Economy Class Syndrome: Rheology, Fluid Balance, and Lower Leg Edema During a Simulated 12-Hour Long Distance Flight

H. LANDGRAF, M.D., Ph.D., B. VANSELOW, M.D., Ph.D., D. SCHULTE-HUERMANN, M.D., Ph.D., M. V. MÜLMANN, M.D., Ph.D., and L. Bergau, M.D., Ph.D.

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In order to study pathological changes that might lead to deep vein thrombosis and pulmonary embolism in long-distance air travel passengers, 12 healthy volunteers were investigated during 4 simulated 12-h flights (day and night). The influence of repeated leg exercise was compared with constant sitting. Plasma viscosity, hematocrit, albumin, fluid balance, and lower leg swelling were measured. Rheological studies showed only circadian rhythm alterations. An average of 1150 ml fluid was retained, which correlated with an increase in body weight. The lower leg volume increase was significant, but not pathological. Periodic leg exercising showed no measurable preventive effects. These changes in healthy human volunteers are within physiological variations and are not sufficient to provide a definitive cause of venous thrombosis in healthy passengers. They do, however, suggest alterations produced by long-distance air travel that could intensify the risk of developing deep venous thrombosis in passengers with predisposing risk factors.

WITH THE ONSET of frequent intercontinental air travel in the 1960's, an increasing number of deep venous thromboses (DVT) and pulmonary embolisms were observed during, or within 48 h after, a long distance flight (3). With increased worldwide air travel, during the past decade the problem has become more important, and has been called the "Economy Class Syndrome" (9). This name is based on the hypothesis that long-term constrained sitting in a cramped position is an initiating factor for the development of thrombosis in the deep veins of the leg.

An investigation by Sarvesaran (19) showed that pulmonary embolism was the second leading cause (18%) of inflight or postflight death at London-Heathrow between 1979 and 1983 and that 81% of the cases were women. Some risk factors have been identified. Most of the published Economy Class Syndrome patients were smokers, obese, taking oral contraceptives, or had other risk factors for thrombosis (9,18,5).

The mechanisms of intravascular thrombus formation are still regarded as being based on Virchow's triad (7): 1) reduction of intravascular blood flow (stasis); 2) primary lesions of endothelial cells; and 3) changes of blood coagulability. Immobility, shifts of body fluid, orthostatic stress and compression of the popliteal vein at the edge of the seat are some conditions arising from long term, cramped sitting which might lead to those pathological conditions described by Virchow (14). Stasis, which might contribute to the swelling of the dependent parts of the body, has also been described as causing endothelial lesions (25). Conditions similar to air travel, such as long distance drives (22) or sitting in crowded air-raid shelters in World War II (20), have previously been associated with DVT and pulmonary embolism.

Efficient prophylaxis and its indication have been the subjects of controversy for years. A single scheme for prophylaxis has not been established, as yet. One reason for this is that there have been no specific investigations into pathophysiological conditions in humans during long-term sitting in a cramped position.

This study was undertaken to gain a better understanding of the pathological changes occurring in healthy humans sitting in passenger seats for a period of

From the Department of Internal Medicine, Division of Angiology, University Hospital Frankfurt/M, (H. Landgraf, B. Vanselow, and D. Schulte-Huermann); and Lufthansa German Airlines, Medical Department, Frankfurt/M, (M. V. Mülmann and L. Bergau) Germany.

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Address for correspondence: Prof. Dr. med. Helmut Landgrafl, who is Head of the Medical Department II at the Wenckebach Hospital in Berlin, Professor of Internal Medicine, and Flight Surgeon, II Innere Abteilung, Wenckebach Krankenhaus, Wenckebachstr. 23, D-12099 Berlin, Germany.

12 h. The questions addressed in this study are: 1) are there changes in rheology or fluid balance that might indicate a risk of thrombosis? and 2) to what extent does the lower leg swell in this situation and will periodic leg exercise have a preventive effect on the leg swelling or other variables involved?

MATERIAL AND METHODS

The study was designed with 12 healthy volunteers aged between 22 and 58, 6 women and 6 men. The volunteers had to be healthy, which meant that risk factors for DVT such as chronic venous insufficiency, obesity, use of birth control pills and underlying diseases were excluded by history and physical examination. The study had been approved by the Ethics Committee. Volunteers gave their informed consent to participation and were aware of their right to withdraw from the study at any time.

Four studies, each lasting 12 h, were undertaken in a Boeing 747 passenger cabin mockup at the Deutsche Lufthansa facilities at Frankfurt/Main Airport. Two studies took place overnight (7 p.m. to 7 a.m.) and two during the day (9 a.m. to 9 p.m.).

To study the effects of periodic leg exercise, two groups of six volunteers were formed: a) the "exercising group" had to leave the seats and walk around in the cabin for 5 min once an hour; b) the "sitting group" remained seated during the entire period of the study. These subjects were only allowed to go to an adjacant toilet every 3 h when urine samples were needed.

After two studies the groups were switched. In all other respects the participants were asked to behave as if they were on a real flight. They talked, read or slept during the studies while full passenger service was provided and a movie was presented. Smoking was not allowed in the cabin.

Measurements were made before starting of the studies (baseline) and then every 3 h. These included blood sampling via indwelling venous catheters (Viggo-Venflon 18g, Pfrimmer, Germany), which had been installed in the antecubital vein, and measurements of the lower leg volume. Finally the participants went to the adjacent toilet to empty their bladders for urine sampling.

In order to investigate rheology, measurements were made of plasma viscosity, hematocrit, and albumin concentration. Plasma viscosity was determined by an Ostwald-type capillary viscosimeter (Schott, Mainz, Germany) at 37°C. Hematocrit was measured with the microhematocrit technique. The albumin concentration in the serum was measured photometrically by the bromocresol-green method (Albumin ALB, Boehringer Mannheim Diagnostica GmbH, Germany).

The fluid balance was calculated by measuring the volumes of oral fluid intake and renal output. The test persons were weighed before and after each study. An optoelectronic plethysmograph was used for the determination of the lower leg volume (Volometer A, Bösl, Bad Aachen, Germany). In addition to these variables, heart rate and blood pressure were also monitored.

The results for the exercising group were compared with those of the sitting group. Because of the possible influence of circadian rhythms, the day and night studies were analysed separately. For statistical analysis the Wilcoxon test for paired samples was used. Statistical calculations are used as descriptive data analysis as proposed by Abt (2). The level of significance was set at $p < 0.05$.

RESULTS

Plasma Viscosity

The systemic plasma viscosity results are summarized in Table I. There were no significant changes in viscosity in the night studies. The maximum deviation from the baseline (0 hours) at night was an insignificant increase of 0.017 mPas (0.014%) in the sitting group. However, a moderate and statistically significant increase in viscosity occurred during the day studies. The maximum increase in relation to the baseline was then

TABLE I. PLASMA VISCOSITY: MEAN, STANDARD DEVIATION (SD), SAMPLE SIZE (N) AND SIGNIFICANCE (P) DURING A 12-H SIMULATED FLIGHT WITH 12 HEALTHY VOLUNTEERS. GROUPS WITH (EXERCISING GROUP) AND WITHOUT (SITTING GROUP) HOURLY WALKING EXERCISE WERE FORMED FOR NIGHT AND DAY STUDIES. SIGNIFICANCE P EVALUATED BY WILCOXON TEST IN RELATION TO THE BASELINE MEAN (0 H)

Measurementment Intervals (h)		0	3	6	9	12
Exercising Night	Mean	1.191	1.201	1.197	1.201	1.196
(mPas)	SD	±0.041	±0.046	±0.043	±0.046	±0.041
	n	9	12	11	11	12
	p		ns	ns	ns	ns
Sitting Night	Mean	1.191	1.208	1.195	1.199	1.205
(mPas)	SD	±0.052	±0.054	±0.046	±0.052	±0.040
	n	10	12	11	12	11
	p		ns	ns	ns	ns
Exercising Day	Mean	1.168	1.186	1.193	1.193	1.195
(mPas)	SD	±0.038	±0.045	±0.034	±0.42	±0.046
	n	12	12	12	12	12
	p		p < 0.05	p < 0.01	p < 0.05	p < 0.05
Sitting Day	Mean	1.171	1.188	1.195	1.199	1.196
(mPas)	SD	±0.045	±0.037	±0.037	±0.038	±0.036
	n	12	12	12	12	12
	p		p < 0.01	p < 0.01	p < 0.01	p < 0.01

0.028 mPas (0.024%) in the sitting group. No trend differences between the exercising and the sitting groups could be observed in either night or day studies.

Hematocrit

The results of hematocrit (Table II) revealed moderate changes. The night studies showed a decrease of hematocrit with a minimum after 6 h. Towards the end of the study, the hematocrit values returned to their baseline levels. The changes in the sitting group were greater than in the exercising group; they became significantly different from the pretest values after 6 h ($p < 0.05$). During the day studies, the hematocrit did not change significantly in either group. However, there was a trend toward a slight increase in hematocrit, during the first 6 h in both groups.

Albumin

The concentration of albumin is shown in Table III. Again, there were no distinct differences between the exercising and the sitting groups. During the night studies albumin concentration decreased slightly from the baseline (0 hours) during the first 6 h in the sitting group after which it returned to the baseline. Otherwise, significant deviations from the baseline were not found in the night studies. During the day studies, the concentration of albumin showed a single significant increase in the exercising group after 3 h. None of the other results deviated significantly from the baseline.

Fluid Balance and Body Weight

In all studies, fluid intake exceeded renal excretion and no significant differences were found, in a 12-h period, between the exercising and sitting groups or night and day studies (Table IVa). The average surplus of all groups and studies is 1382 ± 573 ml. Fluid losses by insensible perspiration via skin and lungs and with the stool, as well as fluid gains by meals and oxidation process, are not considered in our measurements. The calculation in Table IV suggests that the average surplus in fluid balance is about 1100–1200 ml. This result corresponds with an average increase in body weight of 0.995 kg (Table IVa).

Volume of the Lower Leg

An increase of the lower leg volume was found in both experimental groups in all studies. The increase was linear with respect to time and did not show asymptotic behavior towards the end of the study. During the night studies, the sitting group showed an increase of 127 ± 53 ml, while the exercising group gained 96 ± 100 ml of lower leg volume. The difference of 29 ml is not statistically significant (Fig. 1a). During the daytime, the sitting group gained a total volume of 83 ± 59 ml and the exercising group 89 ± 52 ml in 12 h (Fig. 1b).

DISCUSSION

The rheological measurements remained stable, subject only to some minor changes throughout the studies. Only plasma viscosity showed any significant alterations.

The results reveal slight, but significant differences between night and day studies. They suggest a major influence of circadian rhythms. The rhythms of plasma viscosity, hematocrit, and total plasma protein have been investigated by Ehrly and Jung (12), who found that after a maximum in the late morning, and a second smaller peak in the late afternoon, rheological variables run through a distinct minimum during the early morning. Ehrly and Jung noted a decrease in plasma viscosity of 4.4% between 11 p.m. and 3 a.m. The alterations in rheology in this study show a similar behavior with a tendency for hemoconcentration in the late morning and for hemodilution after midnight. Our study shows a decrease in plasma viscosity of 0.3% in the exercising group and 1.1% in the sitting group, from 10 p.m. to the minimum at 1 a.m. Compared with Ehrly and Jung's results concerning the early morning minimum of hematocrit, the minima we measured are less distinct. This could be due to the limited number of subjects

TABLE II. HEMATOCRIT: MEAN, STANDARD DEVIATION (SD), SAMPLE SIZE (N) AND SIGNIFICANCE (P) DURING A 12-H SIMULATED FLIGHT WITH 12 HEALTHY VOLUNTEERS. GROUPS WITH (EXERCISING GROUP) AND WITHOUT (SITTING GROUP) HOURLY WALKING EXERCISE WERE FORMED FOR NIGHT AND DAY STUDIES. SIGNIFICANCE P EVALUATED BY WILCOXON TEST IN RELATION TO THE BASELINE MEAN (0 H).

Measurement Intervals (h)		0	3	6	9	12
Exercising Night	Mean	42.0	41.7	41.0	41.5	41.7
(%)	SD	±3.35	±3.26	±3.42	±3.77	±3.92
	n	12	12	11	12	12
	p		ns	p < 0.05	ns	ns
Sitting Night	Mean	42.6	41.6	40.0	41.0	41.8
(%)	SD	±3.85	±4.08	±3.28	±3.96	±4.13
	n	12	12	11	12	11
	p		p < 0.05	p < 0.05	p < 0.05	ns
Exercising Day	Mean	40.2	40.8	40.8	40.0	40.3
(%)	SD	±2.80	±3.13	±3.07	±3.40	±3.68
	n	12	12	12	12	12
	p		ns	ns	ns	ns
Sitting Day	Mean	40.4	40.8	41.1	40.2	39.6
(%)	SD	±3.27	±3.69	±4.01	±3.08	±3.61
	n	12	12	12	12	12
	p		ns	ns	ns	ns

TABLE III. ALBUMIN CONCENTRATION: MEAN, STANDARD DEVIATION (SD), SAMPLE SIZE (N) AND SIGNIFICANCE (P) DURING A 12-H SIMULATED FLIGHT WITH 12 HEALTHY VOLUNTEERS. GROUPS WITH (EXERCISING GROUP) AND WITHOUT (SITTING GROUP) HOURLY WALKING EXERCISE WERE FORMED FOR NIGHT AND DAY STUDIES. SIGNIFICANCE P EVALUATED BY WILCOXON TEST IN RELATION TO THE BASELINE MEAN (0 H).

Measurement Intervals (h)		0	3	6	9	12
Exercising Night	Mean	4.39	4.38	4.31	4.32	4.30
(g/dl)	SD	±0.20	±0.19	±0.20	±0.17	±0.19
	n	12	12	11	12	11
	p		ns	ns	ns	ns
Sitting Night	Mean	4.43	4.34	4.25	4.32	4.36
(g/dl)	SD	±0.23	±0.23	±0.16	±0.25	±0.20
	n	12	11	11	12	11
	p		ns	$p < 0.05$	ns	ns
Exercising Day	Mean	4.16	4.28	4.24	4.21	4.25
(g/dl)	SD	±0.16	±0.18	±0.18	±0.23	±0.27
	n	12	12	12	12	12
	p		$p < 0.05$	ns	ns	ns
Sitting Day	Mean	4.17	4.24	4.28	4.25	4.26
(g/dl)	SD	±0.18	±0.17	±0.20	±0.19	±0.21
	n	12	12	12	12	12
	p		ns	ns	ns	ns

TABLE IVa. FLUID BALANCE AND BODYWEIGHT: MEAN, STANDARD DEVIATION (SD), SAMPLE SIZE (N) AND SIGNIFICANCE P IN 12 H OF A SIMULATED FLIGHT WITH 12 HEALTHY VOLUNTEERS. GROUPS WITH (EXERCISING) AND WITHOUT (SITTING) HOURLY WALKING EXERCISE WERE FORMED FOR NIGHT AND DAY STUDIES. THE TOTAL AVERAGE IS BASED ON THE RESULTS FROM 4 STUDIES. SIGNIFICANCE P EVALUATED BY WILCOXON TEST IN RELATION TO THE BASELINE MEAN (0 H)

		Exercising		Sitting		Average
		Night	Day	Night	Day	Total
Fluid balance	Mean	1269	1420	1440	1402	1382
[ml/12h]	SD	±404	±481	±704	±704	±573
	n	11	11	11	11	44
	p	$p < 0.005$	$p < 0.005$	$p < 0.005$	$p < 0.005$	
Bodyweight	Mean	1.01	0.97	1.19	0.81	0.995
balance	SD	±0.47	±0.56	±0.80	±0.57	±0.66
[kg/12h]	n	11	11	11	11	44
	p	$p < 0.01$	$p < 0.01$	$p < 0.01$	$p < 0.01$	

participating in this study, but could also represent a minimal trend for hemoconcentration in our study. All alterations in plasma viscosity, hematocrit, and albumin in this study are within the range of physiological variation. The significant increase in plasma viscosity during the day studies is obviously the result of a low pretest level according to its circadian rhythm. There is no difference in the behavior of rheology between exercising and sitting groups, which may be because the changes in those variables are too small to measure the effect of leg exercise.

The findings are based on blood from the cubital vein and do not describe the local rheological conditions in the deep leg veins in seated humans. Other studies (15,16) revealed that orthostasis causes an elevation of hematocrit, plasma viscosity, plasma protein concentration, and colloid osmotic pressure in the vessels of the lower extremity. Moyses et al. (15) compared blood samples from the dorsal foot vein with blood from the cephalic vein in seated subjects. After 40 min they found an average hematocrit of 53.2% in the foot vein, while the hematocrit from the cubital vein sample remained 41.3%. Noddeland et al. (16) suggest that high room temperature reduces the effect of orthostasis in causing systemic hemoconcentration in seated humans. They ascribed this effect to an increasing arteriovenous shunt volume in a warmer environment. The average room temperature during the studies in the passenger cabin mock-up was 25.8 (±0.6)°C, which might be too warm to provoke a distinct systemic hemoconcentration. However, if local deep leg vein hemoconcentration also occurred in our study, it was not distinct enough to cause significant systemic effects on the rheology.

Although pathophysiological mechanisms for thrombogenesis in seated human beings were being looked for in this study, the slight alterations in systemic rheology in healthy subjects reported here may be regarded as negligible. Subjects having risk factors may show more pronounced alterations (11).

Approximately 1100–1200 ml of fluid were retained by the test subjects during the study. This corresponds roughly with an increase in body weight of about 1 kg. Regarding the swelling of the lower leg during the same time, it seems very likely that fluid which accumulates in the dependent parts of the body by venous pooling and interstitial edema is replaced. This replacement

TABLE IVb. CALCULATION OF FLUID BALANCE OF FOUR 12-H SIMULATED LONG DISTANCE FLIGHTS WITH RESPECT TO FLUID LOSSES AND GAINS THAT WERE NOT REGISTERED. CALCULATIONS ARE BASED ON GROUND LEVEL CLIMATE CONDITIONS (AV. 25.8° C/41% REL.). THE AVERAGE BODY WEIGHT TO CALCULATE INSENSIBLE PERSPIRATION (0.5 ml • kg • h) WAS 71.8 kg.

	ml/12h
Experimental result of fluid balance: oral intake vs renal output (av.)	+ 1382
Fluid loss via the skin [6]	− 400 to − 431
Fluid loss via lungs calculated acc. to Ulmer*	− 260
Fluid loss via the gastrointestinal tract [6]	− 50
	= 641 to 672
Fluid intake by solid food [6]	+ ca. 350
Water from oxidation process [6]	+ ca. 150
Total calculated fluid balance	= 1141 to 1172

* Ulmer HJ, Hermann H, Bergau L. Forschungbericht-Arbeitsplatzstudie Langstreckenflug (Polflug). Ärztlicher Dienst der Lufhansa AG, Frankfurt/M. Unpublished observations.

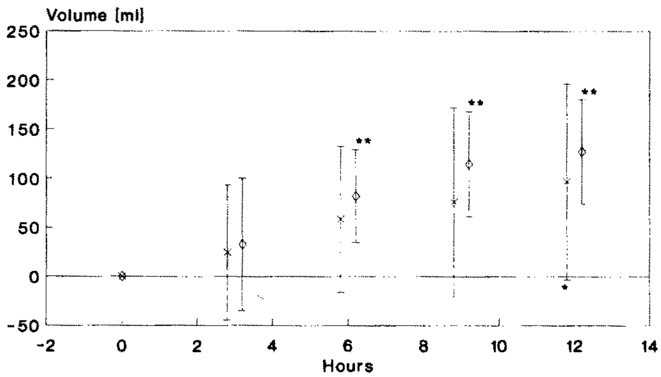

Fig. 1a. Total increase of the lower leg volume of exercising (×) (n = 11) and sitting (◇) (n = 11) groups in a 12-h simulated long distance flight (night-study) with healthy test persons. SD is shown by bars. Significance p in relation to the lower leg volume before the start is indicated by *p < 0.05 and **p < 0.01. X =

might contribute to the stability of the rheological and hemodynamic conditions as monitoring of heart rate and blood pressure showed no distinct alterations. The results concerning fluid balance are difficult to transfer to the actual inflight setting where different climatic conditions influence insensible perspiration. The extremely low humidity (10–20% rel.)in aircraft passenger cabins leads to pronounced fluid losses (8). Ulmer et al. found an average of insensible fluid losses of 84 ml • h^{-1} during an intercontinental flight. Nevertheless, these elevated fluid losses were overcompensated by additional intake of fluid and food, which resulted in an average increase of body weight of 100 g • h^{-1}. [Ulmer HV, Hermann H, Bergau L. Forschungsbericht—Arbeitsplatzstudie Langstreckenflug (Polflug). Ärztlicher Dienst der Lufhansa AG, Frankfurt/M, Unpublished observations.]

The swelling of the lower leg is significant in both groups during both day and night studies. It is an important indicator for the development of edema (23). An argument against an influence of circadian rhythms in these measurements is the continuous increasing leg volume observed in both groups during day and night

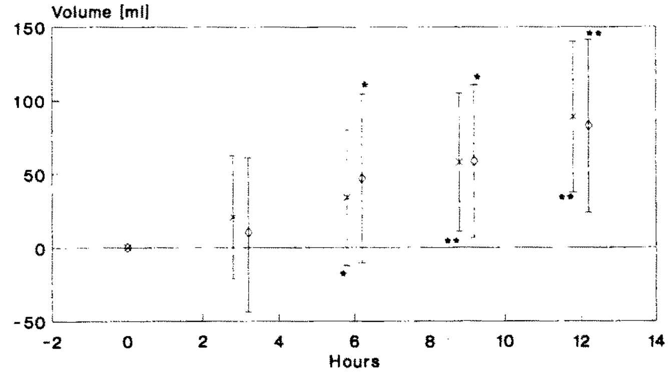

Fig. 1b. Total increase of the lower leg volume of exercising (X) (n = 11) and sitting (◇) (n = 11) groups in a 12-h simulated long distance flight (day-study) with healthy test persons. SD is shown by bars. Significance p in relation to the lower leg volume before the start is indicated by *p < 0.05and **p < 0.01.

studies. It was more evident than that described by Bellinger et al. (4) in healthy, normal working humans who showed an average increase in lower leg volume of 50 ml between morning and late afternoon measurements. In the same study, patients with chronic venous insufficiency showed a threefold higher swelling rate. These results support the assumption that long-term sitting is a principal factor in swelling. The increase of the lower leg volume found in this study is not to be seen as pathological. An underlying circadian rhythm cannot be excluded but, in this study, would be dominated by the effects of sitting.

The results from the night studies show an apparent but statistically insignificant difference in volume, with faster and more pronounced swelling in the seated group. Although the standard deviation in the exercising group is large, the observed mean increase in the sitting group is higher than in all other measurements from day and night studies. The phenomenon might be explained by the different behavior of both groups over night. The group that performed walking exercises hourly got little sleep, whereas the sitting group had only been disturbed by the measurements every 3 h. Getting more sleep, the sitting group might experience less muscular activity or rather complete muscular relaxation, which may affect venous and lymphatic backflow from the lower limbs and lead to more venous stasis and swelling. Moreover, it is more likely that the popliteal vein is compressed at the edge of the seat during sleeping, thus intensifying the risk of stasis. Normal leg activity in seated humans is an important factor in preventing swelling. Noddeland and Winkel (17) found that the swelling of the foot with normal leg activity in the sitting human is 0.33 ml • 100 ml^{-1} • h^{-1}, rising to 0.71 ml • 100 ml^{-1} • h^{-1} in the same test subjects with their legs completely immobile.

On the other hand, the day studies show no differences between exercising and sitting groups. Investigations by Winkel (24) on the lower leg of sitting humans, with and without leg exercise every 15 min, revealed a 44% decrease in the swelling rate of the exercised leg while the non-exercised leg remained absolutely inactive in a water plethysmograph. Another aspect of the same study (24) showed that isometric calf muscle contractions instantly led to decreasing lower leg volume which, however, returned to the pre-exercise volume within minutes of ending the exercises. Between the exercises the leg showed a continuous swelling process which was interrupted but not delayed by the exercises. One might conclude from these results that repeated short-lasting leg exercise is no better at preventing edema than the normal leg activity of awake, seated humans.

Leg muscular activity prevents swelling not only by compressing major veins but also by increasing interstitial pressure, thus causing reduced capillary filtration and elevated lymphatic drainage (1,21). The latter two mechanisms are notably inefficient in the short term; the long term effect is to mobilize and especially, eliminate interstitial fluid, thus preventing further accumulation. This may explain why, in this study, leg exercises did not have a reducing or limiting effect on the swelling of the lower leg.

The net increase in the lower leg volume in this study lies within the normal range of healthy persons. Therefore, the swelling of the lower extremities in orthostasis might be regarded as a self-limited physiological process (26). By increasing the interstitial pressure in the limb, swelling may prevent deep veins from dilating or may even cause some compression like that of a compression stocking. This would improve venous flow and, therefore, prevent stasis. This hypothesis about a physiological anti-thrombotic mechanism has not been experimentally investigated. Patients with risk factors for thrombosis are apt to develop more distinct edema (4).

In this study, a higher risk for deep vein thrombosis in healthy persons sitting in cramped position for 12 h could not be established. Rheology was basically stable, subject only to minimal alterations that can be explained by circadian rhythms. Fluid was retained that might replace intravascular fluid, shifting into the interstitial spaces of the dependent parts of the body.

The test persons developed significant swelling of the lower legs that, however, is not regarded as pathological. Sleeping in the seats in a sitting position may increase swelling and the risk of compression of, and damage to, the popliteal vein by the front edge of the seat. Short-term periodic leg exercising had no preventive effect on leg swelling and rheology, in comparison to the normal leg activity of seated humans.

Patients with disposing risk factors for thrombosis are expected to show more pronounced effects and have to be considered for prophylactic treatment before and during long distance flights. Not all the results from this study can be transferred to the actual conditions in flying aircraft. Factors such as decreased air pressure and humidity, or psychological stress (13), have not been specially simulated in the studies, and further effects on the fluid balance are to be expected [Ulmer HV, Hermann H, Bergau L. Forschungsbericht—Arbeitsplatzstudie Langstreckenflug (Polflug). Ärztlicher Dienst der Lufhansa AG, Frankfurt/M. Unpublished observations.] A connection between additional swelling and high altitude has been denied (17). An effect of hypoxia on rheology has been excluded (10). Further studies in real flight situations are necessary to give more insight into these specific conditions.

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