Investigating the origin of cyclic changes in limb volume using mercury-in-silastic strain gauge plethysmography in man

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1. Vasomotion, a phenomen frequently observed in skeletal muscle microcirculation, has been observed under physiological conditions and found enhanced during critical reduction of tissue perfusion due to hypoxic hypoxia, haemorrhage and local hypotension. We used a computer assisted non-invasive plethysmographic method to investigate periodic changes of limb volume (volumotion), which we previously found in critically ill patients. The current study was designed to investigate the origin of volumotion.

2. Simultaneous recordings of limb circumference of both calves were obtained. In patients with peripheral vascular disease and patients with minor surgery the cross-correlation with spontaneous breathing was investigated. In patients who had undergone major abdominal or vascular surgery we analysed for cross-correlations between MSG plethysmography signals of both legs and changes in central venous, arterial and ventilation pressures. In this group the effects of positive-pressure ventilation and positive end-expiratory pressure (PEEP) were also studied.

3. No ventilation-related volumotion was observed during spontaneous breathing. During positive-pressure ventilation a ventilation-related peak was found in the Fourier transform in agreement with the ventilation frequency applied. The amplitude of ventilation-related volumotion decreased significantly after a pressure cuff applied to the thigh was inflated above central venous pressure. We observed a significant increase in the amplitude of ventilation-related volumotion when PEEP was applied.

4. Ventilation-related volumotion showed significant cross-correlation between both legs. Slow wave volumotion (0·5–7 cycles min^{-1}) was frequently observed, but always appeared unilaterally. Whilst we looked for correlations between slow wave volumotion and changes in central venous pressure and arterial blood pressure, respectively, significant cross-correlation with the MSG plethysmography recordings was only observed at the frequency of the positive-pressure ventilation.

5. The fact that periodic changes of limb circumference matching the frequency of the positive-pressure ventilation were detectable with the MSG plethysmography system demonstrates that small volume changes (less than 0·02 ml (100 ml tissue)$^{-1}$) can be assessed using this system. As slow wave volumotion was observed unilaterally and revealed no correlation either with breathing, ventilation or arterial and central venous pressure, we suggest that slow wave volumotion is a local event most likely reflecting arteriolar vasomotion.

The microcirculation plays a key role in the pathophysiology of many illnesses, such as septic and haemorrhagic shock or ischaemia reperfusion injury, yet it remains very difficult to detect and quantify pathological microcirculatory changes in patients (Messmer & Kreimeier, 1989; Shoemaker, 1991). We recently developed a modification of the mercury-in-silastic strain gauge plethysmography (MSG) technique first described by Whitney (1953) for investigating microcirculatory parameters (Gamble, Gartside & Christ, 1993). MSG plethysmography also allows a non-invasive

continuous recording of limb circumference. Since 1988 we have performed venous occlusion plethysmographic studies on patients in the operating room, in intensive care units (ICU) as well as control studies on healthy young people, to quantify changes of capillary permeability and isovolumetric venous pressure (Christ, Gartside, Kox & Gamble, 1991*b*; Gamble *et al.* 1993). First observations of cyclic fluctuations in limb volume were made in a critically ill patient after a significant drop of cardiac index from 7·1 to 1·7 l min^{-1} m^{-2}, a value known to severely impair tissue survival (Muller, Laughlin & Myers, 1993). As a result of this observation we developed techniques to look for similar activity in other ICU patients using autocorrelation functions and Fourier analysis. The changes occurred with a periodicity ranging from 1·0 to 20·0 cycles min^{-1}. Similar frequencies of periodic events have been described in the microcirculation for changes of microvascular diameter, known as arteriolar vasomotion (Johnson, 1980; Intaglietta, 1991). We termed the periodic changes detected with the plethysmographic method volumotion, because they represent alterations in limb volume (Christ *et al.* 1991*b*). The physiological and pathophysiological function of arteriolar vasomotion has been stressed by many authors (Intaglietta, 1989, 1991; Oude Vrielink, Slaaf, Tangelder, Weijmer, van Velzen & Reneman, 1990; Gustafsson, Wardell, Nilsson & Lewis, 1991; Schmidt, Intaglietta & Borgstrom, 1992; Bouskela & Grampp, 1992; Allegra, Intaglietta & Messmer, 1993). It may be a key factor in local control of perfusion and tissue oxygenation and is known to increase during impaired microvascular perfusion caused by haemorrhage, local hypotension and hypoxic hypoxia (Intaglietta, 1991; Gustafsson *et al.* 1991; Bertuglia *et al.* 1991). We suspected that volumotion originates from arteriolar vasomotion in the limb. A retrospective analysis of studies on control patients performed over the past 5 years (> 300 subjects) revealed cyclic changes in limb circumference in approximately 10% of all healthy subjects. In a preliminary publication we have reported an increase in slow wave volumotion (1·0–7·0 cycles min^{-1}) of critically ill patients which coincided with low cardiac index and low oxygen delivery. We concluded that volumotion is enhanced when peripheral tissue perfusion is rendered critically impaired and that the MSG plethysmography technique may be useful for monitoring changes in microvascular perfusion (Christ *et al.* 1991*b*).

In this paper we outline the analysis system that allows qualitative and quantitative assessment of volumotion. We report on cross-correlations between volumotion and other cyclic events like spontaneous breathing, positive-pressure ventilation, heart rate and arterial and central venous pressure.

METHODS

A detailed description of the MSG plethysmography method for the assessment of peripheral vascular events, including arterial inflow, limb venous pressure, net microvascular fluid exchange (filtration coefficient, K_f) and isovolumetric venous pressure (P_{vi}) has been published elsewhere (Gamble *et al.* 1993). Here we outline only the mathematical procedures used for analysis of volumotion and the procedure for quantification of volumotion.

MSG plethysmography recording and analysis of volumotion

All patients studied lay supine for at least 30 min prior to the recording. To reduce possible artifacts due to involuntary movements, we placed the limbs into a vacuum mattress, which supported the leg laterally, leaving the calf, including the area of the strain gauge, completely free. All conscious subjects were asked to remain as still as possible during the recording and to refrain from talking. No interventions other than slow continuous infusion of drugs (e.g. Midazolam, Fentanyl, Dopamin or potassium chloride) were allowed. Initially limb circumference was determined using a tape measure and skin temperature was recorded. Each strain gauge was calibrated after it was placed around the limb and a standard pre-tension applied (Whitney, 1953; Gamble *et al.* 1993). The signals were sampled and digitized at a frequency of 1 Hz using an analog-to-digital convertor card (Amplicon PC26AT; Amplicon Lifeline, Brighton, UK) in an IBM compatible computer (Fig. 1).

The signals had been filtered using a low-pass filter with a 6 dB octave slope to prevent aliassing, prior to digitization. Separate channels allowed sampling of arterial, central venous and airway pressure. We analysed 256 s segments of recordings as follows (Fig. 2*A*). (1) Initially, any linear trends were removed and the data were windowed with a tapering Hanning window to eliminate square wave noise. A Fourier transform was performed on the data and the amplitude spectrum was constructed from 0·004 Hz (0·24 cycles min^{-1}) to 0·5 Hz (30·0 cycles min^{-1}) (Fig. 2*C*). The Fourier transform does not allow the causes of the phenomena in the frequency spectrum to be elucidated. Peaks could be due to continuous cyclic activity, random fluctuations, or singular events. (2) Autocorrelograms were computed for time shifts from −60 to +60 s in 1 s steps (Fig. 2*B*). A sustained cyclic autocorrelogram indicates a true periodic fluctuation, whilst a flat autocorrelogram reflects random fluctuations in the original record. A large rapidly decaying autocorrelogram is caused by single events in the original recording. (3) Phase space plots of the data (Y) at time t were constructed at a time delay corresponding to the first zero crossing ($t + x$) in the autocorrelogram (Fig. 2*D*). These allowed further investigation of the events shown in the amplitude spectrum; regular cyclic phenomena appeared as loops, whereas 'noise' is depicted as a random distribution. (4) Cross-correlograms between either MSG plethysmography recordings of both legs, or between MSG plethysmography recordings and central venous and arterial blood pressure as well as airway pressure were also computed, again for time shifts from −60 to +60 s (Fig. 3).

The 95% confidence interval for the changes observed were displayed on the computer screen, which allowed us to determine if the cross-correlation between the cyclical events present in both recordings was significant.

Table 1. Demographic data and haemodynamic parameters for the cross-correlation studies between MSG recordings and the listed parameters

Cross-correlation	Age (years)	CVP (cmH_2O)	Syst. RR (mmHg)	Diast. RR (mmHg)	Patients	Observations	Female (*n*)
Ventilation	62·3 (45–84)	11·0 (5–15)	150·0 (100–200)	77·4 (50–90)	17/17	30	6
PEEP	62·3 (45–84)	11·0 (7–15)	150·0 (100–200)	77·4 (50–90)	17/17	23	6
ABP	69·0 (57–84)	11·4 (7–15)	155·9 (130–200)	80·0 (70–90)	12/17	24	4
CVP	68·0 (57–79)	11·5 (7–15)	155·0 (130–200)	82·2 (70–90)	11/17	22	4

The table depicts the demographic data of the patients where cross-correlation between MSG plethysomography records and positive-pressure ventilation, arterial (ABP) and central venous blood pressure (CVP) as well as the effects of PEEP were studied. Displayed are the mean values and the range (in parentheses), number of patients and number of observations analysed. Syst., systolic; Diast., diastolic.

Criteria for inclusion of MSG plethysmography recordings for volumotion analysis

(1) It was necessary for the 256 s of MSG plethysmography recording to be free of artifacts, noticeable as a sharp rise or fall in the curve. (2) No bolus injection of drugs or changes in ventilation and no intervention by the medical staff was allowed during the recording period, only the pre-exisiting continuous infusion of necessary drugs was continued. (3) The autocorrelogram had to reveal a truly periodic event and be present throughout the 256 s of recording.

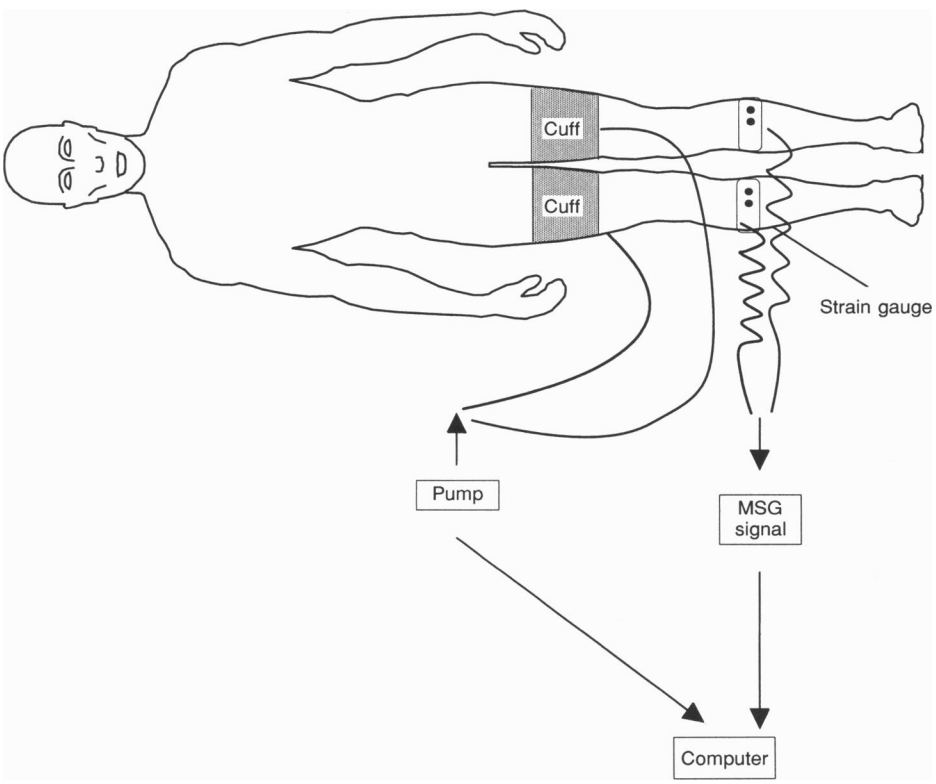

Figure 1. MSG plethysmography measuring device and protocol used

Patients lay supine for more than 30 min prior to the recording. Changes in limb volume were measured using a strain gauge placed around the calf, connected to a Wheatstone bridge and a low voltage circuit. An increase in limb volume resulted in a higher electrical resistance of the strain gauge and that signal was passed via an AD convertor card to an IBM compatible computer. A pressure cuff placed around the thigh and connected to a pump allowed manipulation of venous pressure in the limb. The changes in cuff pressure were also recorded by the MSG plethysmography analysis program.

Quantification of volumotion

To quantify the periodic changes in limb volume we used the frequency spectrum obtained from the Fourier analysis and the values derived from the calibration procedure. We measured the height of the amplitude for each peak observed and calculated the volume change in ml (100 ml tissue)$^{-1}$. An arbitrary unit, which we called summed amplitude (SA), was used when a calibration could not be performed (e.g. measurement of central venous pressure changes). This procedure allowed a quantitative comparison of the observed changes.

Patient studies

A summary of all demographic patient data is given in Table 1.

For all patient studies, written informed consent was obtained from either the patient or, if the patient was unconscious, the next of kin. The studies were authorized by the Ludwig Maximilians University of Munich local ethics committee and carried out on the basis of the Helsinki Declaration and the Good Clinical Practice Code.

Cross-correlation studies

It is known that both spontaneous breathing and positive-pressure ventilation cause changes of both central venous pressure and venous return to the heart resulting in periodic changes of cardiac output and blood pressure (Robotham & Takata, 1990). Therefore periodic changes of limb circumference could be due to ventilation frequency. We investigated this possibility in spontaneously breathing patients scheduled for either vascular surgery ($n = 34$) or minor surgery ($n = 16$) (215 observations were made on 50 subjects, 13 female, mean age 56·0 ± 2·3 years). MSG plethysmography measurements were taken simultaneously on both legs as described above and breathing rate was recorded. Two observations per recording were taken for each patient and most patients were studied more than once during a 5 day period. If possible, a breathing-related peak in the Fourier transform was identified and the volume change recorded. In a second step, cross-correlograms were computed between volumotion and spontaneous breathing.

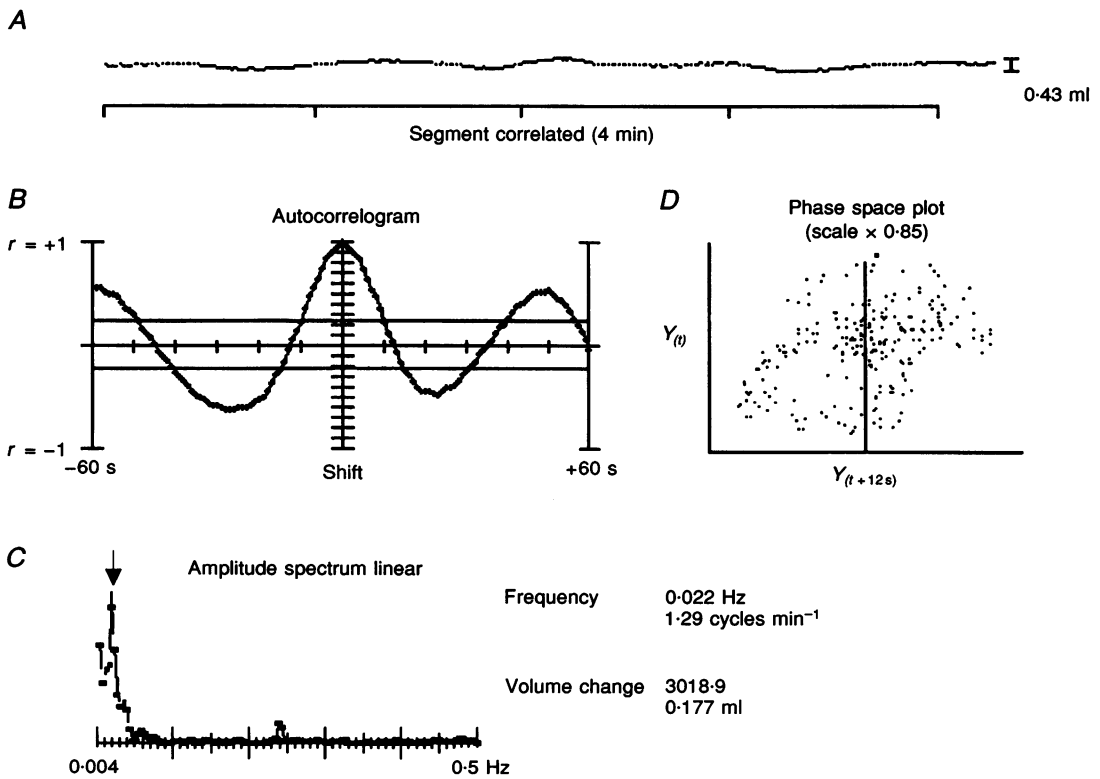

Figure 2. Volumotion analysis procedure for patient R. U.

MSG plethysmography recording for 4·25 min (*A*) were stripped of any linear trends before autocorrelations were computed (*B*). Any periodic events were readily visualized and the correlation coefficient displayed (*Y*-axis). Using Fourier analysis the amplitude spectrum was computed (*C*). With a cursor, represented by the arrow, the corresponding frequency at each discernable peak in the amplitude spectrum was identified and displayed on the right of the computer screen (0.022 Hz, 1·29 cycles min^{-1}). Calculating the height of each peak and using the calibration signal allowed the total volume change of the limb in ml (100 ml tissue)$^{-1}$, to be determined (0·177 ml). The volume change was also given in arbitary units (3018·9) which could be used when no calibration signal was available (e.g. arterial pressure signal). A positive-pressure ventilation-related peak can also been seen in the Fourier analysis at 14·2 cycles min. Finally, phase space plots (*D*) were calculated, which enabled further insight into the type of volumotion observed. The horizontal lines in *B* represent the 95% confidence intervals of the volumotion in this and other figures.

Correlation between volumotion and positive-pressure ventilation, arterial and central venous pressure

These studies were conducted in the intensive care unit (ICU) on seventeen patients after major abdominal surgery ($n = 7$), vascular surgery ($n = 5$) and thoracic surgery ($n = 5$). The demographic data of the patients is given in Table 1. Patients were mechanically ventilated with positive pressure via an endotracheal tube (ventilation frequency 0·15–0·33 Hz, 8·5–20·0 breaths min^{-1}) and analgo-sedated with a continuous infusion of Midazolam (3–10 mg h^{-1}) and Fentanyl (1·25–5·00 $\mu g\ kg^{-1}\ h^{-1}$); usually no muscle relaxant was given. Simultaneous recordings of circumference of both calves were obtained. Ventilation pressure was measured using a Statham transducer (SX 560418m, Medex Medical Inc., UK) connected to a Kontron monitor (Kontron Supermon 7210 003, Watford, UK) at the proximal outlet of the endotracheal tube, so that the correlation between ventilation and volumotion cycle could be investigated. We hypothesized that periodic changes of limb circumference could be attributed to the transmission of fluctuations of central venous pressure and/or cardiac output due to altered intrathoracic pressure. To investigate this hypothesis we used a venous occlusion cuff placed around the thigh. Initially, 8 min of MSG plethysmography recordings from both legs were obtained with leg cuff occlusion pressure (P_{cuff}) = 0 mmHg, followed by 8 min MSG plethysmography recordings while P_{cuff} was elevated above central venous pressure (P_{cuff} = 25 mmHg, mean CVP = 8·4 ± 1·1 mmHg) and 8 min with P_{cuff} at 55 mmHg. Using the Fourier analysis a ventilation-related volumotion frequency was identified. The corresponding volume change of the limb was calculated at 0, 25 and 55 mmHg cuff pressure. Twenty-four observations were made on nine patients (3 female; mean age 58·9 ± 4·6 years)

To study the effect of positive end-expiratory pressure (PEEP) on volumotion, a 10 min MSG plethysmography recording period without PEEP was followed by 10 min ventilation with 6 mmHg of PEEP using the PEEP mode of the Servo900C ventilator (Siemens, Munich, Germany). The amplitude of volumotion at the ventilation-related frequency was measured.

To investigate a possible cross-correlation between volumotion and arterial and central venous pressure we obtained MSG plethysmography recordings of both legs simultaneously with continuous measurements of (1) arterial pressure from an indwelling 20 g catheter in the radial artery and (2) central venous pressure measured with a 16 g central venous line, placed so that the tip was level with the right atrium (X-ray controlled). All pressure signals were recorded using a Statham transducer (Spectramed, Watford, UK) connected to a Kontron monitor (SuperMon 8046 Kontron, Watford, UK).

Statistical analysis

Values for mean and standard error of the mean (S.E.M.) were calculated. All data were tested for normal distribution using the Kolmogorov–Smirnov test with Lilliefors correction and equal variance was tested using Levene Median test. If no violations occurred Student's t test was applied to compare the mean values; if violations were detected the Wilcoxon signed rank test was performed. For correlation analysis the Pearson product moment correlation was used. Repeated measurements were analysed using the one-way ANOVA test. Significance was assumed at $P < 0·05$.

RESULTS

Two case reports are given below to illustrate the periodic changes in limb circumference that were observed.

Patient A. K.

A 64 year old man was admitted to the ICU after a severe head injury. No surgical treatment was possible and a

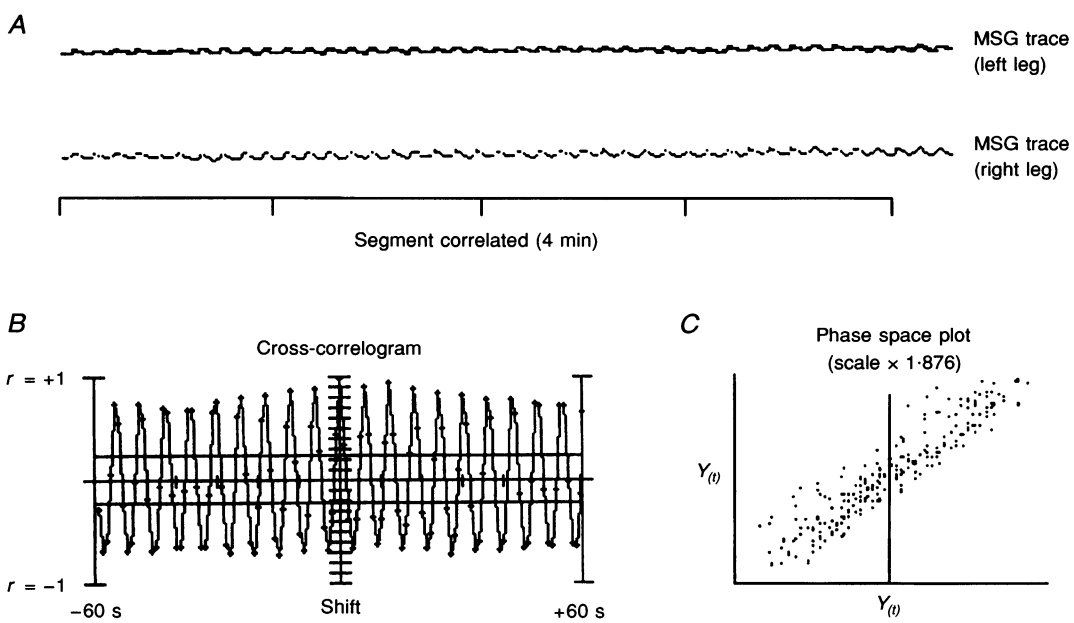

Figure 3. Cross-correlation analysis of two simultaneously recorded MSG-traces from the left and the right calf

The horizontal lines in *B* represent the 95% confidence intervals of the volumotion, which in this case is caused by positive-pressure ventilation.

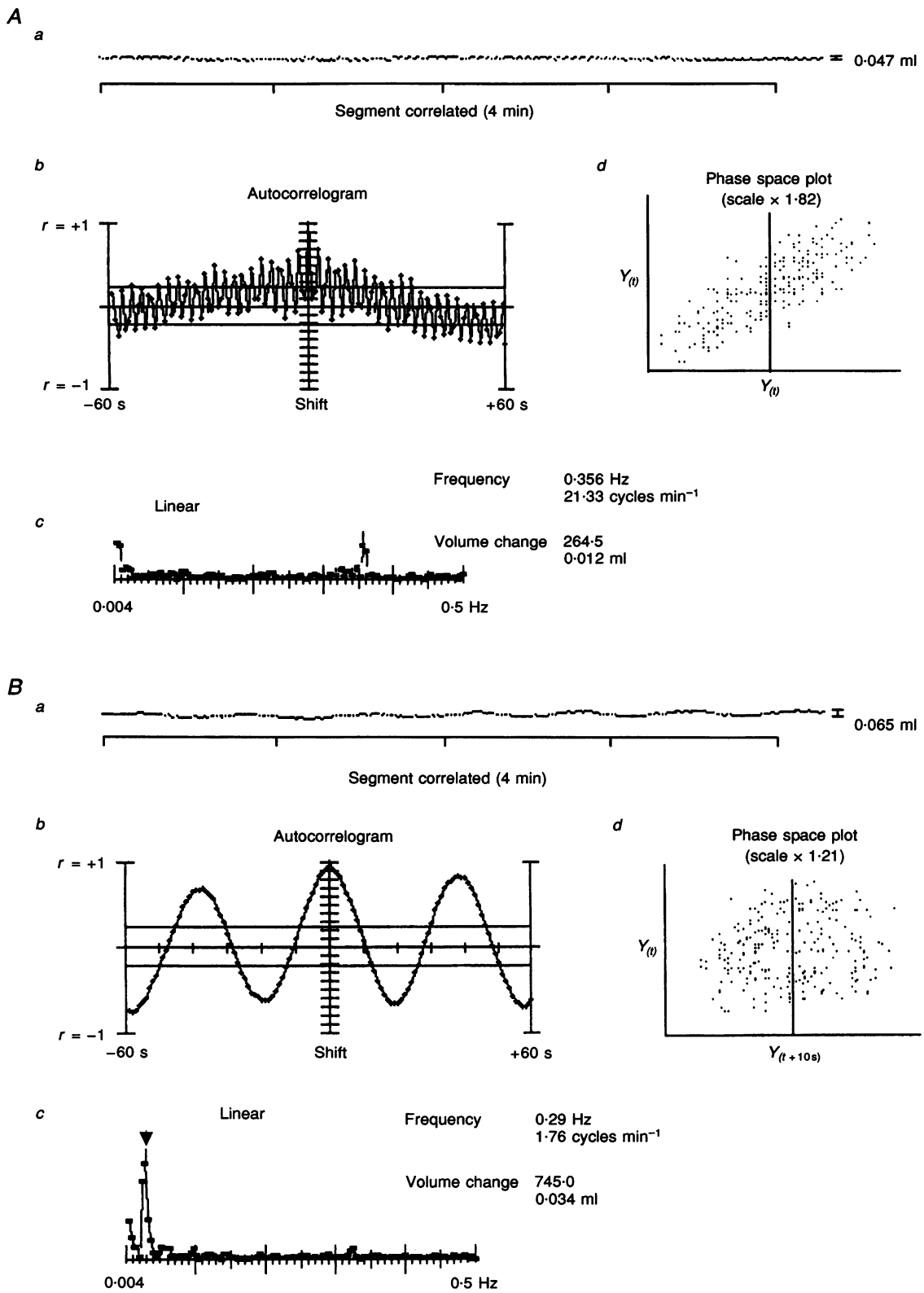

Figure 4. Volumotion analysis procedure for patient A. K.

This depicts the first MSG plethysmography recording with the corresponding Fourier analysis of a critically ill patient (*A*), while haemodynamic parameters were in the normal range (see also Table 1). *B* illustrates the changes in the MSG plethysmography trace after a drop of CI from 7·57 to 1·3 l min^{-1} m^{-2} with the corresponding Fourier analysis. The regular periodic changes in limb circumference are readily visualized. See Fig. 2 for details.

Table 2. The haemodynamic parameters of patient A. K.

Measurement	1	2	3
MABP (mmHg)	91	60	47
CVP (mmHg)	13·3	16·3	16·3
PCWP (mmHg)	15	20	20
CI (l min^{-1} m^{-2})	7·6	1·7	1·3
$D_{O_2}I$ (ml min^{-1} m^{-2})	973	158	130
$\dot{V}_{O_2}I$ (ml min^{-1} m^{-2})	138	84	76
O_2 extraction (%)	14	53	58
SVRI (dyne s^{-5} cm m^{-2})	813	2041	1809
Dobutamine (μg min^{-1} kg^{-1})	30	0	0

PCWP, pulmonary capillary wedge pressure; CI, cardiac index; $D_{O_2}I$, $D_{O_2\ index}$; $\dot{V}_{O_2}I$, $\dot{V}_{O_2}$ index; SVRI, systemic vascular resistance index.

subdural pressure probe was inserted to monitor intracranial pressure (ICP). A continuous infusion of Dobutamine (up to 30 μg min^{-1} kg^{-1}; Lilly Deutschland GmbH, Bad Homburg, Germany) was administered to raise the patients low cardiac output and low mean arterial blood pressure (MABP) and to increase cerebral perfusion pressure. Initially, the patient was sedated with a continuous infusion of Midazolam (Hoffmann-La Roche AG, Grenzbach-Wyhlen, Germany) and Alfentanil (Janssen GmbH, Neuss, Germany), paralysed with Atracurium (Wellcome GmbH, Burgwedel, Germany) and ventilated with positive pressure. After 24 h in the ICU further treatment was withdrawn due to the unfavourable prognosis of the intracranial lesion and only ventilation and intravenous fluid therapy were maintained. One MSG plethysmography measurement was taken before, and two further measurements were taken 1 and 2 h after withdrawal of treatment. Table 2 shows the haemodynamic parameters of the patient at these stages.

The onset of periodic changes in limb circumference coincided with the drop in CI. Fourier analysis of the MSG plethysmography traces revealed four distinct peaks in the amplitude spectrum of the second and third recording; no such events were discernible in the first record (Fig. 4 and Table 3).

Whilst the frequency of peak 4 correlated with the ventilation frequency of 19·5 breaths min^{-1} (Table 3), the origin of the other peaks remained unclear.

Patient R. U.

A 63 year old male with peripheral arterial occlusive disease (grade IIb, Fontaine classification) received a cross-over bypass from the left to the right femoral artery. The measurements were taken at the 6th postoperative day, while the patient was sedated with Midazolam and Fentanyl, paralysed with Pancuronium and ventilated via an endotracheal tube (CMV, 14 breaths min^{-1}). During the measurement the patient had an arterial blood pressure of 140/80 mmHg, a heart rate of 100 beats min^{-1}, CVP was 6·7 mmHg and no PEEP was applied. Figure 2 shows the original MSG plethysmography recording and its Fourier analysis. It reveals that the volumotion was slow (1·29 cycles min^{-1}) and limited to the leg that had received the cross-over bypass 6 days before.

Cross-correlation studies

Volumotion and spontaneous breathing

We could not identify any distinct peaks in the Fourier transform relating to spontaneous breathing in 215 observations made on 50 patients.

Volumotion and positive-pressure ventilation

We observed a significant cross-correlation between volumotion and ventilation at the ventilators frequency in all patients (Table 1 for other haemodynamic parameters). The amplitude spectrum of the MSG plethysmography recording showed a ventilation-related peak between 0·15 and 0·33 Hz corresponding to the ventilation frequency used (Fig. 5).

Table 3. Fourier analysis of the MSG plethysmography traces in patient A. K.

Peak	Frequency (Hz)	Cycles (min^{-1})	Volume change (ml (100 ml tissue)$^{-1}$)
1	0·00391	0·2	0·015
2	0·0273	1·6	0·043
3	0·0586	3·5	0·009
4	0·3200	19·5	0·007

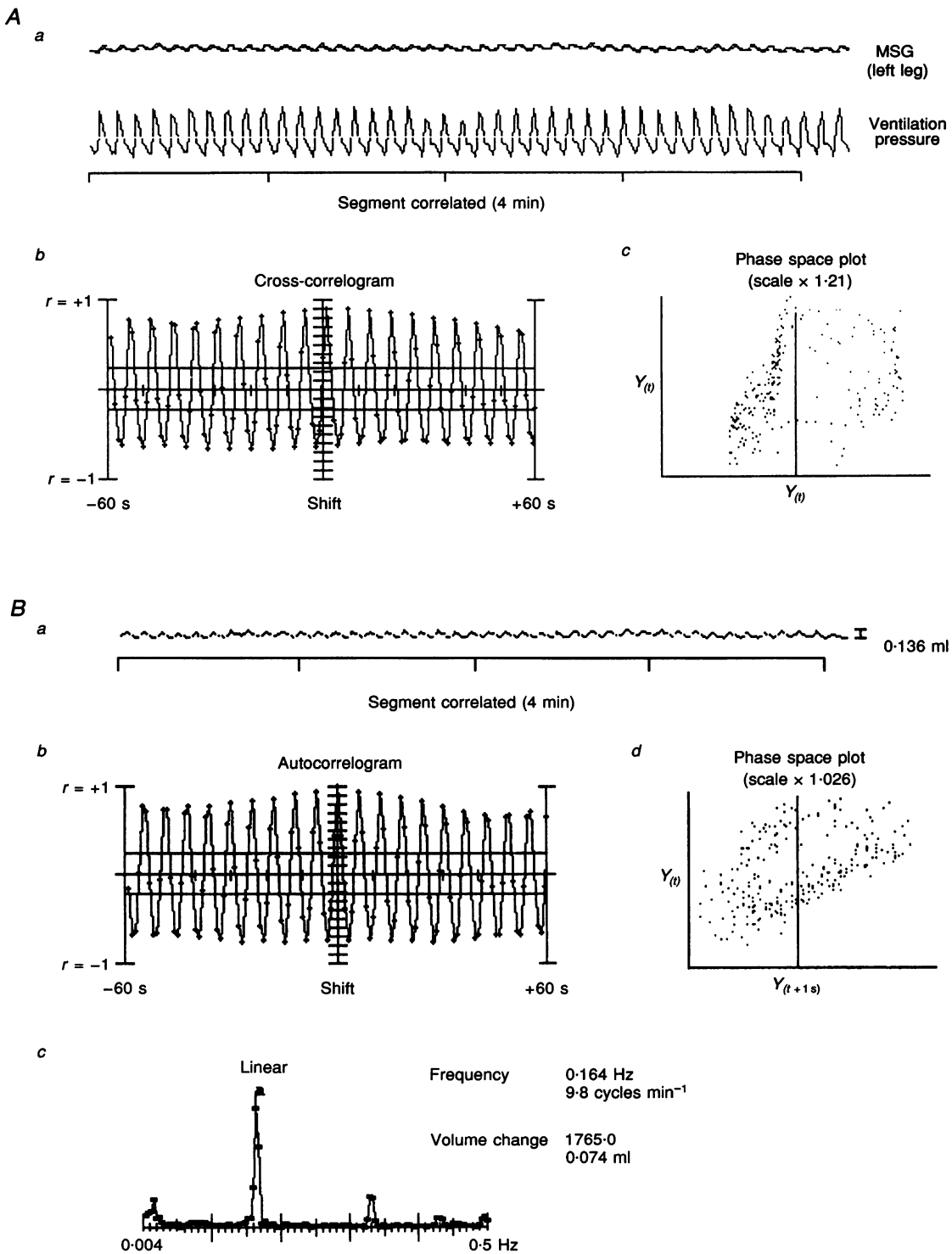

Figure 5. Cross- and autocorrelogram of ventilation-related volumotion

A shows the cross-correlogram of ventilation-related volumotion measured at the right calf and positive-pressure ventilation with 10 breaths min^{-1} (lower trace). The horizontal lines in *A b* and *B b* represent the 95% confidence intervals. The regular pattern is also demonstrated in the phase space plot where typical circles resulted. *B* shows the autocorrelogram of the ventilation-related volumotion. It can be seen that the volume change is 0·074 ml (100 ml tissue)$^{-1}$ and the peak in the Fourier transform is identical with the ventilators setting of ventilation rate.

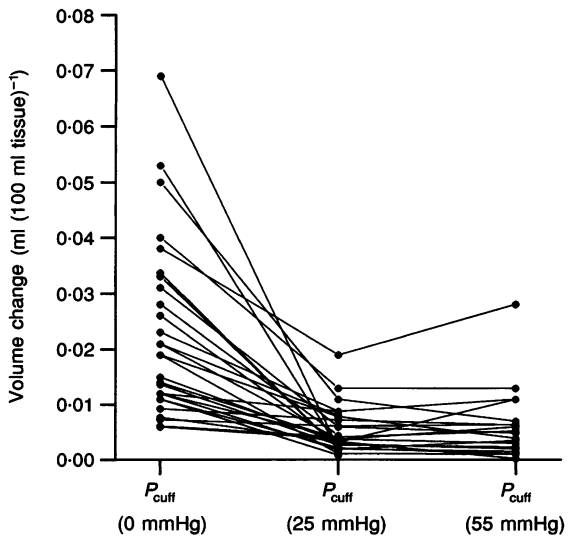

Figure 6. Changes in ventilation-related volumotion amplitude after inflation of a cuff placed around the thigh

A significant ($P < 0{\cdot}001$, one-way ANOVA) reduction in volumotion amplitude was observed when cuff pressure was 25 mmHg. A further increase in cuff pressure to 55 mmHg did not alter volumotion amplitude. All individual changes in the volumotion amplitude are displayed.

The mean volume change without cuff inflation was $0{\cdot}026 \pm 0{\cdot}004$ ml (100 ml tissue)$^{-1}$. Inflating a pressure cuff on the thigh to 25 mmHg caused a significant ($P < 0{\cdot}001$) decrease in the volume change to $0{\cdot}007 \pm 0{\cdot}002$ ml (100 ml tissue)$^{-1}$. A further increase of cuff pressure to 55 mmHg did not alter the amplitude of volumotion ($0{\cdot}006 \pm 0{\cdot}002$ ml (100 ml tissue)$^{-1}$) (Fig. 6).

In this group of patients the occlusion cuff pressure of 25 mmHg always exceeded CVP (mean $8{\cdot}4 \pm 1{\cdot}1$ mmHg).

Effect of PEEP on ventilation-related volumotion

The application of 6 mmHg PEEP resulted in a significant increase in the amplitude of the ventilation-related volumotion from $0{\cdot}005 \pm 0{\cdot}001$ to $0{\cdot}010 \pm 0{\cdot}002$ ml (100 ml tissue)$^{-1}$ ($P < 0{\cdot}001$); furthermore, Fig. 7 demonstrates that the patients with the greatest volume change before application of PEEP showed larger changes in ventilation-related volumotion after PEEP was added.

Volumotion and central venous pressure

Whilst we looked for correlation between slow wave volumotion and changes in CVP, significant cross-correlation between CVP and the MSG plethysmography recordings was only observed at the frequency of the ventilation-related peak (Fig. 8), which was present in all patients. No other cross-correlation was observed for the other volumotion frequencies encountered.

Volumotion and arterial pressure

We found a significant cross-correlation between ventilation-related volumotion and arterial pressure in all

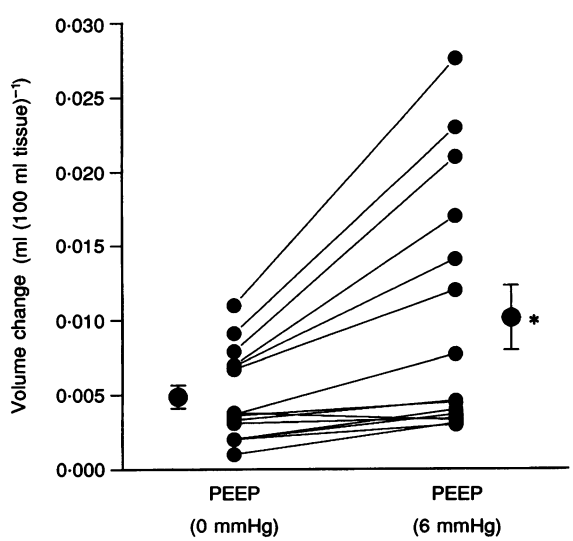

Figure 7. Significant increase in ventilation-related volumotion after addition of PEEP of 6 mmHg ($P < 0{\cdot}001$)

All individual changes and the means ± S.E.M. values of volumotion are displayed.

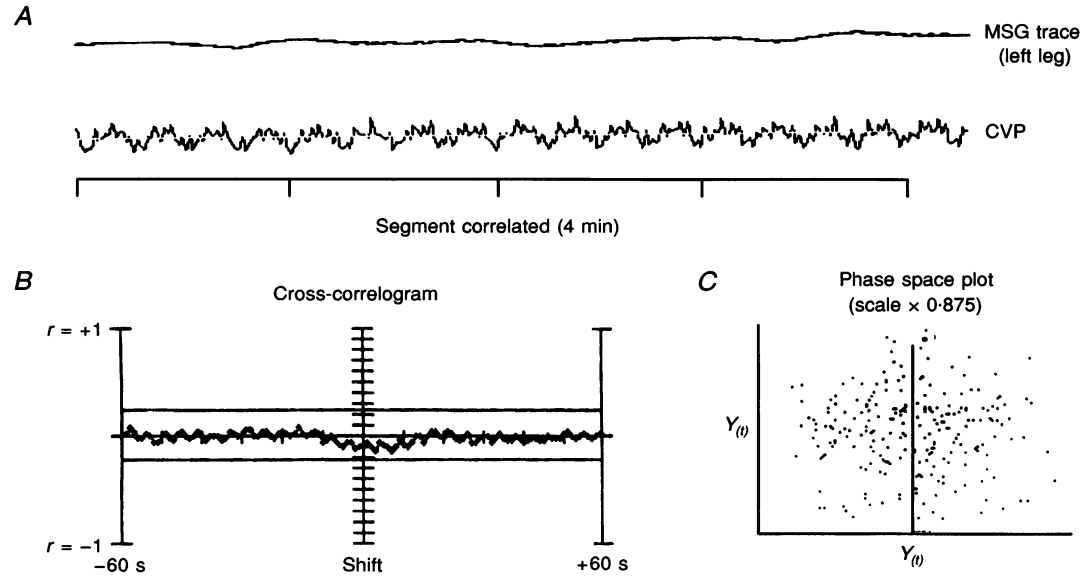

Figure 8. The cross-correlation between changes in central venous pressure (*A*) and volumotion in the leg (*B*) during positive-pressure ventilation

The horizontal lines in *B* represent the 95% confidence intervals of the periodic changes. No significant cross-correlation was observed.

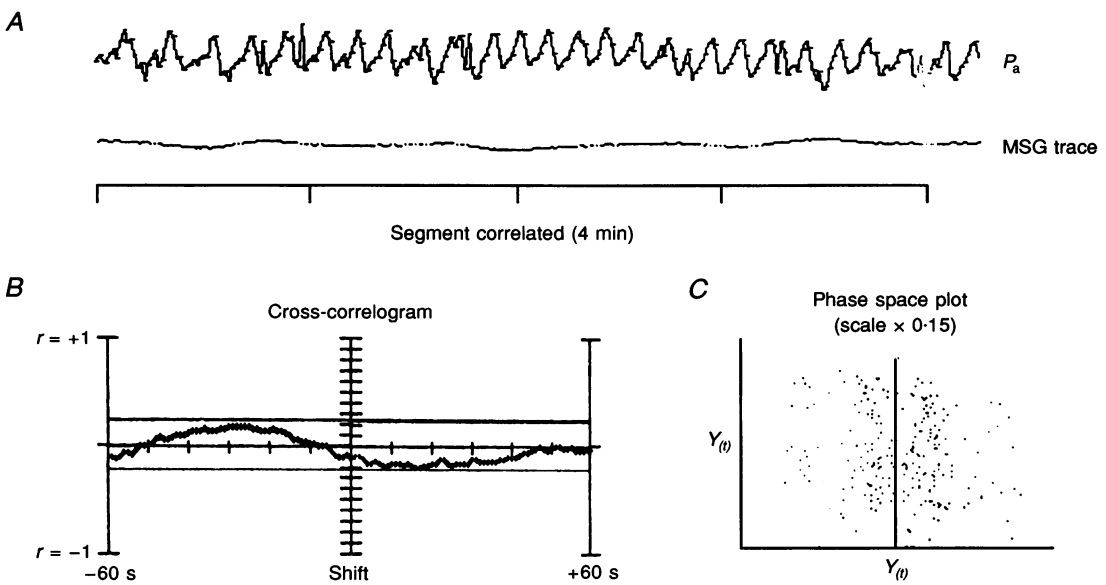

Figure 9. Cross-correlation between changes in arterial pressure (P_a) and volumotion in the leg (MSG trace) during positive-pressure ventilation

The horizontal lines in *B* represent the 95% confidence intervals of the periodic changes. No significant cross-correlation was observed.

twelve patients that we investigated. No other cross-correlation was observed at the remaining volumotion frequencies (Fig. 9).

DISCUSSION

We have observed periodic changes in limb circumference during a variety of physiological (Christ *et al.* 1994) and pathological conditions (Christ *et al.* 1991*a*,*b*) using a computer-assisted plethysmographic method. These events, which we termed volumotion, occurred with a periodicity ranging from 0·5 to 20·0 cycles min^{-1}. Here we report on periodic changes of limb circumference matching the frequency of positive-pressure ventilation (9·0–19·5 cycles min^{-1}). This conclusively demonstrates that, using the MSG plethysmography system, volume changes less than 0·02 ml (100 ml tissue)$^{-1}$ can be detected and that respiratory-related alterations in central venous pressure can influence peripheral tissue volume. We suggest that alterations in intrathoracic pressure are responsible for the ventilation-related volumotion. An increase in intrathoracic pressure during inspiration will reduce venous return to the heart and subsequently reduce cardiac output and possibly also arterial blood pressure (Robotham & Takata, 1990). This was confirmed by the cross-correlation studies, where we observed a good correlation between volumotion at the ventilation frequency and periodic alterations in CVP as well as in ABP. Furthermore, positive-pressure ventilation-related volumotion disappeared when limb venous occlusion pressure was raised above CVP, supporting the above statement. The fact that the application of PEEP causes larger changes in the amount of venous blood returning to the heart (Beyer, Conzen, Schosser & Messmer, 1980; Robotham & Takata, 1990), also confirms this view. Patients with the largest volumotion amplitude before application of PEEP showed the greatest increase in volumotion amplitude after PEEP, which may be explained by the fact that in hypovolaemic patients positive-pressure ventilation causes particularly large changes of venous blood returning to the heart (Beyer *et al.* 1980). Different states of intravascular volumes must be assumed for the investigated patient groups, which may explain our observation. We did not find ventilation-related volumotion during spontaneous breathing (7·0–19·0 breaths min^{-1}), which may result from the irregularity of breathing over the 5 min recording period. Moreover, one must bear in mind that during spontaneous breathing the changes in intrathoracic pressure are much smaller when compared with positive-pressure ventilation (Robotham & Takata, 1990).

We observed slow wave volumotion with a periodicity ranging from 0·5 to 7·0 cycles min^{-1} in this as well as in earlier studies. Those changes persisted when limb venous occlusion pressure was elevated above CVP, thus eliminating CVP-mediated volumotion. Moreover, slow wave volumotion was nearly always observed unilaterally and no cross-correlation was observed between volumotion signals from both legs, which in our opinion excluded Meyer–Hering–Breuer waves causing the phenomen (Golenhofen & Hildebrandt, 1958; Mahler, Muhheim, Intaglietta & Bollinger, 1979). We did not find any cross-correlation between slow wave volumotion and positive-pressure ventilation or spontaneous breathing. Therefore, it seems unlikely that slow wave volumotion is caused by the periodic haemodynamic events resulting from ventilation. The fact that slow wave volumotion persisted when limb venous pressure was elevated above 55 mmHg points towards a vascular, possibly arteriolar, origin. Periodic changes in the diameter of veins were first described by Jones (1852), and Bayliss (1902) suggested that they may also be present in arteries. These phenomena have been subject to extensive investigation and their possible physiological and pathophysiological significance has been stressed (Johnson, 1980; Messmer & Kreimeier, 1989; Intaglietta, 1989, 1991; Allegra *et al.* 1993). Vasomotion is regarded as one of the key factors governing microvascular perfusion, local regulation of precapillary resistance and thus fluid balance between the blood and tissue compartments (Messmer & Kreimeier, 1989). Colantuoni, Bertuglia, Coppini & Donato (1990) concluded that, in skeletal muscle microcirculation, arteriolar vasomotion regulates blood flow distribution between capillary units and controls tissue oxygenation. It has been shown that vasomotion is present or enhanced in various pathologies. Using both intravital microscopy and laser Doppler flowmetry, Intaglietta (1989, 1991) reported an increase in vasomotion activity during local and systemic arterial blood pressure reduction as well as hypoxic hypoxia (Schmidt, Intaglietta & Borgstrom 1992). The authors concluded that enhanced vasomotion is a beneficial reaction of the microvasculature to pathological conditions, particularly when a critical tissue perfusion is reached. Bollinger, Hoffmann & Franzeck (1991) found an increase in fast wave flux motion (20·0 cycles min^{-1}) in patients presenting with peripheral arterial occlusive disease, which decreased after surgical intervention improved leg perfusion. We did not observe any fast wave volumotion in our investigations on patients with peripheral arterial occlusive disease. This may be explained by the different techniques used to investigate these periodic changes. MSG plethysmography records whole-limb circumference whereas LDF and intravital microscopy studies detect local arteriolar and capillary events. Furthermore, Bollinger *et al.* (1991) investigated changes in skin blood flow whereas MSG plethysmography mainly records changes of skeletal muscle blood flow.

Other animal studies provide possible explanations as to what mechanism may have caused changes in whole-limb circumference large enough to be detected by MSG plethysmography. Using intravital microscopy, Oude Vrielink *et al.* (1990) reported a synchronized pattern of vasomotion between first order and transverse arterioles. However, such a synchronized pattern only appears locally and is associated with fast wave vasomotion and may therefore not result in events large enough to appear as periodic changes in limb volume. Bertuglia *et al.* (1991) and Borgström *et al.* (1990) found that vasomotion frequencies were related to the size of the arterioles. The smallest arterioles exhibited the highest vasomotion frequency ($9{\cdot}1 \pm 3{\cdot}9$ cycles min^{-1}), whereas the largest arterioles changed diameter with the lowest frequency ($2{\cdot}1 \pm 0{\cdot}9$ cycles min^{-1}). These data suggest that the slow wave volumotion which occurred with similar frequencies (0·5–7·0 cycles min^{-1}), may be caused by larger rather than smaller arterioles and give rise to detectable changes in whole-limb circumference.

Some authors have suggested that vasomotion may be involved in a metabolic feedback for the regulation of local tissue perfusion (Borgström & Gestrelius, 1987; Lewis, Gustafsson, Wardell & Nilsson, 1993). During haemorrhagic shock peripheral vasoconstriction is observed which initially maintains perfusion of vital organs. The vasoconstriction is due to a centrally mediated increase in sympathetic tone. Profound vasoconstriction will ultimately cause insufficient tissue perfusion of non-vital organs like skin and skeletal muscle. It is possible that metabolic changes like hypoxia, a critical reduction of local pH values or an increase in adenosine and nitric oxide result in vasodilation, thus overriding the centrally mediated vasoconstriction. This would be in accordance with theories formulated by Secomb, Intaglietta & Gross (1989), who speculated that vasomotion represents a compensatory mechanism in response to inadequate organ perfusion. Using modelling techniques they described the effects of vasomotion on the microvascular mass transport and demonstrated that vasomotion, whilst enabling intermittent tissue perfusion, may improve spatial and temporal oxygen delivery to the tissues, reduce perivascular oedema and increase the systemic vascular resistance. Intaglietta (1981) suggested that vasomotion may optimize tissue fluid balance as part of the physiological response to hypovolaemia. Furthermore, vasomotion may improve the rheology of the blood in the capillaries as suggested by Intaglietta (1981) and Fagrell, Intaglietta & Oestergren (1981); this would allow a better nutritive flow to the tissues and could avert impending microvascular failure.

All the above studies illustrate why monitoring vasomotion could give a valuable insight into altered patterns of microvascular perfusion. Despite the obvious implications of these findings in assessing pathological changes in humans, it has hitherto remained difficult to investigate them in patients due to the absence of applicable methods. We believe that MSG plethysmography may provide a non-invasive method of monitoring local microcirculatory events.

In a preliminary publication on critically ill patients, we reported slow wave volumotion that correlated with accepted indices of cardiovascular instability. We found an increased volumotion associated with a decrease in cardiac index (CI), oxygen delivery (D_{O_2}) and an increase in oxygen consumption ($\dot{V}_{O_2}$) (Christ *et al.* 1991*b*). In such patients an impaired microcirculation is frequently found and associated with organ failure. We concluded that volumotion is most probably caused by arteriolar vasomotion and may reflect an impairment of microcirculatory perfusion.

There is evidence that slow wave vasomotion may be neurally mediated, since it disappears after pharmacological blockade of the supplying sympathetic fibres (Kastrup, Bülow & Lassen, 1989). We found a reduction in both amplitude and incidence of volumotion after sympathetic blockade was induced by spinal anaesthesia (Christ *et al.* 1994). This finding on volumotion is in aggreement with the reports on arteriolar vasomotion.

Since periodic changes of lymph vessel diameter and intraluminal pressure have been reported, lymphatic activity must be considered as a potential cause of volumotion (Olszewski & Engeset, 1980). Olszewski & Engeset reported a periodicity of 5·3 and 9·0 cycles min^{-1} in the human leg; however, we rarely observed periodic changes with that frequency. Whilst the lymphatics are considered a low pressure system, they are capable of producing intraluminal pressures as high as 100 mmHg (Olszewski & Engeset, 1980). These vessels cannot be excluded as a source of volumotion, until further information on total lymphatic volume and flow pattern from the leg is available.

Regarding the limitations of the MSG plethysmography, it must be stressed that changes in whole-limb circumference are measured. This does not allow us to distinguish between phenomena resulting from skin and skeletal muscle microcirculation. We believe, however, that volumotion mainly originates from changes in skeletal muscle, as it accounts for most of the volume of the calf (excluding tibia and fibula). Currently we simultaneously record LDF signals close to the strain gauge, which we hope enables us to address this question.

In conclusion, we used computer-assisted mercury-in-silastic strain gauge plethysmography to investigate periodic changes in limb circumference. We reported on the mathematical procedures for both qualitative and quantitative assessment of these events which we called volumotion. Volumotion appeared with slow

(1–7 cycles min^{-1}) and fast (8–20 cycles min^{-1}) frequency. The latter showed good correlation with positive-pressure ventilation, arterial pressure and central venous pressure. No such correlations were found for the slow wave volumotion which occurred unilaterally in critically perfused limbs. We believe that slow wave volumotion originates from arteriolar vasomotion and may be triggered by critical microcirculatory perfusion. We have shown that MSG plethysmography enables non-invasive investigation of microcirculatory events in man and may be used to monitor changes in microvascular perfusion of skeletal muscle.

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