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Vasomotion in Human Fingers

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Vasomotion · Photoplethysmography · Microcirculation · Alpha-2 adrenoceptor agonist · Spontaneous vascular oscillations

Abstract
Introduction: We describe methods by which vasomotion can be recorded in awake and anesthetized human subjects without significant interference from other spontaneous vascular oscillations. ***Methods:*** In three separate studies, we used photoplethysmography (PPG) to record vasomotion in fingertips. In Study 1, we induced chemical sympathectomy in the studied hand of 11 awake subjects who received intravenous dexmedetomidine infusions. In Study 2, we administered four progressively increasing intravenous dexmedetomidine infusions to 16 awake volunteers. In Study 3, we recorded vasomotion simultaneously from 6 fingers of 7 patients who were under dexmedetomidine-based anesthesia. Five-minute epochs of PPG recordings that displayed slow vascular oscillations were analyzed for frequency and amplitude. ***Results:*** In Study 1, vasomotion frequencies were 0.025 ± 0.008 Hz. In Study 2, vasomotion frequencies were 0.033 ± 0.006 Hz, and 0.032 ± 0.008 Hz during the two highest dexmedetomidine infusion steps. In Study 3, vasomotion frequencies ranged from 0.020 to 0.037 Hz and were observed in all 6 fingers, with no synchrony between the six fingers. ***Conclusion:*** The vascular oscillations we observed without significant interference from other spontaneous oscillations are independent of neural activity (Study 1), local in nature (Study 3), and associated with alpha-2-adrenoceptor activation, consistent with known properties of vasomotion.

Introduction

Myogenic oscillations (vasomotion) are slow spontaneous oscillations of blood vessel diameter. Vasomotion is intrinsic to vascular smooth muscle cells (VSMCs) and thus, independent of neural activity. Vasomotion leads to flowmotion, which is thought to aid the delivery of oxygen and nutrients to tissues [1].

Multiple intra- and intercellular systems are involved in vasomotion. In brief, individual VSMCs periodically release calcium from intracellular stores (the sarcoplasmic reticulum). Vasomotion appears when these transient intracellular calcium bursts become synchronized between VSMCs. Vasomotion is sustained by a synchronized depolarizing current which spreads to VSMCs through gap junctions and causes influx of

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calcium into VSMCs [1, 2]. It is not clear how vasomotion is initiated.

Vasomotion has been studied in several species in vivo and in isolated arteries in vitro [3–9]. Vasomotion has been observed in most vascular beds and blood vessels, although vasomotion predominantly occurs in arterioles. The frequency of spontaneous vasomotion seems to differ depending on the size of the blood vessels, anatomical location, function of the vascular bed, and species being studied. In arterioles, analysis of video microscopy recordings indicates that the frequency of these oscillations varies depending on the order of the arteriole. Each order of the arterioles seems to have a fundamental frequency. For example, A1 arterioles have higher frequencies than A4 arterioles [10]. Once vasomotion becomes synchronized in a vascular bed, blood vessels in that vascular bed seem to adopt the same frequency of vasomotion. Because vasomotion is a local phenomenon, it does not result in oscillations in systemic blood pressure [11, 12].

Several different mechanisms can cause spontaneous blood flow oscillations (flowmotion) [1, 13, 14]. In humans, the frequencies of these oscillations have been largely studied using laser Doppler flowmetry (LDF) which measures cutaneous flowmotion. The following five mechanisms and frequency bands have been described for spontaneous flowmotion [15]: (1) cardiac oscillations due to pulsatility of cardiac output (0.4–1.6 Hz), (2) respiratory oscillations due to stroke volume variability secondary to respiration-related changes in cardiac preload (0.15–0.4 Hz), (3) sympathetic nervous system (SNS; neurogenic) oscillations, mediated by norepinephrine release at the perivascular plexus (0.02–0.06 Hz), (4) myogenic oscillations (vasomotion) due to local intrinsic VSMC activity (0.06–0.15 Hz), and (5) endothelial oscillations (0.0095–0.02 Hz).

Studies of vasomotion in humans are scarce. This could be in part because vasomotion is difficult to separate from the frequently superimposed SNS mediated vascular oscillations which have similar frequencies but have larger amplitude than those of vasomotion.

In two previous clinical studies on alpha-2 agonists employing photoplethysmography (PPG) recordings, we observed spontaneous low-frequency high amplitude vasomotor oscillations [16, 17]. To our knowledge, our observations are unique in that vasomotion was recorded in humans without interference from other low-frequency oscillations. The aim of the third study was to record PPG simultaneously from six fingertips of each participant to verify that these vascular oscillations are local in nature and consistent with previously described properties of vasomotion.

Despite decades of investigation, the physiological significance of vasomotion remains elusive. Our aim here was to describe experimental techniques that for the first time allow vasomotion recordings without interference from other low-frequency vascular oscillations in humans. Ability to record vasomotion in isolation from other interfering oscillations could aid future studies of vasomotion in human health and disease and help investigate mechanisms of substances on microcirculation.

Methods

We report slow, spontaneous vascular oscillation recordings from three different clinical investigations. All procedures were in accordance with the ethical standards of the institutional and/or national research committees. Written informed consent was obtained from all participants.

Study 1 Protocol

Study 1 was conducted in 2007 after obtaining approval from the Ethics Committee of the Southwest Finland Hospital District, Turku, Finland (IORG# 0001744, IRB# 00002216). These data were collected as part of a larger study that evaluated effects of nitric oxide (NO) synthase inhibition on vasoconstriction evoked by an alpha-2-adrenoceptor agonist (dexmedetomidine) [16]. We enrolled 11 healthy, nonsmoking, drug-free male volunteers between 18 and 45 years of age who were in good general health as assessed by medical history and physical examination and had a negative urine drug screening result. We excluded individuals with history of cardiac, renal, or hepatic disease, alcohol or drug abuse, or were taking prescription medications. The study subjects were investigated in the fasted state and had been instructed to abstain from alcohol for 48 h, caffeine for 12 h, and heavy exercise for 24 h prior to the experiments. A detailed description of the study methods has been published previously [16].

The experimental sessions started at approximately 8 a.m. Subjects were in a supine position in a temperature-controlled room. A peripheral intravenous catheter was inserted to administer fluids and dexmedetomidine (Precedex®; Abbott Laboratories, Abbott Park, IL). Intra-arterial blood pressure, electrocardiography, and PPG (see below) were monitored continuously using a Datex-Ohmeda S/5 Anesthesia Monitor with E-PRESTN hemodynamic module (Datex-Ohmeda; GE Healthcare,

Helsinki, Finland). Blood pressure and heart rate were recorded once every 10 s using S/5 Collect software (S/5 iCollect version 5.0, GE Healthcare, Helsinki, Finland).

Pharmacological sympathectomy was induced (with mepivacaine) to the studied hand by a brachial plexus block, after which a cannula was placed into the brachial artery to permit measurement of arterial blood pressure and infusion of N^G-monomethyl-L-arginine (L-NMMA, Clinalfa, Merck Biosciences, Rahway, NJ). Thirty min after the induction of brachial block, an i.v. infusion of dexmedetomidine was started and continued for 50 min. Dexmedetomidine was administered as a target-controlled infusion aiming at pseudo-steady-state plasma drug concentrations of 1.2 ng/mL. Thirty-five min after the beginning of the dexmedetomidine infusion, a 5-min i.a. infusion of L-NMMA (8 mmol) was started.

Study 2 Protocol

Study 2 was conducted after obtaining approval from the Institutional Review Board of the University of California San Francisco (IRB# 10-00969). The trial was registered at clinicaltrials.gov (NCT01116700). These data were collected as part of a larger study that evaluated the pharmacokinetic properties of dexmedetomidine [17].

We enrolled 16 healthy, drug-free volunteers between 18 and 45 years of age. We excluded individuals who had history of cardiac, renal, or hepatic disease, or alcohol or drug abuse. Volunteers taking any prescription medications other than oral contraceptives or antiepileptics were excluded. The study subjects were fully fasted and instructed to abstain from alcohol and caffeine for 24 h prior to the study. A detailed description of the study methods has been published previously [17].

The experimental sessions were started at approximately 8 a.m. Subjects were in a supine position in a temperature-controlled room. A peripheral intravenous catheter was inserted to administer fluids and dexmedetomidine (Precedex®; Abbott Laboratories, Abbott Park, IL). A cannula was placed into the radial artery to permit continuous measurement of arterial blood pressure. Intra-arterial blood pressure, electrocardiography, and PPG (see below) were monitored continuously using a Datex-Ohmeda S/5 Anesthesia Monitor with E-PRESTN hemodynamic module (Datex-Ohmeda; GE Healthcare, Helsinki, Finland). Blood pressure and heart rate were recorded once per second using S/5 Collect software (GE Healthcare, Helsinki, Finland).

After all monitors were in place and operational, subjects rested for 10–15 min followed by intravenous administration of dexmedetomidine at four progressively increasing dose rates. Dexmedetomidine was administered as a target-controlled infusion aiming at pseudo-steady-state plasma concentrations of 0.3, 0.6, 1.2, and 2.4 ng/mL. The duration of each infusion step was 15 min.

Study 3 Protocol

Study 3 was a feasibility study to test whether PPG data could be collected from six finger sensors simultaneously. The study was conducted after obtaining approval from the Institutional Review Board of the University of California San Francisco (IRB# 15-16925). We enrolled 7 neurosurgical patients who were over 18 years of age and were to undergo intracranial surgery for epilepsy with intraoperative cortical EEG recordings under dexmedetomidine-based general anesthesia. We excluded patients who had cardiac, hepatic, or renal diseases or were taking cardiovascular medications.

All patients fasted overnight. Surgeries started at 7:30 a.m. Prior to induction of anesthesia, a peripheral intravenous catheter was inserted to administer fluids and medications. Standard anesthesia monitors were applied (5-lead electrocardiography, noninvasive blood pressure monitoring, and a pulse oximeter probe). Six additional pulse oximeter probes were attached for PPG data collection purposes (see below). A cannula was placed into the radial artery to permit continuous measurement of arterial blood pressure which was recorded at 100 Hz using S/5 Collect software (GE Healthcare, Helsinki, Finland). During the study, the patients were in an operating room in a semi-lateral position covered with surgical drapes.

Patients received fentanyl (up to 100 μg) as premedication. Baseline blood pressure and heart rate were recorded noninvasively prior to induction of anesthesia. After preoxygenation with 100% oxygen, anesthesia was induced with intravenous propofol as per the attending anesthesiologist. Rocuronium was administered after loss of consciousness to facilitate endotracheal intubation. Anesthesia was maintained with inhaled oxygen and nitrous oxide (30%/70%) and with continuous intravenous dexmedetomidine and remifentanil infusions as per the attending anesthesiologist. Positive pressure ventilation was controlled mechanically using an 8 mL/kg tidal volume, and the respiratory rate was adjusted to maintain end-tidal CO_2 between 30 and 35 mm Hg.

PPG Measurements

PPG is the measurement of blood volume increase or decrease in a tissue using light absorption. Looking at a PPG plot, one can discern rhythmic oscillations that are

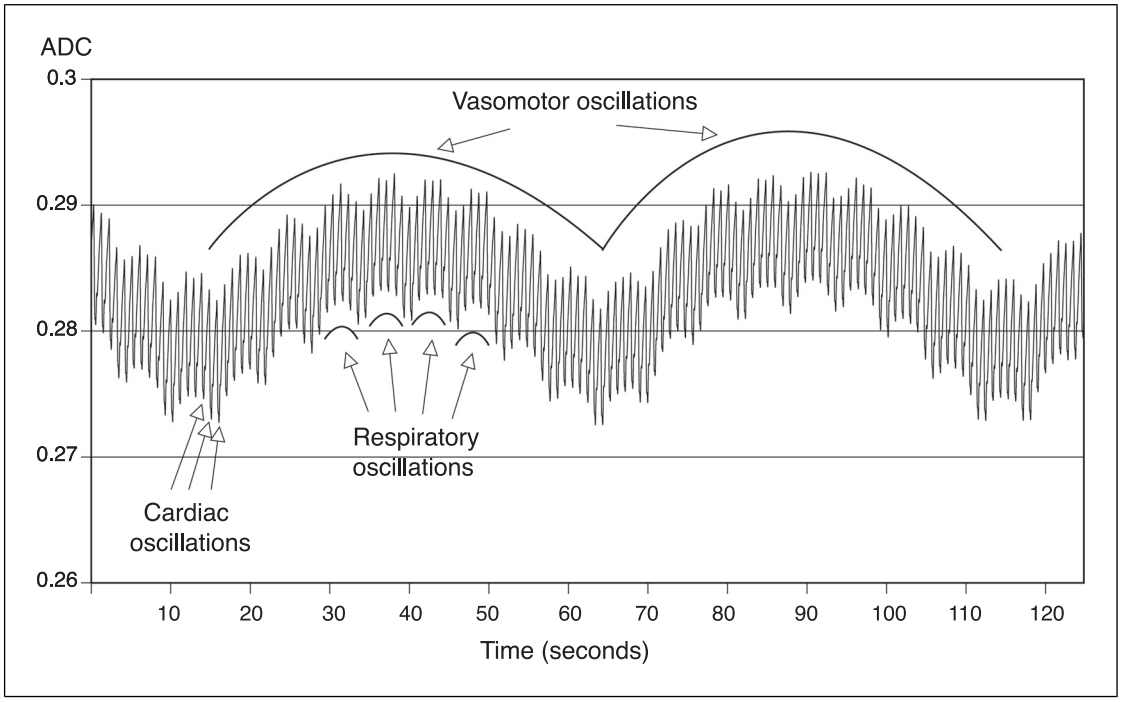

Fig. 1. Illustration of an intraoperative PPG recording that shows slow vasomotor oscillations (0.02 Hz), rhythmic mechanical ventilator induced respiratory oscillations (0.17 Hz), and cardiac oscillations (arterial pulses) (1 Hz). ADC, analog-to-digital converter counts.

synchronous with cardiac oscillations (arterial pulses). Typically, these cardiac oscillations ride on top of other slow oscillations which we refer to as vascular oscillations (shown in Fig. 1).

Vascular oscillations were measured using infrared PPG. The PPG sensor contains a low-voltage, light-emitting diode that emits infrared light (wavelength approximately 910 nm). A portion of the light that is transmitted through the finger is detected by a photodiode in the sensor which generates an electrical current proportional to the amount of light transmitted through the fingertip. This electrical current is converted to a voltage which is sampled using an analog to digital converter. The detected signal is low-pass filtered (22 Hz in Study 1 and 10 Hz in Studies 2 and 3). The generated analog-to-digital converter count data were transmitted to a computer, sampled at 100 Hz (Study 1) or 62.5 Hz (Studies 2 and 3), and saved with no further signal processing.

Since short-term (seconds to minutes) volume changes in the distal phalanx of the finger are mainly due to changes in vascular volume, light transmission through the finger serves as a relative measure of blood volume changes and, hence, quantitates vasoconstriction/vasodilation. Increases in overall PPG values (increased light transmittance) reflect lower blood volume in the digit (vasoconstriction) and conversely, decreased PPG values reflect an increase in blood volume (vasodilation). On the other hand, the AC component of PPG, which is due to cardiac oscillations (shown in Fig. 2), acts in opposite way, decreasing during vasoconstriction and increasing during vasodilation.

In Study 1 infrared light transmitted through the fingertip was measured using a Datex-Ohmeda S/5 Anesthesia Monitor with an E-PRESTN hemodynamic module (GE Healthcare, Helsinki, Finland) for which an adhesive OxyTip OXY-AF sensor (GE Healthcare, Helsinki, Finland) was placed on the distal phalanx of the index finger of the hand with the sympathetic block. PPG data were recorded continuously (100 Hz) throughout the study session using an automated data-acquisition system (S/5 iCollect version 5.0, GE Healthcare, Helsinki, Finland).

In studies 2 and 3, infrared light transmitted through the fingertip was measured using a Masimo Radical-7 pulse oximeter (Masimo Corp., Irvine, CA, USA; Masimo SET software version 7.0.3.3), for which an adhesive LNCS Adtx sensor (Masimo Corp., Irvine, CA, USA) was placed on the distal phalanx of left index finger (Study 2) and distal

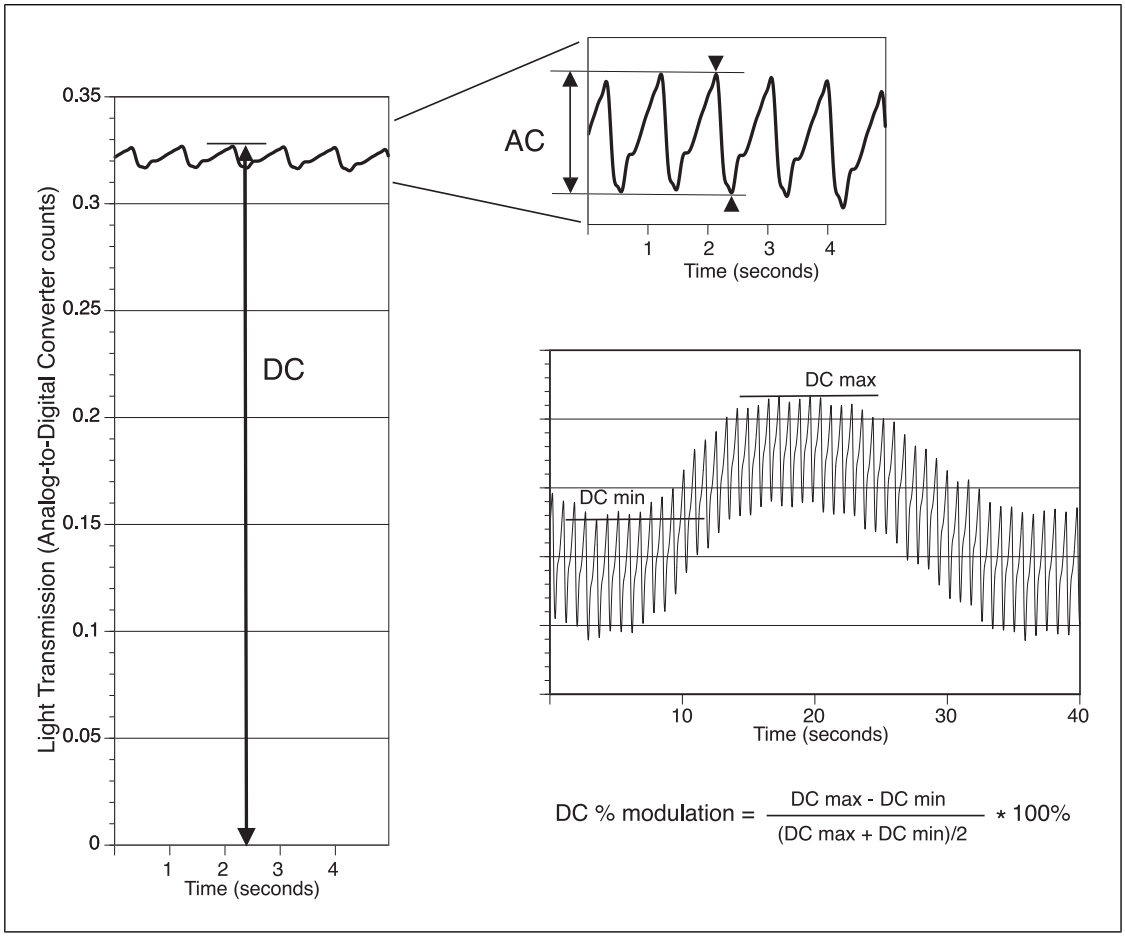

Fig. 2. Illustration of PPG DC and AC components and DC % modulation calculation. The DC value corresponds to the smallest blood volume in the finger (end diastole), when the maximum amount of light is transmitted through the finger. The AC values are due to cardiac pulses and is defined as the difference between the highest (end diastole) and lowest (end systole) light transmission values of each cardiac pulse. DC % modulation is calculated by identifying the maximum and minimum DC value for each vasomotor cycle. DC % modulation is then calculated as shown in the figure.

phalanxes of right and left ring, middle, and index fingers (Study 3, six sensors). In Study 3, the sensors were optically isolated to prevent crosstalk by covering the pulse oximeter probes with black 6 mil plastic. PPG data were recorded continuously (62.5 Hz) throughout the study session using an automated data-acquisition system (Pulse Ox Automated Data Collection software, Masimo Corp., Irvine, CA, USA; ADC v3.1.1.0).

Blood Pressure Measurements

For Study 1, intra-arterial blood pressure was measured using a brachial arterial catheter. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were recorded every 10 s. From these data, we extracted SBP and DBP data immediately before the beginning of dexmedetomidine infusion (baseline), toward the end of the dexmedetomidine infusion and immediately after the L-NMMA infusion. During Study 2, radial artery SBP and DBP values were recorded manually immediately before beginning of the dexmedetomidine infusion (baseline) and at the end of each infusion step. For Study 3, baseline SBP and DBP were measured noninvasively and recorded manually immediately before induction of anesthesia. Radial artery blood pressure was recorded at 100 Hz intraoperatively. From these data, we extracted SBP and DBP values during the epoch that was used for vasomotor oscillation analysis.

Data Analysis

All PPG data were analyzed offline. The frequency and amplitude of low-frequency vascular oscillations were analyzed from the PPG data. For frequency analysis of the

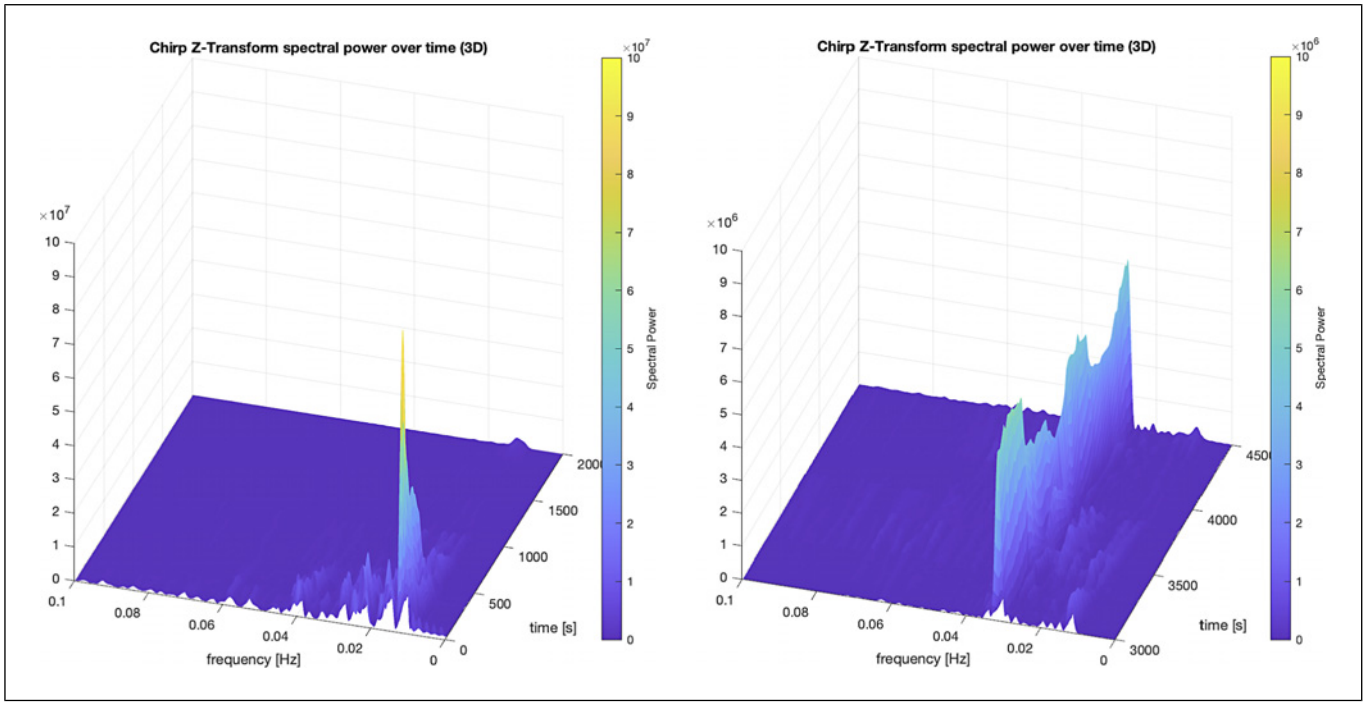

Fig. 3. Spectrograms of chirp Z-trans-form analysis of a subject in Study 1. Left panel: data recorded while the subject rested in supine position prior to brachial plexus block, showing multiple vascular oscillation frequencies. At approximately 500 s, a brachial plexus block was performed, resulting in significant attenuation or disappearance of these vascular oscillation frequencies. Right panel: spectrogram recorded after the brachial plexus block during dexmedetomidine infusion revealing a single dominant frequency oscillation (vasomotion). Note the 10-fold difference in spectral power compared to the left panel.

low-frequency oscillations, PPG data were low-pass filtered at 0.5 Hz. These data were then decimated by 50 (Study 1) or 32 (Studies 2 and 3), to achieve data frequencies at or close to 2 Hz followed by band pass filtering (0.01–0.5 Hz). Five-Min segments with 10-s overlaps of these filtered data were then frequency transformed using chirp Z-transform spanning 0–0.25 Hz with 0.0005 Hz resolution (MATLAB, MathWorks, Inc., Natick, MA).

For each study subject, we generated spectrograms and videos of the chirp Z-transform outputs (shown in Fig. 3). Using these spectrograms and videos, after visual inspection, we identified 5-min PPG epochs that displayed low-frequency, artefact-free oscillations. For Study 1, we selected two separate 5-min PPG epochs during dexmedetomidine infusion, one before the L-NMMA infusion and one toward the end of the L-NMMA infusion. For Study 2, we also selected two epochs, one during step 3 (1.2 ng/mL) and another during step 4 (2.4 ng/mL) of the dexmedetomidine infusion. For Study 3, we selected a 5-min epoch during which data from all six sensors displayed low-frequency oscillations.

For vasomotion amplitude analysis, we used the original unfiltered data. We identified the maximum and minimum infrared light transmittance for each cardiac pulse using programs written in MATLAB (MathWorks, Inc., Natick, MA). These data were used to determine the AC and DC values of each cardiac pulse (shown in Fig. 2). The AC values signify the pulsatile portion of the transmitted light (cardiac oscillations), and the DC values signify the non-pulsatile portion of the transmitted light. The words AC and DC come from electrical engineering meaning "alternating current" and "direct current." Here, we use the term DC loosely to indicate a background signal level that can vary slowly.

To analyze the amplitude of the low-frequency oscillations, we calculated % modulation values of the AC and DC components of PPG. We first selected three vasomotor oscillatory cycles during each of the 5-min epochs that were used for frequency analysis. For each of the three oscillatory cycles, we identified the maximum and minimum AC and DC values (shown in Fig. 2). We calculated % modulation as $(X_{max} - X_{min})/X_{mean} \times 100\%$ where X was either AC or DC values. We averaged the resulting three AC and DC % modulation values of each epoch for further analysis.

Table 1. Demographics

	n	M/F	Age	Weight, kg	Ht, cm
Study 1	7	7/0	27±5 (21–36)	75±14 (56–94)	178±7 (169–189)
Study 2	11	7/4	26±6 (20–41)	72±12 (50–86)	171±19 (120–184)
Study 3	6	1/5	34±9 (21–45)	61±10 (44–74)	161±8 (152–170)

Values are means ± SD (range). *n*, number of subjects; M, male; F, female; Wt, weight; Ht, height.

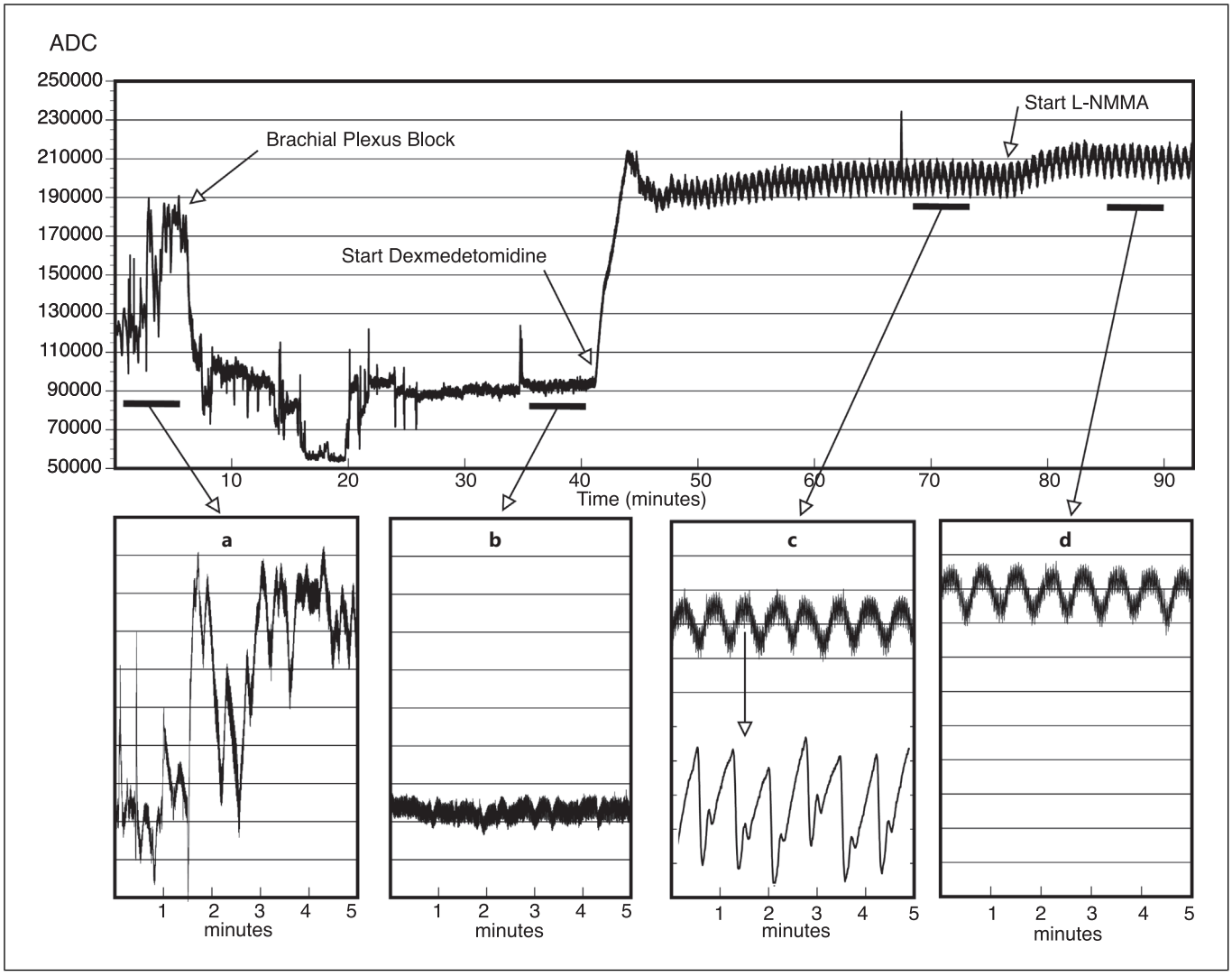

Fig. 4. Example of a photoplethysmography (PPG) recording from one Study 1 subject (upper panel). Changes in PPG values between minutes 15 and 22 are due to movement artefact. The black horizontal bars in the upper panel signify 5-min data segments, which are shown in more detail in the lower panels. **a** PPG recording from a resting subject showing typical SNS associated vasoconstrictive activity. **b** PPG recording of a vasodilated finger after brachial plexus neuraxial block. Note the lack of vasoconstrictive events. **c** Slow spontaneous vascular oscillations (vasomotion). The insert is a 7-s segment of the 100 Hz recording to illustrate that the PPG recordings are composed of cardiac pulses. **d** Vasomotion during L-NMMA infusion. ADC, analog-to-digital Converter counts.

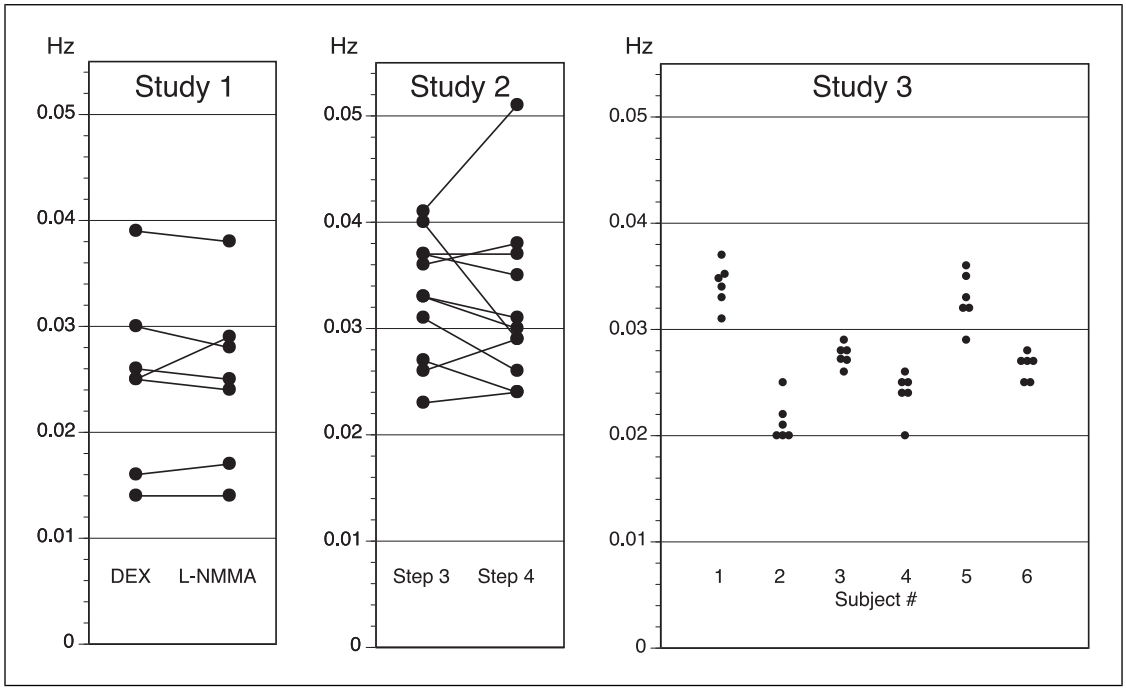

Fig. 5. Vasomotion frequencies (Hertz) of all study subjects. For Study 1 the frequencies are plotted during dexmedetomidine infusion (DEX), and after the beginning of L-NMMA infusion (L-NMMA). For Study 2, the frequencies are shown for infusion steps 3 and 4. For Study 3, frequencies from all 6 sensors for each subject are shown.

Data are reported as mean ± SD. We performed within-group comparisons using paired Student's *t* test with Bonferroni correction when appropriate. All statistical tests were two-tailed and $p < 0.05$ identified statistical significance.

Results

Study 1

Of the 11 subjects, 4 were excluded from the analysis. One was excluded due to local anesthetic toxicity and three subjects due to poor quality PPG data. The demographic data of the remaining 7 subjects are shown in Table 1. The brachial plexus nerve block (sympathectomy) eliminated all low-frequency vascular oscillations (example in Fig. 4). Only respiratory- and cardiac pulse-related oscillations were present before dexmedetomidine infusion. Vasomotion could be observed within minutes after beginning of the dexmedetomidine infusion and continued throughout the dexmedetomidine infusion (shown in Fig. 4). Vasomotion frequencies were 0.025 ± 0.008 Hz (range 0.014–0.039 Hz) before the L-NMMA infusion and 0.025 ± 0.008 Hz (range 0.014–0.038 Hz) during the L-NMMA infusion (shown in Fig. 5). The L-NMMA infusion did not have a significant effect on the frequency of vasomotion ($p = 1.0$).

During the dexmedetomidine infusion, % modulation of the vasomotion was 14 ± 10% (range 8–31%) and 5 ± 3% (range 2–10%) for the AC and DC components of PPG, respectively. During the L-NMMA infusion, % modulation was 14 ± 10% (range 6–36%) and 4 ± 3% (range 1–10%) for the AC and DC components of PPG, respectively. The L-NMMA infusion did not have a significant effect on % modulation of vasomotion of either the AC ($p = 0.83$) or DC ($p = 0.28$) component of PPG. SBP and DBP values are shown in Table 2.

Study 2

Two of the 16 subjects were excluded from analysis due to incomplete PPG data. SNS-related vascular oscillations were attenuated over time by the dexmedetomidine infusion (dexmedetomidine is a central sympatholytic agent) [18–21] (shown in Fig. 6). By visual inspection, one of the 14 subjects had no identifiable episodes of vasomotion. Of the remaining 13 subjects, 3, 9, 11, and 13 subjects had identifiable vasomotion during

Table 2. SBP and DBP values

		Baseline	Dex	L-NMMA
Study 1	SBP, mm Hg	109±6	115±10	119±9§
	DBP, mm Hg	66±2	71±6	73±7§
		Baseline	Step 3	Step 4
Study 2	SBP, mm Hg	134±7	115±14*	131±16§
	DBP, mm Hg	68±5	63±8	75±10*§
		Baseline		Epoch
Study 3	SBP, mm Hg	116±10		121±62
	DBP, mm Hg	69±5		62±9*

SBP, systolic blood pressure; DBP, diastolic blood pressure; Dex, during dexmedetomidine infusion; L-NMMA, during L-NMMA infusion; Epoch, during the 5 min time segment that was used for vasomotor analysis. Values are means ± SD. *$p < 0.05$ compared with baseline using paired *t* tests with Bonferroni correction when appropriate. §$p < 0.05$ compared with Dex or Step 3 using paired *t* tests with Bonferroni correction when appropriate.

dexmedetomidine infusion steps 1, 2, 3, and 4, respectively. During dexmedetomidine infusion steps 1 and 2, we could not identify long enough episodes of slow vascular oscillations for frequency analysis, mainly due to superimposed SNS activity.

For the 11 subjects that demonstrated vasomotion during both steps 3 and 4, the demographic data are shown in Table 1. For these subjects, the vasomotion frequencies were 0.033 ± 0.006 Hz (range 0.023–0.041 Hz) during step 3 and 0.032 ± 0.008 Hz (range 0.024–0.051 Hz) during step 4 (shown in Fig. 5). Doubling of the dexmedetomidine target concentration in plasma from 1.2 ng/mL (step 3) to 2.4 ng/mL (step 4) did not have a significant effect on the frequency of vasomotion ($p = 0.56$, example shown in Fig. 7).

The % modulation of the AC component of PPG was 11 ± 6% (range 6–23%) and 14 ± 8% (range 6–29%) for steps 3 and 4, respectively ($p = 0.2$). The % modulation of the DC component of PPG was 3 ± 2% (range 1–7%) and 3 ± 1% (range 1–4%) for steps 3 and 4, respectively ($p = 0.07$). Average DC values of PPG (tonic vasoconstriction) increased from step 3 to step 4 by 6 ± 7%. SBP and DBP values are shown in Table 2.

Study 3

Of the 7 subjects, one was excluded from analysis due to poor quality PPG data. Demographic data of the remaining six subjects are shown in Table 1. Intraoperative PPG data were collected for 108 ± 49 min (range 41–167 min).

Low-frequency vascular oscillations were recorded from all six sensors of all six subjects during most of the PPG recordings. The chirp Z-transform analysis showed two distinct frequency peaks in each subject. One was at the frequency of the mechanical ventilator. The second frequency peak had a significantly larger amplitude. Its minimum and maximum frequencies during the study sessions were 0.020 and 0.037 Hz. In each subject, these oscillations had different frequencies in all six fingers, i.e., none of the oscillations were synchronous in any of the subjects. Vasomotion frequencies for the six subjects (all six probes) are illustrated in Figure 5 and summarized in Table 3. Figure 8 illustrates unfiltered and filtered PPG data and chirp Z-transformed frequency data from all six probes for one subject.

The % modulation values for the AC and DC components of PPG are shown in Table 3. SBP and DBP values are shown in Table 2. Patients received 1.4 ± 0.6 μg/kg/h dexmedetomidine and 0.3 ± 0.1 μg/kg/min remifentanil during the data analysis epochs.

Discussion

Our results demonstrate that the slow vascular oscillatory activity observed in our studies is consistent with definitions of vasomotion, and that this vasomotor activity can be observed in awake and anesthetized human subjects without significant interference from other spontaneous vascular oscillations. Consistently with existing literature, our findings show that this vasomotor activity is independent of neurogenic mechanisms, is limited to small segments of the microcirculation, and is associated with alpha-2-adrenoceptor activation. To our knowledge, these recordings of vasomotion in humans are novel in part by the lack of interference from other spontaneous vascular oscillations and in part by occurring during three different experimental conditions, enabling future studies to investigate these spontaneous oscillations in more detail.

Our results are consistent with previous studies which demonstrate that vasomotion is independent of neural activity [3, 7–9]. In Study 1, we blocked nerve conduction to one arm using a brachial plexus neuraxial block with mepivacaine. Brachial plexus nerve block results in pharmacological sympathectomy of the arm, which can be seen as significant dilation of the blood vessels of that hand [22]. Administration of dexmedetomidine after the neuraxial block resulted in peripheral vasoconstriction in the previously vasodilated hand and initiated vasomotion. The

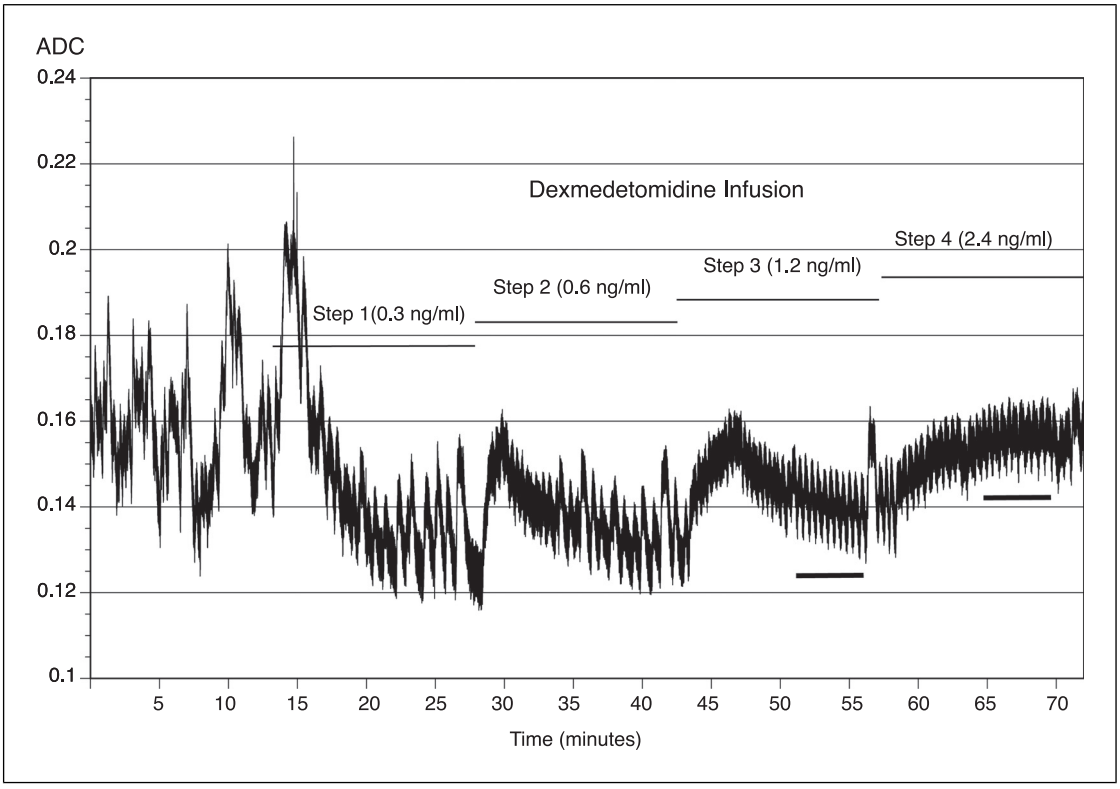

Fig. 6. PPG recording from one Study 2 subject before dexmedetomidine infusion and during each of the four dexmedetomidine infusion steps. The black horizontal bars signify two 5-min data segments that are illustrated in more detail in Figure 7. ADC, Analog-to-Digital Converter counts.

vasomotor activity continued throughout the dexmedetomidine exposure. Vasomotion is thought to be modulated by vascular shear stress and optimized to operate when the vascular wall tension is within the autoregulatory range and is less likely to be detected in highly dilated or constricted blood vessels [2, 5, 8, 23]. Our experimental design cannot tell whether dexmedetomidine-evoked peripheral vasoconstriction activated vasomotion by returning the vasomotor tone toward the normal operating range of the previously vasodilated vasculature, or directly by pharmacological alpha-2-adrenoceptor activation, or both.

The role of NO in the regulation of vasomotion has not been clearly defined [6, 7, 9]. In Study 1, blocking NO synthesis had no effect on the frequency or amplitude of vasomotion. Our previous publication demonstrated that in these same subjects, administration of L-NMMA caused an increase in vascular tone indicating that we inhibited NO release in that hand [16]. Thus, we conclude that NO does not modulate vasomotion in human fingers.

Vasomotion has been observed in most vascular beds [4, 5, 7, 9, 11, 12, 15]. Because vasomotion is a local phenomenon, it is not associated with fluctuations in systemic blood pressure. The results of our Study 3 demonstrate the local nature of vasomotion in humans. In Study 3, none of the vasomotor oscillations of the six fingertips were synchronous. Thus, our data suggest that the vasomotor activity originates and is regulated independently in each finger, confirming the local nature of vasomotion. Another novel observation is that the vasomotion frequencies of the 6 simultaneously investigated fingers tended to be similar within a subject. This is consistent with previous observations that vasomotion is characterized by a distribution of frequencies around a fundamental frequency [10].

Alpha-2-adrenoceptor agonists have central and peripheral sympatholytic effects and are direct peripheral vasoconstrictors [19–21, 24, 25]. Dexmedetomidine infusions reduce circulating norepinephrine (NE) concentrations in surgical patients and in healthy volunteers [19–21]. In Study 2, consistently with known effects of dexmedetomidine, SNS-related vascular activity was attenuated over time during increasing dexmedetomidine infusion steps. SNS activity is characterized in the

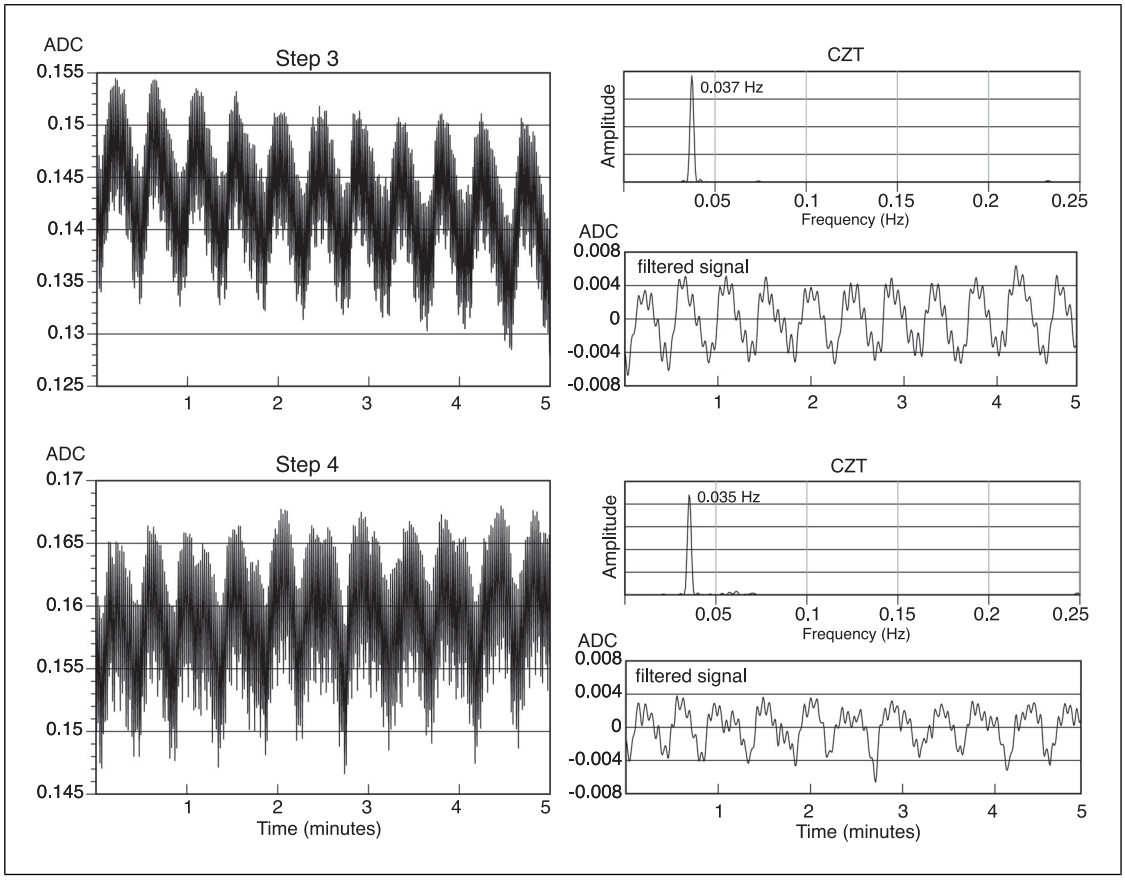

Fig. 7. Two 5-min PPG recordings from a subject in Study 2. The three upper panels show the original PPG signal (left), signal after filtering (lower right), and the chirp Z-transform output (CTZ) of the filtered signal from step 3 of dexmedetomidine infusion. The lower panels show similar data from step 4 of the dexmedetomidine infusion. ADC, Analog-to-Digital Converter counts.

PPG signal by episodes of peripheral vasoconstriction that are synchronous bilaterally [26], often many times larger in amplitude than the AC portion of the PPG signal, and have a rapid initial vasoconstrictive portion followed by a slower vasodilation portion. Although we were unable to analyze the frequency of vasomotion during the first two dexmedetomidine infusion steps, vasomotion was visually identified in some of the subjects during the first two infusion steps, suggesting that vasomotion was either unmasked by diminishing SNS activity or was activated already by low concentrations of dexmedetomidine in plasma.

In Study 2, by infusion steps 3 and 4 we were able to analyze the vasomotion frequencies and amplitudes. The frequency and amplitude of vasomotion did not change from infusion step 3 to step 4 even though the dexmedetomidine target plasma concentration was doubled. It is possible that a ceiling effect was reached for vasomotion frequency and amplitude, i.e., our doses at step 3 were high enough to saturate the concentration-effect curve.

Our finding that vasomotion is associated with alpha-2-adrenoceptor activation is consistent with observations from numerous animal (in vivo and in vitro) studies [4, 9, 27]. Various vascular preparations display rhythmic contractions either when pretensioned or stimulated with NE, which has alpha-2-adrenoceptor agonist activity [3, 8]. In rat mesenteric small arteries, NE facilitates the spontaneous discharge of Ca^{2+} in VSMCs [9]. It is believed that slow, regular, nearly sinusoidal oscillations in tone (vasomotion) appear when this periodic influx of Ca^{2+} in VSMCs becomes synchronized [12, 28]. This is thought to happen by electromechanical coupling of the phasic oscillations of the membrane potential in the VSMCs, with the signal passing between cells through gap junctions. Our ability to observe

Table 3. Vasomotion frequencies and % modulation values for the subjects in Study 3

Subject	Frequency, Hz	AC, %	DC, %
1	0.034±0.002 (0.031–0.037)	12±3 (9–16)	3±2 (2–6)
2	0.021±0.002 (0.020–0.025)	12±2 (9–15)	3±1 (3–4)
3	0.028±0.001 (0.026–0.029)	6±2 (3–7)	1±1 (1–2)
4	0.024±0.002 (0.020–0.026)	4±1 (2–5)	1±1 (1–2)
5	0.033±0.002 (0.029–0.036)	11±3 (8–16)	4±1 (3–4)
6	0.027±0.001 (0.025–0.028)	9±4 (5–16)	2±0 (2)

Values are means ± SD (range), frequency values are from all six fingers for each subject. Hz, Hertz; AC, AC component of PPG; DC, DC component of PPG.

vasomotion with PPG in the human fingertip in vivo implies that most of the microvasculature in the fingertip oscillates in a synchronized fashion. The above-mentioned electrical coupling would be one feasible explanation for this synchronization. To further investigate the extent and potential propagation of this synchronized vasomotor activity, other techniques than conventional PPG might be better suited for this purpose, such as strain gauge plethysmography, multiplexed PPG, high gradient phase contrast MRI or thermography-based blood flow imaging with spectral filtering.

Vasomotion frequencies ranged from 0.014 Hz to 0.042 Hz in our study subjects. The vasomotion frequency ranges were similar between our three studies even though there were significant differences in our experimental conditions. Stefanovska et al. identified five different frequency ranges of spontaneous vascular oscillations (flowmotion) in humans [15]. In contrast to our results, they attributed the 0.02–0.06 Hz frequency interval to neurogenic activity and the 0.06–0.15 Hz frequency interval to myogenic activity (vasomotion). There are several potential explanations for these discrepancies. Most of the data on spontaneous vascular oscillations in humans have previously been provided by LDF measurements. LDF measures flowmotion of the skin microvasculature (superficial 1 mm), whereas transmission PPG reflects vasomotion in a cross section of a fingertip [29]. Thus, the two techniques sample different volumes and different segments of the microvasculature. Furthermore, LDF sensors were also applied to a different anatomical location (forearm), which may have different microvascular control mechanisms and adrenergic innervation than fingertips where we placed the sensors. Another likely explanation for discrepancies between our findings and those of previous studies relates to our experimental techniques, which eliminated SNS activity from our recordings, and our use of pharmacological alpha-2-adrenoceptor activation. A less likely explanation is that we specifically selected segments of vasomotion that were nearly sinusoidal and had high amplitude. Vasomotion can range from sinusoidal to quasiperiodic rhythms. Choosing other data segments would have resulted in slightly different vasomotion frequencies.

We attribute our ability to observe vasomotion without significant interference from other spontaneous vascular oscillations to our techniques that eliminated SNS activity, by neuraxial block in Study 1, by systemic administration of dexmedetomidine in Study 2, and by nitrous oxide/narcotic general anesthesia and dexmedetomidine infusion in Study 3. Without attenuating SNS activity, it is difficult to segregate the vasomotor activity from the PPG signal simply by frequency or amplitude analysis as neuronally driven signals are orders-of-magnitude larger and similar in frequency to those of vasomotion.

Intaglietta et al. suggested that vasomotor activity could constitute a mechanism by which tissue fluid is propelled into lymphatic vessels, and vasomotion could thus aid the propulsion of lymph [30]. Data from animal experiments show increased glymphatic system activity with ketamine/xylazine (another alpha-2-adrenoceptor agonist) anesthesia [31]. Because some reported slow glymphatic propulsion frequencies in humans are similar to the vasomotion frequencies, we observed in our studies, our data are consistent with the notion that alpha-2-adrenoceptor associated low-frequency vasomotor activity may play a role as a mechanical driving force of enhanced glymphatic flow. Under this hypothesis, assessment of vasomotor function may provide insights into conditions possibly associated with glymphatic dysfunction, such as Alzheimer's disease and traumatic brain injury [32, 33].

Under normal conditions vasomotion is thought to aid the delivery of oxygen and nutrients to tissues. However, vasomotion can be altered under pathological conditions and increases when blood supply to an organ is threatened. For example, vasomotion is upregulated in patients with essential hypertension or with intermittent lower extremity claudication [34]. On the other hand, vasomotion is abolished in patients with peripheral arterial occlusive disease with critical ischemia and has been reported to be reduced in patients with microcirculation pathologies, such as diabetes, retinal disease and

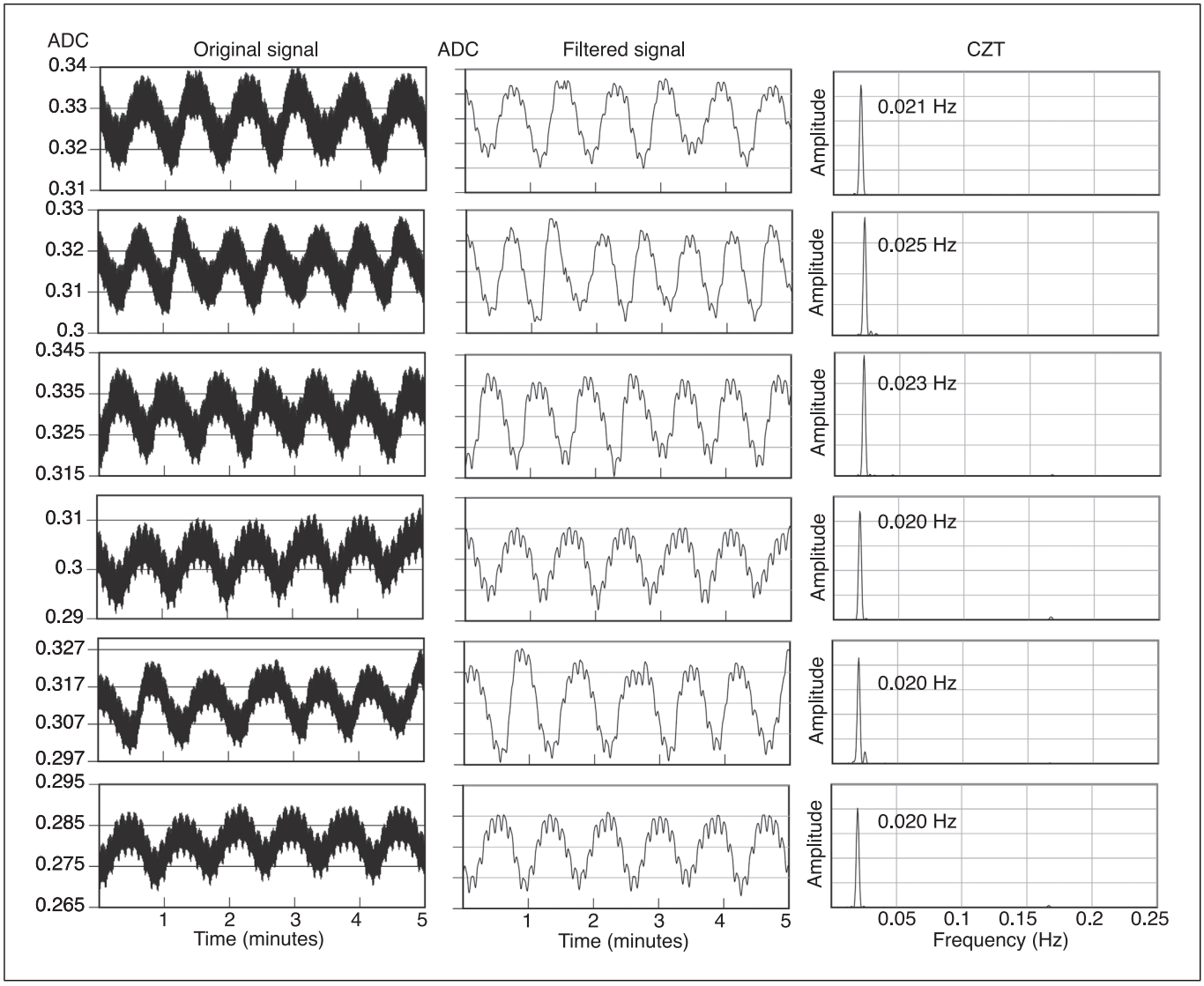

Fig. 8. Simultaneous 5-min 62.5 Hz PPG recordings from all 6 sensors of a subject in Study 3 (left). Middle panels show the signals after filtering, and right panels show chirp Z-transform outputs of the filtered signals. The slow oscillations are due to vasomotion, and the faster oscillations which, are best seen in the filtered signals, are due to pulse volume changes secondary to mechanical ventilation. ADC, Analog-to-Digital Converter counts.

obesity [1, 35]. Studies of vasomotion could aid in diagnosing microcirculatory impairment in various pathological conditions.

Our findings are limited by the small sample sizes and the retrospective nature of two of the studies. However, this is an exploratory analysis of unique data that provides novel insight into vasomotion in humans as measured by PPG. Because we collected data only from the fingertips, our results may not be valid for other vascular beds. Vasomotion frequencies and amplitudes are known to vary over time. Our analysis was limited to segments of vasomotion that we chose because they were nearly sinusoidal and had high amplitudes because the purpose of this exploratory study was to demonstrate our ability to record vasomotion under various experimental conditions in humans. Even if L-NMMA increased vascular tone in Study 1, we did not observe changes in % modulation of either the AC or DC components of PPG. Our data are not sufficient to explain whether this was due to the small magnitude of the increase in vascular

tone, or whether tonic vasomotor tone and spontaneous vasomotion are mediated by different mechanisms. Similarly, our data are not sufficient to explain whether the observed spontaneous vasomotion is actually dependent on the presence of an alpha-2 agonist or simply due to the drug-induced increase in vascular tone and related changes in membrane potentials.

In conclusion, we describe methods by which slow, spontaneous vascular oscillations, which are independent of neural activity, local in nature and associated with alpha-2-adrenoceptor activation, can be recorded in humans. The properties of these oscillations are consistent with vasomotion. These exploratory findings cannot address questions on the origin or physiological significance of vasomotion, but we hope that our results will stimulate and enable further studies to expand our understanding of vasomotion in human health and disease.

Statement of Ethics

Study 1: This study protocol was reviewed and approved by the Ethics Committee of the Southwest Finland Hospital District, Turku, Finland, Approval No. [IORG# 0001744, IRB# 00002216]. Written informed consent was obtained from all participants. Study 2: This study protocol was reviewed and approved by the Institutional Review Board of the University of California San Francisco, Approval No. [IRB# 10-00969]. Written informed consent was obtained from all participants. Study 3: This study protocol was reviewed and approved by the Institutional Review Board of the University of California San Francisco [IRB# 15-16925]. Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors had no conflict of interest to declare.

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Author Contributions

P.T. and M.S. conceived and designed research and performed experiments; P.T., J.S.M., M.T., M.S., and M.K.D. analyzed data, edited and revised manuscript, approved final version of manuscript, and interpreted results of experiments; P.T. prepared figures.

Data Availability Statement

All data generated during this study are included in this article. Further enquiries can be directed to the corresponding author. The high frequency PPG datasets used for analysis will be available for the reviewers from the corresponding authors. The authors plan to have all high frequency photoplethysmography datasets used in this study available in a repository after publication of the manuscript.

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