in blue), and *Z*-scores < −3 were considered 'overt' (example in red). The bottom panel shows logratio values. The mean of all valid samples in the early period was the 'sustained magnitude' of the early period; here, only some samples are indicated by vertical lines. The sustained amplitude of the late period (45–90 s after onset of massage) was calculated similarly. HR, heat rate.

## Statistical analysis

Distributions were checked with the Kolmogorov–Smirnoff test. Only MAP, HR, SV, and TPR featured in the logratio analysis, but we also reported SBP and DBP. We used analysis of variance (ANOVA) when all involved variables were normally distributed, or the Kruskal–Wallis test otherwise, with *post hoc* tests. Effects of massage duration were conducted with the one-tailed Mann–Whitney test. Effects of CI and aVD on quantitative variables were investigated with two-factor ANOVA using overt and obscure CI and aVD to define the factors CI and aVD. Count data were compared with the $\chi^2$ test. Analysis was performed with Matlab (MathWorks). As the study was exploratory, we used a significance threshold of $P < 0.01$; values $0.01 < P < 0.05$ will be reported as trends.

As all data were gathered exclusively in the context of patient care, Dutch law did not require assessment by a medical ethics committee.

# Results

We included 244 massages from 90 persons with a median of one syncope in the year before testing [interquartile range (IQR) 0–2]. The number of massages per person was 1 ($n = 5$), 2 ($n = 48$), 3 ($n = 4$), or 4 ($n = 33$). Mean age was 62.4 ± 11.9 years. There were 50 men (55.6%). Massages were performed on the right side 123 times and on the left side 121 times. Massages were performed supine 85 times and upright 159 times; 83 massages in 43 persons were performed in Leiden and 161 massages in 47 persons in Amsterdam. For differences between Leiden and Amsterdam, we refer to the Supplementary material. Massage lasted a median of 11.4 s (IQR 10.2–13.4 s). Massages resulted in syncope 10 times (4%) and in symptoms in 68 massages (28%).

## Overall haemodynamic events

Supplementary material online, *Figure S1* shows mean MAP, HR, SV, and TPR for all massages and for massages with at least one overt response.

*Figure 2* shows averaged logratios. In the early period, MAP and HR temporarily decreased, while SV temporarily increased and TPR first reached a small maximum and then a minimum. Peaks occurred in the following order: HR, MAP, SV, and TPR. Mean $HR_{LR}$ reached its minimum when $MAP_{LR}$ was still decreasing, and average $TPR_{LR}$ reached its minimum when $MAP_{LR}$ was already recovering.

## First aim: relative contributions of cardioinhibition and arterial vasodepression

Heart rate responses included 118 overt peaks (48.4%), 92 obscure ones (37.7%), and 34 missing data (13.9%). The median latency of

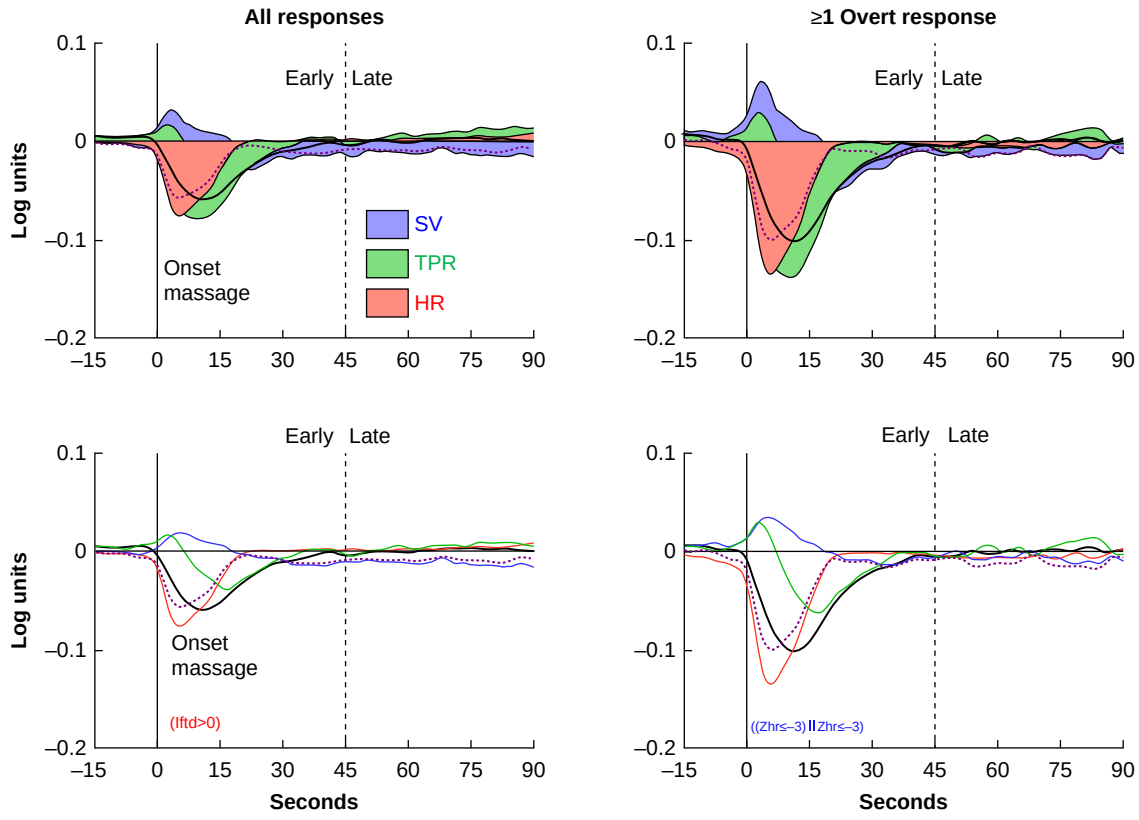



**Figure 2** Overall logratio effects of responses to carotid sinus massage. Logratio values are shown for all massages (left) and for massages with at least one overt HR or TPR response (right). In these logratio diagrams, mean $MAP_{LR}$ (black lines) represents the sum of the means of $HR_{LR}$ (red area), $SV_{LR}$ (blue area), and $TPR_{LR}$ (green area). Likewise, the logratio of mean cardiac output ($CO_{LR}$; purple dotted line) is the sum of $HR_{LR}$ and $SV_{LR}$. Top panels show cumulative areas of HR, SV, and TPR, meaning all BP-increasing effects for any point in time are stacked upwards starting at the horizontal zero line; likewise, BP-decreasing effects are shown stacked downwards. Parameters were stacked away from baseline in the following order: $HR_{LR}$, $TPR_{LR}$, and $SV_{LR}$. Bottom panels show overlaid means for the same data. $CO_{LR}$ and $MAP_{LR}$ are shown as overlaid lines in all graphs. Note that the negative BP-decreasing $HR_{LR}$ peak occurs earlier than the $TPR_{LR}$ peak and that minimum BP occurs between the HR and aVD peaks.

overt HR peaks was 6.0 (3.5–8.5) s. Total peripheral resistance responses included 74 overt ones (30.3%), 150 obscure ones (61.5%), and 10 missing data (4.1%); median latency of overt TPR peaks was 17.0 (13.0–22.0) s. Stroke volume responses comprised 65 overt responses (26.6%), 138 obscure ones (65.6%), and 40 missing data (16.4%), with a median latency of 10.5 (7.2–14.5) s. The proportions of overt, obscure, and missing responses differed between the three parameters ($\chi^2$ $P < 0.0001$).

Characteristics of the four CI and aVD groups are shown in *Table 1*. This categorization excluded missing values, resulting in pure CI ($n = 69$), pure aVD ($n = 23$), CI and aVD ($n = 44$), and neither CI nor aVD ($n = 62$).

Age showed trends for effects of CI and the interaction of CI and aVD. After exclusion of missing values for HR and TPR, the younger half of the population had a lower proportion of CI (51/102, 50.0%; older 62/96, 64.6%; $P = 0.038$) and more often showed no overt responses at all (younger 41/102; 40.2%; older 21/96; 21.9%; $P = 0.006$). The proportions of aVD did not differ between age groups.

Sex ratios did not differ between the four groups ($P = 0.38$).

Peak latencies were related to CI in that minimum HR and minimum DBP occurred earlier in the presence of CI, with trends for earlier SBP and SV; peak latencies did not differ according to presence or absence of aVD. The presence of CI led to larger decreases of SBP, MAP, and DBP and to a larger increase of SV. The presence of aVD led to larger falls of MAP and TPR and a larger increase of SV.

In the early period, the presence of CI resulted in more negative sustained magnitudes of $MAP_{LR}$ and $HR_{LR}$ (i.e. MAP and HR had decreased more); the presence of aVD led to more negative values for $MAP_{LR}$ and $SV_{LR}$ and self-evidently also for $TPR_{LR}$.

In the late period, the presence of CI was associated with more negative $HR_{LR}$, while the presence of aVD was associated with more negative $TPR_{LR}$, showing that the HR decrease of CI and the TPR decrease of aVD persisted well after onset of massage. In the group with neither CI nor aVD, all three parameters $HR_{LR}$, $TPR_{LR}$, and $SV_{LR}$ differed from one another in the late period.

## Second aim: co-occurrence of cardioinhibition and arterial vasodepression

Deletion of missing values left 198 massages. The four CI and aVD groups yielded 106 concordant massages (44 + 62) and 92 discordant ones (69 + 23). Based on the overall counts of 133 CI responses (69 + 44) and 67 aVD responses (23 + 44), we expected 94 concordant responses and 104 discordant ones. The actual and expected rates did not differ ($P = 0.23$).

**Table 1** Description of cardioinhibition and arterial vasodepression in the response to carotid sinus massage

| | Pure CI $n = 69$ | Pure aVD $n = 23$ | CI and aVD $n = 44$ | CI nor aVD $n = 62$ | *P*-value (CI) | *P*-value (aVD) | *P*-value (CI × aVD) |
|---|---|---|---|---|---|---|---|
| Age (years) | 65.0 ± 10.3 | 63.9 ± 11.4 | 63.4 ± 11.1 | 57.7 ± 13.2 | 0.029 | 0.088 | 0.014 |
| M:F (*n*) | 38:31 | 13:10 | 30:14 | 32:30 | — | — | — |
| SBP fall ≥ 50 mmHg (*n*) | 17 | 1 | 13 | 1[a] | — | — | — |
| Asystole ≥ 3 s (*n*) | 8 | 0 | 6 | 0 | — | — | — |
| Syncope last year (*n*; median IQR) | 1 (0–4) | 1 (0–1) | 1 (0–2) | 2 (0–4) | | | |
| Latencies | | | | | | | |
| T-min SBP | 16.0 ± 10.1 | 15.9 ± 10.7 | 14.4 ± 7.9 | 19.8 ± 13.0 | 0.044 | 0.22 | 0.74 |
| T-min MAP | 14.0 ± 9.1 | 14.4 ± 8.5 | 12.0 ± 4.6 | 15.7 ± 11.2 | 0.10 | 0.39 | 0.57 |
| T-min DBP | 13.7 ± 9.4 | 15.1 ± 8.7 | 13.8 ± 7.3 | 19.2 ± 3.2 | 0.0082 | 0.41 | 0.40 |
| T-min HR | 7.3 ± 6.1 | 11.1 ± 9.2 | 7.5 ± 4.9 | 14.5 ± 14.0 | 0.0002 | 0.19 | 0.15 |
| T-min TPR | 18.9 ± 10.3 | 18.8 ± 8.6 | 17.2 ± 5.7 | 17.6 ± 11.9 | 0.91 | 0.92 | 0.33 |
| T-max SV | 10.6 ± 10.1 | 12.5 ± 6.7 | 10.9 ± 6.4 | 17.8 ± 12.7 | 0.013 | 0.16 | 0.12 |
| Peak amplitudes | | | | | | | |
| Delta SBP | 35.0 ± 24.1 | 28.0 ± 16.6 | 39.4 ± 21.5 | 16.5 ± 13.8 | <0.0001 | 0.057 | 0.64 |
| Delta MAP | 24.4 ± 16.5 | 20.1 ± 11.6 | 29.3 ± 15.5 | 10.2 ± 9.0 | <0.0001 | 0.0038 | 0.54 |
| Delta DBP | 18.7 ± 12.5 | 16.7 ± 8.7 | 24.5 ± 12.5 | 8.1 ± 7.0 | <0.0001 | 0.0002 | 0.82 |
| Delta HR | 25.2 ± 21.9 | 4.2 ± 4.0 | 23.4 ± 21.9 | 5.4 ± 5.8 | <0.0001 | 0.49 | 0.96 |
| Delta TPR | 0.26 ± 0.33 | 0.40 ± 0.20 | 0.44 ± 0.23 | 0.13 ± 0.15 | 0.029 | <0.0001 | 0.20 |
| Delta SV | 10.5 ± 10.5 | 11.6 ± 11.7 | 16.8 ± 12.2 | 4.8 ± 6.3 | 0.0012 | 0.0003 | 0.98 |
| Sustained magnitude early period | | | | | | | |
| $SusMag_{LR}$ MAP | −43.2 ± 55.8 | −29.7 ± 31.1 | −58.1 + 58.6 | 1.1 + 34.8 | <0.0001 | 0.0071 | 0.49 |
| $SusMag_{LR}$ HR | −42.6 ± 40.7 | 2.4 ± 30.6 | −34.5 + 27.7 | −1.3 + 22.6 | <0.0001 | 0.19 | 0.71 |
| $SusMag_{LR}$ TPR | 1.9 ± 69.2 | −47.4 ± 44.6 | −53.8 + 51.9 | 15.0 + 50.9 | 0.62 | <0.0001 | 0.65 |
| $SusMag_{LR}$ SV | −11.9 ± 62.9 | 23.0 ± 29.4 | 28.5 + 51.3 | −16.4 + 35.8 | 0.54 | <0.0001 | 0.73 |
| Sustained magnitude late period | | | | | | | |
| Late $SusMag_{LR}$ MAP | −2.4 ± 40.7 | −4.8 ± 2.5 | −1.0 ± 27.1 | 2.3 ± 32.8 | 0.77 | 0.71 | 0.54 |
| Late $SusMag_{LR}$ HR | −7.5 ± 28.6 | 27.1 ± 42.7 | −6.1 ± 34.9 | 7.2 ± 34.7 | <0.0001 | 0.066 | 0.11 |
| Late $SusMag_{LR}$ TPR | 9.9 ± 69.8 | −25.7 ± 44.7 | −12.7 ± 61.8 | 14.4 ± 61.0 | 0.28 | 0.0036 | 0.37 |
| Late $SusMag_{LR}$ SV | −13.3 ± 57.7 | −0.90 ± 22.5 | 12.4 ± 63.2 | −22.0 ± 53.1 | 0.31 | 0.021 | 0.67 |

Local minima of HR and TPR were 'overt' when their amplitude was lower than 3 SD below the mean of baseline for SBP, MAP, HR, and TPR and higher for SV. Massages were divided into four combinations of presence or absence of overt peaks for HR and TPR: 'pure CI' means overt HR and obscure TPR; 'overt aVD' means obscure HR and overt TPR; 'both CI and aVD' means overt HR and overt TPR; and 'CI nor aVD' means obscure HR and obscure TPR. Logratio values are shown after multiplication by 1000 to help appreciate their relative sizes. *P*-values represent ANOVA with the factor CI (present or absent) and aVD (present of absent) and their interaction.
Delta, difference between period of interest and baseline period; SusMagLR, sustained magnitude in logratio units.
[a]This case represents a combination of HR and TPR decreases that were 2.5 and 2.6 SD away from the mean, so neither reached the threshold to be recognized as CI or aVD.

## Third aim: transient nature of carotid sinus massage response

Splitting according to median duration yielded groups of shorter and longer massages (*Table 2*; *Figure 3*). Age and sex did not differ between these groups. Absolute peak amplitudes did not differ between groups, but amplitude differences from baseline ('delta') showed larger and longer falls of SBP, MAP, and DBP and a trend for a larger TPR decrease in those with longer massages. Peak DBP latency was longer for longer massages, with trends in the same direction for SBP, MAP, and TPR. Sustained amplitudes of the early period showed a stronger MAP decrease and a similar trend for TPR for longer-lasting massages. No HR parameter responded to duration of massage.

Second, we investigated whether CSMR evoked corrective responses. *Figure 4* and Supplementary material online, *Table S1* and *Figure S2* show sustained magnitude of the late period. There were overall differences between sustained magnitudes of HR, TPR, and SV in the late period within three groups: pure CI, pure aVD, and the neither-CI-nor-aVD group. *Post hoc* tests showed differences between $HR_{LR}$ and $TPR_{LR}$ in the pure CI and pure aVD groups. In the pure CI group, negative sustained $HR_{LR}$ magnitude in the late period indicated an ongoing BP-decreasing effect of low HR. $TPR_{LR}$ was then *positive*, showing a corrective BP-increasing effect of increased TPR. In the pure aVD group, we observed the opposite pattern: $TPR_{LR}$ was negative, meaning TPR kept decreasing MAP, while $HR_{LR}$ was *positive*, exerting a BP-increasing effect. Sustained magnitudes did not differ between $HR_{LR}$ and $TPR_{LR}$ within the CI-and-aVD group, nor within the CI-nor-aVD group. In the latter group, *post hoc* tests showed a trend for SV to differ from both HR and TPR.

**Table 2** Effects of shorter and longer massage

| | Shorter | Longer | *P*-value |
|---|---|---|---|
| Descriptors | | | |
| Number of subjects | 115 | 116 | |
| Duration; seconds median (IQR) | 10.2 (9.4–10.8) | 13.4 (12.0–15) | <0.0001 |
| Age | 60.9 ± 11.3 | 63.5 ± 11.9 | 0.09 |
| Sex (male:female) | 64:51 | 61:55 | 0.64 |
| Hospital (Leiden: Amsterdam) | 15:100 | 59:57 | <0.0001 |
| Peak amplitudes | | | |
| Min SBP | 117.7 (102.1–132.6) | 115.9 (92.2–133.9) | 0.32 |
| Min MAP | 85.5 (77.2–96.0) | 84.6 (69.0–96.0) | 0.16 |
| Min DBP | 66.0 (59.9–74.0) | 65.1 (53.6–76.3) | 0.31 |
| Min HR | 59.1 (46.6–67.1) | 58.8 (49.0–67.1) | 0.82 |
| Max SV | 70.0 (60.0–87.6) | 66.1 (57.0–82.1) | 0.11 |
| Min TPR | 1.07 (0.83–1.35) | 1.06 (0.83–1.39) | 0.36 |
| Peak latencies | | | |
| SBP | 26 (16–44) | 31.5 (20–49.5) | 0.043 |
| MAP | 21 (13.3–32.8) | 28.5 (17.0–36) | 0.014 |
| DBP | 23 (13–41.75) | 30 (20–41.5) | 0.005 |
| HR | 13.9 (7–28.2) | 13 (7–27) | 0.65 |
| SV | 20 (10.2–34.5) | 21 (12–30.4) | 0.50 |
| TPR | 30 (20–46) | 35 (24–44.5) | 0.023 |
| Delta amplitudes | | | |
| SBP | 18.2 (11.7–29.7) | 25.8 (17.2–42.4) | 0.0018 |
| MAP | 13.3 (7.7–21.8) | 19.6 (12.2–29.6) | 0.0008 |
| DBP | 10.4 (6.6–17.6) | 15.6 (9.4–22.2) | 0.0006 |
| HR | 9.6 (4.4–17.8) | 9.7 (5.9–15.8) | 0.45 |
| SV | 7.2 (3.0–12.8) | 7.5 (3.3–12.7) | 0.41 |
| TPR | 0.22 (0.07–0.32) | 0.24 (0.10–0.42) | 0.041 |
| Sus amp early | | | |
| MAP | −0.010 (−0.028 to 0.005) | −0.026 (−0.053 to 0.000) | 0.0029 |
| HR | −0.012 (−0.035 to 0.001) | −0.017 (−0.035 to −0.004) | 0.21 |
| SV | −0.001 (−0.026 to 0.020) | 0.001 (−0.015 to 0.022) | 0.84 |
| TPR | −0.000 (−0.030 to 0.027) | −0.011 (−0.046 to 0.011) | 0.0117 |

Massages were divided in 'shorter' and 'longer' groups by the median massage duration of 11.39 s. Results shown as mean ± SD indicate normal distributions for both groups, and *P*-values then indicate the *t*-test; otherwise, data are indicated as median (IQR) and *P*-values indicate the Mann–Whitney test. The hypothesis was that longer massages led to lower peak amplitudes, longer peak latencies, larger delta amplitudes (differences between baseline and peak value), and more pronounced sustained amplitudes (more negative LR values); one-tailed *P*-values are stated.

# Discussion

This study on the pathophysiology of CSMR confirmed some findings and yielded new ones. First, we confirmed that CI occurred more often than aVD, with pure CI occurring more than twice as often as pure aVD. Second, there was no evidence that CI and aVD occurred in the same test more often than randomly. When CI and aVD occurred together, their time course overlapped, so BP minimum occurred when HR was already increasing again. Minimum HR occurred 10 s before minimum TPR, with CI causing a larger but shorter BP decrease than aVD. Third, longer massage did not affect CI but caused a larger BP decrease, probably through stronger aVD. Fourth, both CI and aVD acted beyond 45 s after onset of massage. Fifth, the BP decrease of CSMR evoked corrective BP-increasing responses consisting of increases of HR and TPR, lasting at least 90 s after onset of massage.

## First aim: relative contributions of cardioinhibition and arterial vasodepression

Pure CI occurred more than twice as often as pure aVD. The HR decrease lasted shorter than the TPR decrease, with the HR minimum occurring 10 s before the TPR minimum (*Table 1*), as reported earlier.[8–11] At their respective peaks, HR decreased BP more than TPR. This difference in BP effect is readily apparent from the HR logratio minimum in pure CI (*Figure 4*), which is lower than the TPR logratio minimum of

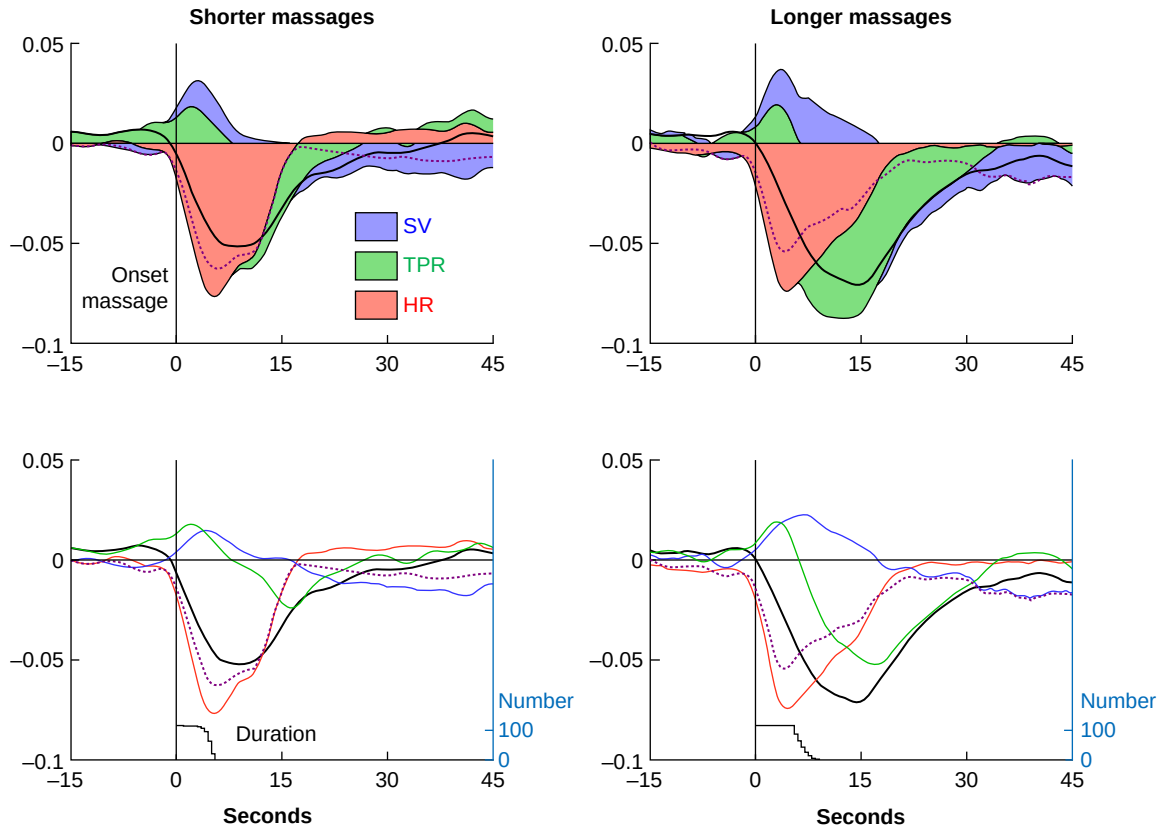



**Figure 3** Logratio effects of massage duration. Massages shorter than the median duration are shown at the left and longer ones at the right. The presentation is similar to previous figures. Only the early analysis period is shown. The number of ongoing massages is shown as 'duration', with the axis indicated at the right-hand side. Note that HR responses show no appreciable differences between shorter and longer massages, while TPR responses to longer massages were more negative (i.e. decreased more) and lasted longer, together producing stronger aVD. HR, heart rate; TPR, total peripheral resistance; SV, stroke volume.

pure aVD. The fall in SBP in pure CI was at 35.0 mmHg larger than the 28.0 mmHg BP fall in pure aVD (*Table 1*).

However, the longer duration of the TPR decrease meant that the sustained magnitude over the entire early period did not differ between logratios of HR in pure CI (−0.043 ± 0.04 units) and logratios of TPR in pure aVD (−0.047 ± 0.04 units, $P = 0.61$). The difference in duration of effect is most noticeable when comparing pure CI and pure aVD in *Figure 4*: in pure CI, the HR decrease is largely over well before the end of the early period, whereas the TPR decrease in pure aVD persisted throughout the entire late period. BP decreased most when CI and aVD occurred together (*Table 1*; *Figure 4*).

## Second aim: co-occurrence of cardioinhibition and arterial vasodepression

We incorrectly assumed that HR and TPR would respond jointly, albeit with differences in magnitude and timing. The independence of CI and aVD was suggested by the existence of pure CI and pure aVD, and fits with rat studies show not only that aortic and carotid baroreceptors respond to different BP ranges but also give rise to different responses, with aortic receptors causing CI more readily than carotid ones.[12,13] A similar differential responsivity in man may explain our findings.

## Third aim: the transient nature of carotid sinus massage response

It is not known whether the BP-decreasing effect of CSM is constant or wears off during massage continues, but animal studies allow for such differential responses.[18–20]

Longer massage caused more pronounced BP decreases, with trends pointing to TPR decreases, i.e. stronger aVD, as the cause. We found no effect of massage duration on CI. This suggests that CI represents a phasic vagal response to the earliest part of massage, while aVD exhibits a more latent sympathetic withdrawal response to ongoing massage. Our results therefore suggest that shorter massages lead to a smaller BP decrease and less aVD.

The hypotension following CSM may evoke reflexive correction through the carotid sinus not massaged and aortic baroreceptors. Vagal HR responses can respond within one heartbeat, fitting with HR dropping immediately after onset of massage. Slow sympathetic nerve conduction and the slow contraction of smooth muscle cells mean that TPR responds much later. In *Figure 2* and Supplementary material online, *Figure S1*, TPR starts to decrease below baseline ~5 s after onset of massage. We could only prove correction in the late period for pure CI and pure aVD, but we assume that corrections always take place. In pure CI, corrective $TPR_{LR}$ first became positive (exerted a net BP-increasing effect) ~30 s after onset of a massage (*Figure 4*). In

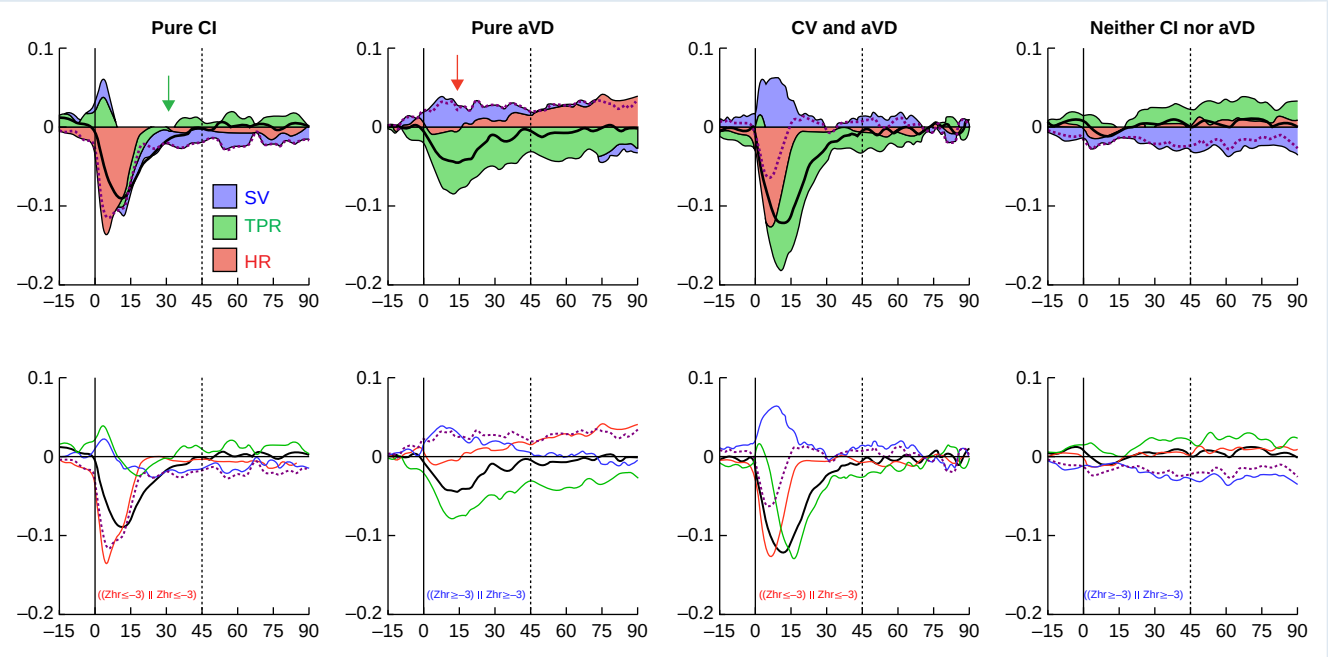



**Figure 4** Groups divided by CI and aVD. Four groups were formed by whether responses showed CI and aVD or not. The top panels show logratios of HR (red), SV (blue), and TPR (green) as cumulative areas as in *Figure 3*. The bottom panels show overlaid logratio means. The purple dotted line shows CO as the sum of logratios of HR and SV. The dotted vertical line at 45 s after onset of massage divides the early and late periods of analysis. Results are interpreted in the main text. The green arrow in the pure CI panel shows where mean TPR first becomes positive as proof of a corrective effect, ~30 s after onset of massage. The red arrow in the pure aVD panel shows when HR first became positive as proof of a corrective BP-increasing effect, ~15 s after onset of massage. aVD, arterial vasodepression; CI, cardioinhibition.

pure aVD, a similar $HR_{LR}$ effect became positive ~15 s after the onset of massage. However, corrective efforts may have started early enough to dampen the decreases of HR and TPR, likely in view of the turnaround times of ~1 s for HR and 5 s for TPR responses. The actual times and magnitudes of minimum HR and TPR may well depend on competition between BP-decreasing massage effects and BP-increasing correction efforts. Corrective efforts were noticeably smaller than abnormal BP-decreasing effects in the present study, which suggests either that corrective efforts have limited relevance or that inadequate correction efforts were the prime reason for large BP decreases.

## Limitations

The study was based on retrospective data and was performed on patients presenting with syncope. The data cannot be generalized to the general population. Protocol differences between Leiden and Amsterdam included that Leiden patients were rarely tested supine and that in Amsterdam, an abnormal response meant no further massages were performed. The lack of massages performed regardless of the response meant we could not adequately study repeatability, left–right differences, and effects of supine vs. upright position or habituation.

In clinical practice, a return of BP to baseline was used to permit another CSM or to change tilt position. An effect of this choice was that the number of valid observations of the late period was relatively low.

Modelflow is best at tracking relative changes, which the logratio method relies on; we provided a short review of its reliability previously.[5] Massage often provoked a temporary small TPR increase, reminiscent of the 'TPR spike' in vasovagal syncope during sudden profound BP fall.[5] Modelflow may not be able to follow quick BP changes, underestimating SV and overestimating TPR.[5] Alternate explanations are, firstly, that mechanical closure of a carotid artery closes off part of the arterial tree causing a true TPR increase. Secondly, pressure on the carotid body may have stimulated carotid chemoreceptors, leading to an increase in breathing, TPR and BP. Finally, anxiety may have played an unknown role as well.

## Clinical implications

Longer massage duration led to a larger BP fall and stronger aVD, which may help explain differences in diagnostic CSM yield between hospitals.[3,4] The need to assess vasodepression has long been stated as a reason to massage for 10 s.[21] Massage is probably most relevant if it manages to mimic spontaneous syncope, but the balance between CI and aVD in spontaneous syncope is unknown. Hence, we cannot advocate a specific duration to mimic spontaneous carotid sinus syncope. We add that this uncertainty also affects the current standard of 10 s.

Corrective responses may be relevant. It was known that minimum BP depends on the summed effects of CI and aVD,[8] to which we now add that CI and aVD may each depend on a balance between abnormal BP-decreasing effects and BP-increasing corrections; if so, symptoms and syncope must depend on this balance of balances. To which extent does carotid sinus syncope depend on the integrity of corrective baroreflex responses? A weakening corrective capacity with age may help explain why CSMR is more pronounced with age. A direct comparison of CSMR magnitude with a separate measure of baroreflex capacity, for instance, the speed of BP correction after standing up,[22,23] could answer this question.

At the end of the late period, 90 s after the start of massage, HR, SV, and TPR could still differ from baseline, most noticeable for pure aVD (*Figure 4* and Supplementary material online, *Figure S2*). We stress that BP had then already returned to baseline, underlining that stable BP does not guarantee similar haemodynamics. It may be best to also observe SV and TPR rather than HR and BP only as suggested recently.[3]

If this is not feasible, 90 s after onset of massage would be a minimum rest period.

# Conclusion

Carotid sinus massage provoked CI more often than aVD. Cardioinhibition is a phasic response to the onset of massage independent of aVD that is a more latent response and more prominent in those with longer massage duration. The haemodynamic effects of CSM can last for more than 90 s, and the BP decrease of CSMR evokes a corrective BP-increasing response. We hypothesize that the corrective response may contribute to how deep BP falls in the CSMR and that an age-related deterioration of these corrections may explain why CSMR becomes more relevant with age, which may ultimately help improve the diagnostic role of massage.[24]

# Supplementary material

Supplementary material is available at *Europace* online.

**Conflict of interest:** none declared.

## Data availability

Data are available upon reasonable request.

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