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Synchronous Rhythmical Vasomotion in the Human Cutaneous Microvasculature during Nonpulsatile Cardiopulmonary Bypass

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Background: **The origin, control mechanisms, and functional significance of oscillations in microvascular flow are incompletely understood. Although the traditional belief has been that only low-frequency oscillations (0.04–0.10 Hz) can originate at the microvascular level, recent evidence in healthy volunteers has suggested that high-frequency oscillations (> 0.10 Hz) also may have a microvascular origin (as opposed to being mechanically transmitted respiratory-induced variations in stroke volume). The current study determined if such oscillations would emerge in the absence of cardiac and respiratory activity during nonpulsatile cardiopulmonary bypass (NP-CPB).**

Methods: **Forehead and finger laser Doppler flow, arterial pressure, and core temperature were simultaneously recorded in eight patients during NP-CPB. Analyses included time–domain indices, frequency–domain indices (auto power spectral density), and a measure of regularity (approximate entropy) for standardized time segments.**

Results: **Nonpulsatile cardiopulmonary bypass was associated with the emergence of rhythmical oscillations in laser Doppler flow, with characteristic frequencies for the forehead (0.13 ± 0.03 Hz) and finger (0.07 ± 0.02 Hz). Forehead vasomotion became progressively synchronized, with a gain in high-frequency spectral power from 17.5 (minute 1) to 89.1 (minute 40) normalized units, and a decrease in approximate entropy from 1.2 (before NP-CPB) to less than 0.5 (minute 40).**

Conclusions: **The emergence of forehead microvascular oscillations at greater than 0.10 Hz (characteristic of parasympathetic frequency response), in the absence of cardiac and respiratory variability, demonstrates their peripheral origin and provides insights into parasympathetic vasoregulatory mechanisms. The progressive synchronization of forehead vasomotion during NP-CPB, suggestive of increased coupling among microvascular biologic oscillators, may represent a microcirculatory homeostatic response to systemic depulsation, with potential implications for end-organ perfusion.**

DURING the past two decades, multiple animal and human studies have shown that oscillations in cardiovascular signals are indicative of changes in autonomic activity. Application of spectral analysis to electrocardiographic signals has identified sinusoidal patterns of heart rate variability with very-low-frequency (VLF; < 0.04 Hz), low-frequency (LF; 0.04–0.10 Hz), and high-frequency (HF; > 0.10 Hz) spectral components. VLF oscillations are primarily attributable to sympathetic activity but also may be modulated by thermoregulation and the renin-angiotensin system.[1–4] LF oscillations are mediated jointly by the sympathetic and parasympathetic nervous systems, with the arterial baroreflex playing a critical role in their genesis. In contrast, HF oscillations are purely parasympathetic and typically related to respiration.[1–4] The physiologic basis for the distinction between the frequency response characteristics of sympathetic and parasympathetic cardiovascular control mechanisms has been ascribed to the complex second-messenger and reuptake systems at sympathetic neuroeffector sites, which do not effectively generate oscillations at greater than 0.10 Hz.[5,6] Therefore, only the parasympathetic nervous system reacts rapidly enough to mediate HF fluctuations in cardiovascular signals.[1]

Very-low-frequency, LF, and HF oscillations also have been identified in peripheral blood pressure[7,8] and microvascular flow.[8–10] However, whereas sympathetic control mechanisms responsible for cardiovascular variability have been demonstrated both in the heart and peripheral vasculature, the parasympathetic nervous system has been considered an "outcast" at the level of vascular smooth muscle,[11] with only a minor role in peripheral vasoregulation and "virtually no effect on peripheral resistance."[12] Hence, when HF oscillations were detected in blood pressure or microcirculatory flow, they were attributed solely to mechanical transmission of respiratory-induced fluctuations in heart rate and stroke volume to passive portions of the peripheral vasculature.[7–10]

Two recent studies have led us to question the traditional dogma. Using laser Doppler flowmetry (LDF) to delineate microcirculatory responses to systemic α-adrenergic agonist infusions in healthy volunteers, we have previously documented that, whereas there was intense vasoconstriction of the adrenergically rich finger, flow was maintained in more central regions (forehead, forearm),[13,14] where an active vasodilator control mechanism appears to coexist with the adrenergic system.[15,16] Moreover, consistent with the rich cholinergic innervation of the external and internal carotid arteries and their branches,[17] maintenance of forehead perfusion was associated with emergence of HF, atropine-sensitive oscillations.[14,18] Power spectral analysis delineated that the forehead microvascular oscillations occurred at 0.14 ± 0.02 Hz, a frequency that was distinct from that of respiration and respiratory sinus arrhythmia, which

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were centered at 0.20 Hz in response to a metronome.[18] That finding suggested a peripheral origin of HF microvascular oscillations and thus prompted the current attempt to determine if such HF oscillations would occur with the complete removal of cardiac variability and cardiorespiratory interactions. We put forth the hypothesis that nonpulsatile cardiopulmonary bypass (NP-CPB) is associated with the emergence of HF oscillations in specific microvascular networks characterized by prominent cholinergic innervation (*i.e.*, forehead skin microcirculation). Confirmation of this hypothesis would provide strong support for a peripheral etiology to HF microvascular oscillations. This might have a major impact on our understanding of basic vascular autonomic control, as well as provide insight into local autoregulation and the physiologic responses to nonpulsatile perfusion.

Materials and Methods

Patients

The Human Investigation Committee of Yale University School of Medicine (New Haven, CT) approved the study protocol. After obtaining written informed consent, seven male patients and one female patient aged 53 to 76 yr undergoing elective coronary artery bypass grafting with hypothermic NP-CPB were enrolled in the study. Exclusion criteria were the presence of symptomatic peripheral vascular disease, diabetes mellitus, or diagnosed autonomic neuropathy. The anesthetic technique was similar for all eight patients and consisted of weight-related doses of sufentanil, midazolam, and pancuronium bromide, with a volatile anesthetic (isoflurane 0.5%) used during NP-CPB. NP-CPB was conducted with a membrane oxygenator (Gish Vision, Irvine, CA) and a nonpulsatile roller pump (Cobe, Arvada, CO), using crystalloid prime. Pump flow rates were kept between 2.2 and 2.5 $l \cdot min^{-1} \cdot m^{-2}$, mean arterial pressure (MAP) was maintained between 50 and 70 mmHg by use of phenylephrine hydrochloride or sodium nitroprusside as required, and hematocrit was maintained between 20% and 25% during NP-CPB. Patients were cooled to a core (bladder) temperature (t°C) of 30–32°C, with active rewarming to 37°C at the end of NP-CPB.

Data Acquisition

The LDF probes (Periflux 2B; Perimed, Stockholm, Sweden) were applied on the forehead and palmar surface of the index finger contralateral to the arterial catheter site to quantify the cutaneous microcirculatory flux of erythrocytes, a measure of blood flow within the 1-mm^3 sampling volume. The LDF methodology and validation techniques have been reviewed in detail elsewhere.[19] LDF, MAP (*via* radial artery catheter), and t°C signals were simultaneously recorded at a sampling frequency of 250 Hz using an analog–digital converter and custom data acquisition and analysis software (SnapMaster v3.02; HEM Data Corp., Southfield, MI). Pump flow rate was manually recorded every minute and with every change during NP-CPB; systemic vascular resistance (SVR) was calculated using the formula [(MAP − central venous pressure)/(pump flow)] × 80. Hematocrit was measured in arterial blood before NP-CPB and at four time points during NP-CPB (minutes 8, 25, 40, and at 10 min after the onset of systemic rewarming) using a blood gas analyzer (Stat Profile 5; Nova Biomedical, Waltham, MA).

Data Analysis

The study period was divided into 12 standardized segments: pre-CPB (immediately before the start of NP-CPB); minutes 0–1, 1–3, 4–6, 7–9, 11–13, 17–19, 20–22, 25–27, 30–32, and 40–42 during NP-CPB; and 10 min after the onset of systemic rewarming. Each segment was analyzed with respect to changes in overall values (time–domain analysis), as well as for the development of organized oscillatory activity (approximate entropy determination and frequency–domain analysis).

Analysis in the Time–Domain. For each measured variable (MAP, $LDF_{forehead}$, LDF_{finger}, and t°C), the instantaneous values within each study segment were averaged to obtain one data point per segment. From these, ensemble mean ± SE across the eight subjects was subsequently calculated, resulting in an overall time series for each variable.

Analysis of Oscillatory Activity.

Approximate Entropy. A model-independent statistic quantifying regularity (orderliness) in serial data were computed for each study segment as the logarithmic likelihood that patterns in the continuous laser Doppler waveforms that were similar remained similar on subsequent incremental comparisons.[20,21] This was accomplished with a custom-made C program, following a previously described algorithm[21] that used the length of the epoch (N), the number of previous values used for the prediction of the subsequent value (m), and a filtering level (r). The noise filter (r) was normalized to the SD of the N amplitude values. For each study segment, we used m = 2, r = 20% of the SD of the amplitude values, and N = 900, because theoretical considerations suggested these parameters as optimal.[20,21] The first 3 min of NP-CPB were not included in analysis due to the wide fluctuations in LDF. Average values across the eight subjects were subsequently calculated for each study segment.

Analysis in the Frequency Domain. The frequency and spectral power of LDF and MAP oscillations were characterized for each study segment by auto power spectral density (APSD) analysis, using a Parzen window with a frequency resolution of 0.005 Hz. The mean value of the signal was subtracted from each time point to eliminate its influence on the APSD.[22] Power spectra

were separated into LF (0.04–0.10 Hz) and HF (> 0.10 Hz) bands. The spectral power in each frequency band was calculated by integrating the area under the APSD curve and was expressed in normalized units (NU), which represented the ratio (in percent) of each power component to total spectral power, to minimize the effect of changes in total power on assessments of LF and HF power.[8,22] When oscillatory activity occurred simultaneously in $LDF_{forehead}$, LDF_{finger}, or MAP, we computed the cross-power spectra, coherence function, and phase spectra to assess the power interchanged and the phase delays between pairs of signals, as previously described.[10] All frequency–domain analyses were performed using commercially available software (SnapMaster v3.02, HEM Data Corp.).

Statistical Analysis

Data were expressed as mean ± SEM. Changes from baseline in $LDF_{forehead}$, LDF_{finger}, MAP, SVR, t°C, as well as in the $APSD_{MAP}$, $APSD_{forehead}$, and $APSD_{finger}$ were tested by H-test (Kruskall-Wallis); $P < 0.05$ was considered statistically significant. As previously recommended,[23] if one or more time– or frequency–domain indices for a given analysis had a highly skewed distribution (*i.e.*, skewness coefficient ≥ 1.00), logarithmic transformation of these indices was performed to provide an approximately normal distribution for the purpose of statistical analysis.

Both univariate and multivariate generalized estimating equations (GEE) were constructed using LDF and APSD as dependent variables and MAP, SVR, t°C, and hematocrit as covariates (using SAS v.8; SAS Institute, Cary, NC), with $P < 0.05$ accepted as statistically significant. The GEE method takes into account the potential correlation among measurements in the same subject between time points by estimating the covariance structure of the data and adjusting the significance levels accordingly. This provides greater power to find an effect in studies with relatively large numbers of observations per subject.[24] Since LDF, APSD, and all independent variables were highly correlated with time, the multivariate GEE analysis excluded time as a covariate to avoid redundancy.

Results

Onset of NP-CPB consistently resulted in a transient increase in $LDF_{forehead}$ (mean, 4 min; range, 3.5–5 min), followed by a decrease to approximately 50% below baseline values for the remainder of the NP-CPB period (fig. 1A). Conversely, LDF_{finger} remained near baseline during NP-CPB (fig. 1B). The time courses of simultaneously recorded hemodynamic variables (MAP, SVR) and t°C are displayed in figures 1C and D. By univariate GEE analysis, $LDF_{forehead}$ was inversely correlated to MAP ($P = 0.004$) and SVR ($P = 0.002$), directly correlated to t°C ($P = 0.09$), and not correlated to hematocrit. In con-

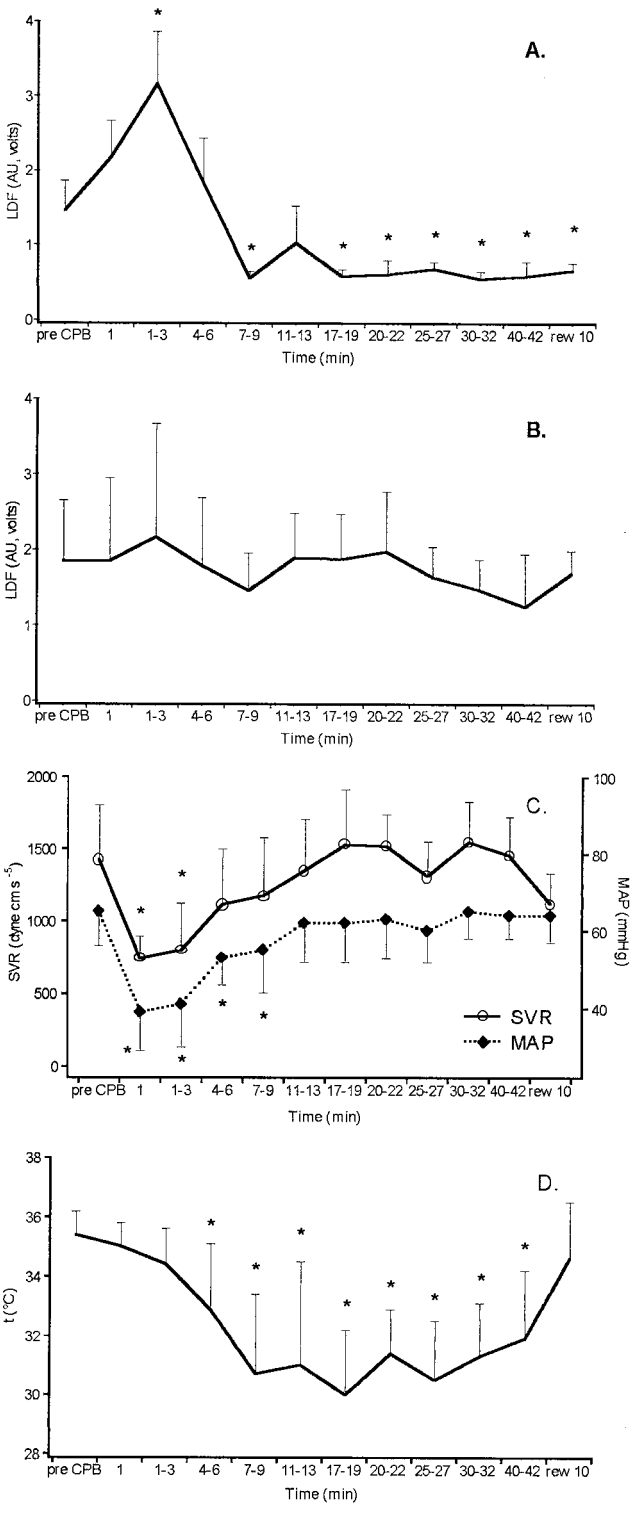

Fig. 1. Time courses of changes in (*A*) forehead skin blood flow ($LDF_{forehead}$), (*B*) finger skin blood flow (LDF_{finger}), (*C*) mean arterial pressure (MAP) and systemic vascular resistance (SVR), and (*D*) core temperature (t) before and during standardized intervals of nonpulsatile cardiopulmonary bypass. Values shown as mean ± SEM. *$P < 0.05$. AU = absolute laser Doppler units (in volts); rew 10 = 10 min after the onset of systemic rewarming.

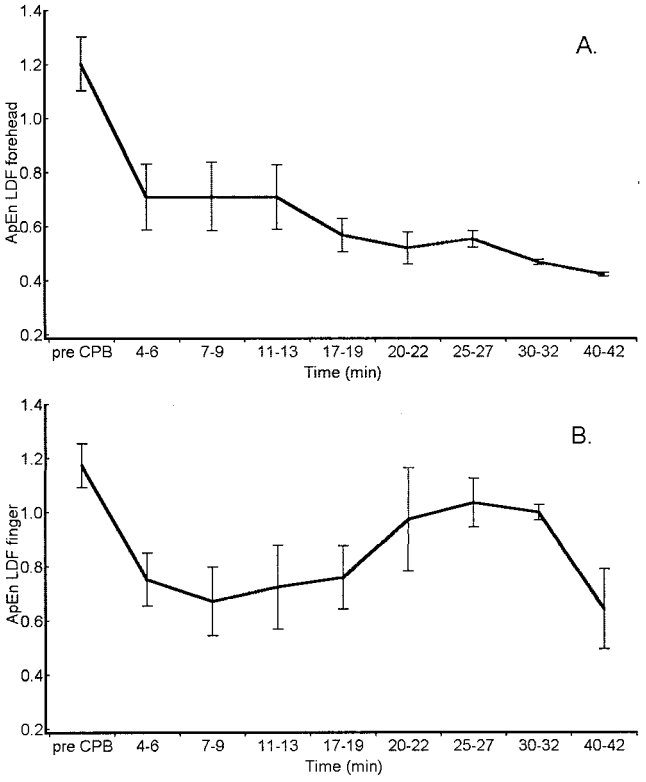

Fig. 2. Changes (mean ± SEM) in approximate entropy (ApEn) of (*A*) forehead skin blood flow ($LDF_{forehead}$) and (*B*) finger skin blood flow (LDF_{finger}) in all subjects during nonpulsatile cardiopulmonary bypass. $LDF_{forehead}$ signal regularity progressively increases during nonpulsatile cardiopulmonary bypass as measured by a decrease in approximate entropy.

trast, univariate models for LDF_{finger} were nonsignificant for all of the aforementioned independent variables.

The average approximate entropy of $LDF_{forehead}$ signal was significantly reduced during NP-CPB, from 1.2 at baseline (pre-CPB) to less than 0.5 after 40 min of NP-CPB (fig. 2A; $P < 0.001$ by univariate GEE model). The increase in regularity, as reflected by a decrease in approximate entropy, occurred early and persisted throughout the measurement period. On average, approximate entropy of $LDF_{forehead}$ decreased by 0.17 units for every 10 min during NP-CPB. In contrast, the average approximate entropy of LDF_{finger}, after an initial decrease, showed an upward trend during much of NP-CPB (fig. 2B).

Although short epochs of regular activity alternating with highly irregular ones were present in the $LDF_{forehead}$ during the baseline period (pre-CPB), the increased regularity of $LDF_{forehead}$ with NP-CPB was associated with visible self-sustained oscillations (fig. 3A) in all eight subjects, with a median onset time of 5.25 min (range, 4.5–16 min). Power spectral analysis identified the frequency of forehead flow oscillations at 0.13 ± 0.03 Hz (within the HF band; fig. 3B).

Finger skin blood flow displayed oscillatory variations in only five of eight patients (fig. 3C). These occurred in the LF band, with a median frequency centered at 0.07 Hz (range, 0.04–0.09 Hz; fig. 3D). Simultaneously recorded MAP was nonoscillatory, characteristic for NP-CPB (figs. 3E and F).

During NP-CPB, $APSD_{forehead}$ showed a progressive gain of spectral power in the HF band, from 17.5 NU in the first minute after NP-CPB onset to 89.1 NU after 40 min of NP-CPB (fig. 4A). Univariate GEE models for HF power in the $APSD_{forehead}$ confirmed direct associations with MAP ($P < 0.001$) and SVR ($P < 0.001$) and inverse associations with $LDF_{forehead}$ ($P < 0.001$) and t°C ($P = 0.002$). In the multivariate model, all of these covariates retained their significance. No association was found between $APSD_{forehead}$ and hematocrit.

There were no statistically significant changes during NP-CPB in the LF spectral power of $APSD_{finger}$ (fig. 4B). Univariate GEE analysis for LF power in the $APSD_{finger}$ identified a direct association with t°C ($P = 0.05$), inverse associations with LDF_{finger} ($P < 0.001$), MAP ($P < 0.001$), and SVR ($P = 0.04$), and no association with hematocrit. In a multivariate model, only the relation with LDF_{finger} and MAP remained significant.

No relation could be established between the amplitude and the frequency of spontaneous LDF oscillations at the forehead and finger sites. Whenever simultaneous oscillations in $LDF_{forehead}$ (fig. 5A) and either LDF_{finger} (fig. 5B) or MAP (fig. 5C) were detected, cross-spectral

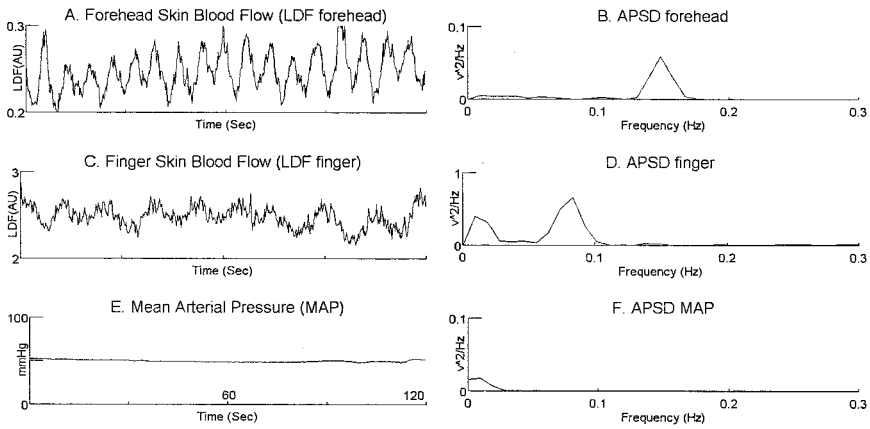

Fig. 3. Simultaneous 2-min recordings during nonpulsatile cardiopulmonary bypass (minutes 11–13) in a representative subject: (*A*) forehead skin blood flow ($LDF_{forehead}$), (*C*) finger skin blood flow (LDF_{finger}), and (*E*) mean arterial pressure (MAP); (*B*, *D*, *F*) their respective associated auto power spectral densities (APSDs). Note different fundamental oscillatory frequencies in the forehead (0.15 Hz) and finger (0.07 Hz) microvasculature during systemic nonpulsatile flow.

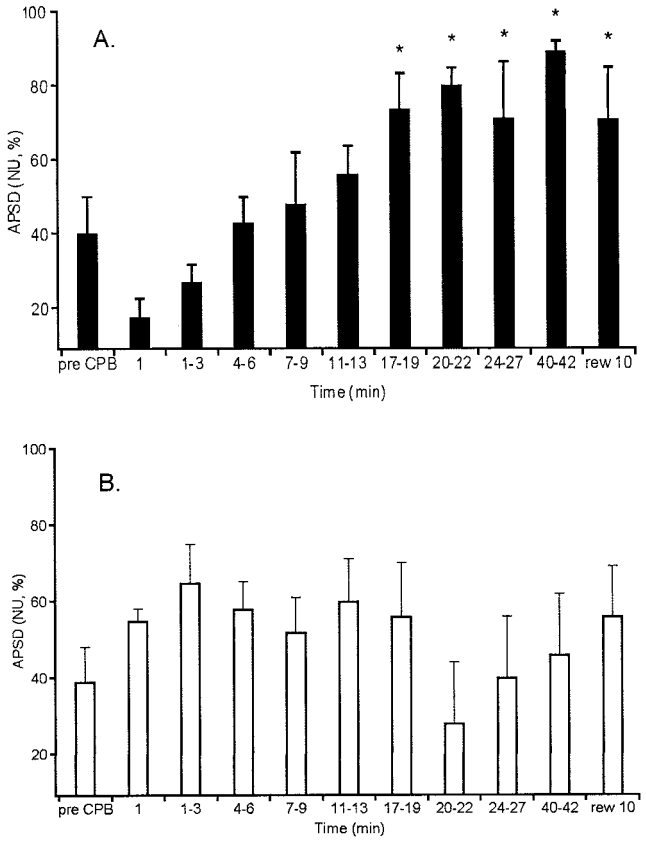

Fig. 4. Progressive changes (mean ± SEM) in (*A*) forehead auto power spectral density ($APSD_{forehead}$) high-frequency (HF) band power and (*B*) finger auto power spectral density ($APSD_{finger}$) low-frequency (LF) band power during nonpulsatile cardiopulmonary bypass. Values reported in normalized units (NU) obtained by expressing power in the LF and HF bands as percentage of total power in the 0.04–0.30 Hz range; *$P < 0.05$.

analysis confirmed the independence of HF band oscillations in the $LDF_{forehead}$ (fig. 5D). In contrast, when present, LF oscillations in LDF_{finger} and in MAP were highly coherent, with a positive phase lag (*i.e.*, LDF leading MAP) of $\pi/6$ rad, suggestive of peripheral (microvascular) origin with upstream transmission (figs. 5E and F).

Discussion

The cutaneous microcirculatory network, like other body tissues, exhibits spontaneous oscillations in diameter and flow (vasomotion) ranging from periodic, nearly sinusoidal, to highly irregular, chaotic patterns.[25,26] Although well documented for more than half a century, the origin, fundamental mechanisms, and significance of these fluctuations remain debated, with some researchers hypothesizing that skin blood flow is exclusively under local control[27–29] and others suggesting both central adjustments and baroreflex-induced changes.[16,30,31] Traditionally, autonomic neural responses at the microvascular level have almost exclusively been attributed to adrenergic pathways, resulting in oscillations with sympathetic frequency response characteristics (*i.e.*, VLF and LF bands); analysis of oscillations in the HF range typically has been confounded by variability in other cardiovascular signals, which often are synchronous with respiration-induced changes in heart rate, stroke volume, and blood pressure.[7–10]

The current study is the first to document the development of HF oscillatory activity in the microvasculature in the absence of cardiac contractions and respiration. Furthermore, the increasingly regular oscillations (at 0.13 ± 0.03 Hz) in the forehead microcirculatory flow were independent of oscillations in LDF_{finger} or MAP. Prior studies have identified the emergence of oscillations in systemic arterial pressure in the absence of natural heartbeat in experimental animals[32–34] and humans,[35,36] referred to as vasomotor waves or idiopheral pulsations. These oscillations always have been in the VLF and LF range and have been attributed to baroreceptor-induced variations in sympathetically mediated vascular resistance.[32–36] The current documentation of LF oscillations in the microvasculature of a region with rich adrenergic innervation (finger) is consistent with these previous studies that focused on arterial pressure. However, the identification of HF oscillations has not previously been reported in the absence of cardiac and respiratory factors. Their presence supports our hypoth-

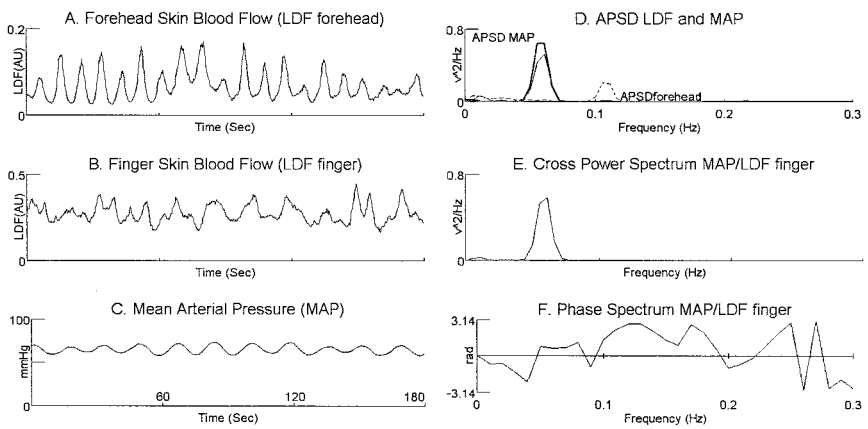

Fig. 5. Simultaneous 3-min recordings of oscillations in (*A*) forehead skin blood flow ($LDF_{forehead}$), (*B*) finger skin blood flow (LDF_{finger}), and (*C*) mean arterial pressure (MAP) in a subject during nonpulsatile cardiopulmonary bypass (minutes 20–22). Associated auto power spectral densities (APSDs) (*D–F*) document high-frequency oscillations (at 0.12 Hz) in the $LDF_{forehead}$ (dotted line) and low-frequency oscillations (at 0.06 Hz) in MAP (thick line) and LDF_{finger} (thin line) signals. (*E*) Cross-spectral analysis reveals common power in the $APSD_{MAP}$ and $APSD_{finger}$ at 0.06 Hz, but no common power in the $APSD_{forehead}$ and the other signals in the high-frequency band. (*F*) Phase spectrum reveals that low-frequency oscillations in LDF_{finger} precede those in MAP with a $\pi/6$ rad (30°) phase lag.

esis as to their peripheral origin. In light of the confirmation that similar HF oscillations of the forehead microvasculature (0.14 ± 0.02 Hz) during systemic infusion of phenylephrine were abolished by atropine,[14,18] we propose that the comparable activity in the current investigation constitutes a mechanism of cholinergic oscillatory control at the level of the microvasculature.

Functional Significance of Oscillatory Control

In the absence of extrinsic control, vascular smooth muscle cells contract and relax independently, such that neighboring vessels typically oscillate out-of-phase, thus offsetting one another in the summated laser Doppler signal.[37,38] The emergence of periodic self-sustained oscillations suggests that the different oscillating microvessels are phase-locked by a control mechanism that causes an entire local microcirculatory network to oscillate in synchrony at a single frequency, thereby coordinating the fluctuations of the 10–60 capillaries in the 1-mm^3 sampling volume of the laser Doppler probe.[10,19] The different fundamental frequencies of the periodic oscillations observed in the two microvascular regions studied herein are consistent with the frequency response characteristics of the predominant autonomic supply to the respective region (*i.e.*, adrenergic for finger microvasculature, cholinergic for forehead microvasculature). It has been suggested that oscillatory perfusion may confer specific physiologic advantages over steady state flow.[26,37–39] Both theoretical and experimental models have suggested that the onset of periodic vasomotion results in an increase in the effective diameter of a single vessel.[26,39] Moreover, the impedance of a vessel whose diameter varies sinusoidally is lower than that of a constant-caliber vessel with the same average diameter.[39] Thus, consistent with Poiseuille's determination that changes in flow are proportional to the fourth power of the radius, the potential physiologic significance of rhythmical vasomotion include enhancement of microcirculatory flow and mass transport and promotion of lymphatic drainage.[26,37–39] Such phenomena would likely be beneficial during pathophysiologic conditions of compromised tissue perfusion. In addition to their development during NP-CPB described in this study, HF microvascular oscillations have been observed during clamping of a regional feeding artery,[40,41] in the rat cerebral cortex during norepinephrine infusion and hypoperfusion,[42] in the feline mesentery during vasoconstriction,[43] and in the human forehead microcirculation during systemic infusion of phenylephrine[14,18] and hyperventilation.[44]

Our data suggest that nonpulsatile perfusion was associated with different microvascular oscillatory responses, not only in terms of fundamental frequencies, but also in regularity of oscillatory behavior. LF oscillations in LDF_{finger} and MAP, as may be caused by baroreflex-mediated variations in sympathetic nerve activity,[32–36] were an inconsistent finding (in only five of the eight studied patients) and did not display increasingly regular patterns during NP-CPB. In contrast, there was a progressive increase in regularity of HF oscillations in the forehead in every patient, suggesting an active homeostatic control mechanism that becomes increasingly more efficient in synchronizing neighboring oscillating microvessels during NP-CPB. Here, a distinction needs to be made between regularity, which describes the recurrence of patterns within the LDF signal, and power spectra, which describe the relative magnitudes of oscillatory components. Therefore, increased regularity of a signal cannot be accounted for simply by an increase in the amplitude of the oscillations. In the case of forehead HF oscillations, both phenomena seem to occur during NP-CPB, as the decrease in approximate entropy is accompanied by a progressive gain in HF spectral power.

Nonpulsatile Perfusion, Autonomic Activity, and Microvascular Oscillations

Depulsation of the systemic circulation results in a progressive increase in sympathetic nerve activity[45,46] (due to suppression of baroreflex-mediated inhibition of the vasomotor center), leading to progressive arterial vasoconstriction and increase in SVR,[46,47] which was confirmed in the current study (fig. 1C). It is generally accepted that the pathophysiologic processes under nonpulsatile perfusion are primarily related to the behavior of the sympathetic pathways that regulate tissue perfusion. Using multivariate generalized estimating equations, we found increased SVR and decreased LDF to be independent predictors of HF spectral power gain in the forehead. This suggests that progressive increases in peripheral vascular resistance and altered local tissue perfusion are associated with the activation and progressive synchronization of HF oscillations in forehead microvascular flow. Toda *et al.*[46] studied the simultaneous changes in sympathetic nerve activity and regional blood flow to vital organs and found organ-specific responses to nonpulsatile perfusion, with a decrease in renal cortical blood flow (consistent with increased renal sympathetic nerve activity), but no change in cerebral and myocardial regional blood flow. They raised the possibility that efferent vagal activity may modulate regional blood flow to certain organs in the face of increased sympathetic activity, but prior to the current study this potential process had not been explored. We speculate that the emergence and progressive synchronization of cutaneous microvascular oscillations—in a region of cholinergic innervation (forehead), at a frequency associated with parasympathetic activity (0.10–0.18 Hz), and in response to a known activator of sympathetic activity (*i.e.*, nonpulsatile perfusion)—may represent a manifestation of the counterregulatory processes proposed by Toda and colleagues.[46]

Thus, the potential implications for the anesthesiologist are that monitoring microvascular oscillatory phenomena may more effectively identify states of altered tissue perfusion and, perhaps more importantly, may identify a patient's ability to adapt to such alterations. Understanding and better characterizing these oscillatory control mechanisms may lead to therapeutic interventions designed to reduce end-organ injury following procedures requiring extracorporeal nonpulsatile perfusion and provide physiologic basis for the long-term function of nonpulsatile ventricular assist devices. Further studies are required to assess to what extent the changes observed in the forehead are reflective of other cholinergically innervated microvascular beds (*e.g.*, cerebral, coronary). However, in a porcine model of NP-CPB, Mutch *et al.* demonstrated that computer-controlled biologically variable pulsatile NP-CPB that incorporated HF oscillations in flow was associated with significant improvements in cerebral oxygenation when compared with NP-CPB[48] or conventional pulsatile CPB.[49] Their findings emphasize the impact that preservation of biologic variability in microvascular flow during NP-CPB may have on critical end-organ perfusion. This theoretically could be achieved either by applying external biologically variable pulsations or by monitoring and modulating the adaptive mechanisms proposed in the current study.

Study Limitations

Studies designed to assess the pathophysiologic effects of NP-CPB on microvascular control mechanisms should take into account the potential effects of pharmacologically induced alterations in vascular tone and of hemodilution on tissue perfusion. Although our study did not control for variations in the doses of vasoactive drugs during NP-CPB, this should not detract from the significance of confirming a peripheral etiology to HF microvascular oscillations, which was our primary hypothesis. Future studies designed to further investigate the potential significance of these oscillatory phenomena should be powered to allow corrections for such confounding variables.

We found no correlation between changes in hematocrit during NP-CPB and any of the time– or frequency–domain indices of cutaneous microvascular flow. This is in agreement with recent studies demonstrating that the linear relation between blood flow and blood velocity is not affected by changes in hematocrit in clinical ranges and can be explained by the Fahraeus-Lindquist effect.[50] In addition, by actually measuring the flux of erythrocytes, not plasma flow, LDF is a hematocrit-independent measure of tissue perfusion within clinical ranges.[19]

In conclusion, the current documentation of HF microvascular oscillatory control during NP-CPB confirms that HF oscillations in the microvasculature may arise independently of cardiac or respiratory activity. The dynamic changes in synchronization of forehead microvascular oscillations may represent a microvascular homeostatic mechanism in response to the increased sympathetic nerve activity that occurs during nonpulsatile perfusion.

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