Original Article

Limb Muscle Hemodynamics and Arterial Distensibility Depend on Atmospheric Pressure in Hypertensive Men

Vladimir N. MELNIKOV[1,#], Sergey G. KRIVOSCHEKOV[1], Tamara G. KOMLYAGINA[1], Svetlana Y. RECHKINA[2], and Nathan S. CONSEDINE[3]

1. Institute of Physiology, Siberian Branch of the Russian Academy of Medical Sciences, Novosibirsk, 630117, Russia; 2. Sanatorium "El'tsovka," Novosibirsk, Russia; 3. Department of Psychological Medicine, University of Auckland, New Zealand

Abstract

Objective To verify whether peripheral blood circulation and arterial wall distensibility are influenced by atmospheric pressure (AtPr) and to examine if their association is dependent on age and/or sex.

Methods Associations among natural AtPr levels (on the examination day as well as 1 and 2 days prior), limb muscle hemodynamics, and distensibility of conduit arteries were retrospectively examined in an observational study of 276 untreated patients with primary moderate hypertension (mean age 56.4 years, 194 men). Forearm and calf circulations at rest and 3 min after ischemia were measured by venous occlusion plethysmography. Compliance of the brachial and shank arteries was assessed by oscillometry.

Results After adjustment for age, degree of hypertension, and season, correlation and multiple regression analyses revealed a season-independent but age-dependent direct correlation between the stiffness of limb arteries and AtPr levels on the examination day in men, but not women. The association weakened with the degree of hypertension, disappeared with age, and was more evident in the arms than in the legs.

Conclusion Parameters of arterial wall distensibility in adult hypertensive men are susceptible to AtPr changes within the usually observed limits (730-770 mmHg). It is proposed that reduction of arterial wall barometric responsiveness in women and aging men is a likely mechanism underlying their meteosensitivity.

Key words: Atmospheric pressure; Arterial stiffness; Compliance; Venous circulation; Age-dependence; Sex difference; Season

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INTRODUCTION

There is a large body of literature devoted to the effects of barometric stimuli on human health[1-3]. One emergent trend is that certain people appear to be differentially sensitive to atmospheric pressure (AtPr) or changes in pressure, i.e., they are meteorosensitive. Until date, no study has investigated whether AtPr changes within the normal range found in South Siberia (730-770 mmHg) influence the mechanical properties of human blood vessels. However, several areas of research are suggestive of such a relationship.

[#]Correspondence should be addressed to Vladimir N. MELNIKOW. Tel/Fax: 7-383-3359556; E-mail: mevlanic@yandex.ru

Biographical note of the first author: Vladimir N. MELNIKOW, Ph.D., Dr. Sci., associate professor, Laboratory of Organism's Functional Reserves, Institute of Physiology.

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First, it has been clinically noted that hypotensives feel better on days of high AtPr whereas hypertensive subjects have the opposite characteristic[4]. Associations between episodes of low AtPr and cases of abdominal aorta[3] and aneurysmal subarachnoid[2] ruptures as well as episodes of acute severe non-migraine[5] and migraine[6] headaches have also been noted, but the mechanisms underlying these associations remain unclear.

Second, a number of epidemiological studies have suggested an association between the incidence of ischemic stroke and AtPr. One examination of 1286 consecutive stroke patients found that the incidence of non-lacunar stroke was related to falls in AtPr whereas the incidence of intracerebral hemorrhage was associated with increases in AtPr[7]. Other studies have suggested that these associations may be stronger among younger (age 25-64 years) rather than older (age 65-74 years) subjects and in men rather than women[8-9].

However, none of these studies have considered the *in vivo* responses of blood vessels to barometric changes within the normal range over multiple hours to days. Thus, the primary objective of this retrospective cross-sectional study was to evaluate the associations among AtPr (on the examination day as well as 1 and 2 days prior), peripheral hemodynamics, and arterial mechanical properties. In addition, the study attempted to verify the possible sex difference and age dependency of both immediate and delayed ambient pressure effects among a cohort of hypertensive patients. Considering the absence of previous studies in this area, we decided to concentrate our examination on subjects who were suggested to be particularly susceptible to the impact of weather changes[4]. Because of (a) the large degree of monthly variation in AtPr at the sampling site (Siberia, Russia) and (b) the well-documented seasonal fluctuation in cases of aneurysm rupture[3,9-10], we considered the independent and combined effects of both air pressure and season on hemodynamic and vascular characteristics. An additional specific aim of the study was to verify whether vascular barometric responsiveness is a function of the degree of permanent wall distension and hence dependent upon the degree of hypertension.

MATERIALS AND METHODS

Participants

All participants were from the Cardiology Clinic in Novosibirsk, Russia and were examined between 2001 to 2004. The initial database consisted of 1 502 patients who presented with several somatic diseases. Among these, 276 were ultimately diagnosed as newly hypertensive (194 men aged 35-75 years and 82 women aged 32-78 years). The patients were examined before being prescribed a course of medication for hypertension. The participants were not actively involved in regular physical activity and none had a special diet at the time of investigation.

Patients newly diagnosed with primary moderate hypertension had diastolic and systolic blood pressure values within 80-100 and 130-160 mmHg, respectively. According to the American Heart Association criteria, the patients had prehypertension or stage 1 hypertension[11]. In 21% of these patients, hypertension was associated with a concurrent diagnosis of ischemic heart disease. Patients who had a history of smoking, any indication of peripheral vascular disease, or diabetes mellitus were excluded from the study.

Procedure

Upon presenting at the laboratory, the participants had the study explained to them and were then fitted with a standard sensory cuff (10-cm wide) around either shoulder or on the lower third of the shank. The controlled pressure in the cuff, which contained a pressure transducer, was reduced from above systolic to below diastolic. All physiological measurements were performed by the same trained observer in the morning at a constant room temperature of 24-26 °C with participants in a supine position following a 20-min rest and a fast of at least 8 h with no alcohol or coffee. The instrumentation was regularly examined with a precise manometer. No evident trends in the readings suggested that the technical conditions remained constant across all observations.

Measures

Arterial inflow (AIF), baseline venous outflow (VOF), peak blood flow 3 min after occlusion (reactive hyperemia, RH), and venous capacity (VC) were measured in the forearm and calf muscles by strain-gauge venous plethysmography using the Periquant 3500 device (Gutmann, Germany). Regional vascular resistance (RVR) was calculated by dividing the mean arterial pressure by AIF (P_m/AIF). Heart rate (HR) and systolic (P_s), diastolic (P_d), and pulse (P_p) blood pressures were measured by

tachooscillography. Mean pressure (P_m) was calculated according to the equation (systolic + 2diastolic)/3.

The elastic resistance of the mechanically relaxed arterial walls (K_{rel}), resistance of intact vessel (K_{in}), bulk modulus of the intact vessel elastic resistance (E_{in}), and effective inner diastolic radius (R_d) were measured by the oscillometric method[12-16], which is a standard technique for examining the peripheral pulse wave and arterial mechanical properties[17]. The elastic resistance or stiffness of an intact artery was computed according to the formula $K_{in} = \Delta P_p$ dyn·cm^{-2}/ΔV cm^3, where ΔP_p is the pulsative increment in blood pressure. In a physical sense, this metric characterizes the additional intraluminal pressure that should be applied in order to increase the vessel's volume under the cuff by ΔV cm^3. The resistance of the mechanically relaxed artery, K_{rel}, was determined as the counterpressure in the cuff equal to the diastolic pressure[12]. The compliance or distensibility is the inverse of stiffness, $\Delta V/\Delta P$. Arterial compliance is known to be greatest at zero transmural pressure, i.e., when the arterial wall is relaxed in the case of equal internal and external forces[16]. E_{in} is K_{in} normalized by the initial vessel volume, $E_{in}=(\Delta P/\Delta V)/V$[18].

Data on the mean daily AtPr values were obtained from the Geophysical Observatory situated near the investigation site. The possible relevance of delayed effects of AtPr at the time of measurement was considered, and AtPr values were also measured 1 and 2 days before the actual examination. The mean daily AtPr during the period of investigation was 751.2±7.8 mmHg (range 733-774 mmHg). During the study, the mean monthly pressure values demonstrated a sinusoidal variation (P=0.001, ANOVA) with a peak in January (757.7±8.0 mmHg) and a trough in July (738.0±4.3 mmHg, P<0.001, Bonferroni's test). The recorded mean pressure values were greater in the colder half of the year than that in the warmer half (754±7 *vs.* 747±7 mmHg, P=0.001, Student's *t*-test).

Data Analysis Strategy

Consistent with our aims, data analysis proceeded in several phases. First, descriptive characteristics were examined and the data presented as mean±SD. Second, linear associations were assessed by correlation analysis. Since the arterial compliance was found to be age dependent[19], bivariate and partial (for control of age) Pearson or Spearman correlations were computed between AtPr and the physiological variables. In order to verify possible non-linear effects of AtPr, correlation analysis was supplemented with comparative analysis using ANOVA or Kruskal-Wallis test. All patients were retrospectively divided into 3 groups according to the tertiles of natural AtPr values observed on examination day or 1-2 days prior. Furthermore, multiple regression analysis (General Linear Model, GLM) was performed to control for age, degree of hypertension, temperature, and warm season (April-October)/cold season (November-March) differences. The final regression model predicting the specific hemodynamic and vascular characteristics included AtPr (independent variable or predictor), blood pressure and age (covariates), season (fixed factor), and interactions among these factors. Limbs were compared by paired *t*-test or by Wilcoxon test.

The SPSS-19 statistical package was used for computational purposes.

RESULTS

Physiological Difference as a Function of Sex and Limb (Table 1)

In line with our research and previous studies, we first present descriptive findings regarding sex and the source of parameter measurements before concentrating on the predictive models. As can be seen in Table 1, arterial and venous blood flows, RH, and VC in men exceeded those in women. This is probably due to the lower vascular resistance in male extremities. Similarly, the R_d and E_{in} in men were greater than those in women, but not K_{rel}. Despite the lower vascular resistance in men's arms, no sex difference in blood pressure levels or HR was detected (Table 1).

Also evident in Table 1 is the fact that blood pressure levels, K_{rel}, and RVR were significantly higher and R_d, E_{in}, and AIF were significantly lower in the legs than those in the arms in both sexes. However, no differences in K_{in}, RH, and VC were observed. The venous outflow velocity was greater in the upper versus lower limbs. The difference reached an acceptable level of reliability in men. The K_{rel} and E_{in} values demonstrated a contradistinctive difference between extremities. That is, K_{rel} for the shank arterial wall exceeded that for the arm artery, whereas E_{in} was higher for the radial vessel.

Table 1. Descriptive Physical and Hemodynamic Variables in the Left Extremities of Hypertensive Patients as a Function of Sex and Limb

Parameter	Women		Men	
	Arm	Leg	Arm	Leg
n	82	82	194	194
Age (years)	57.0±11.6		56.1±9.3	
Body mass index (kg × m^{-2})	30.5±5.7		29.4±4.5	
Heart rate (bpm)	70±11		71±11	
P_d (mmHg)	86±4	92±5[b]	88±3	94±6[b]
P_s (mmHg)	146±11	159±16[c]	148±12	163±17[c]
P_m (mmHg)	105±5	115±9[b]	108±6	118±11[c]
P_p (mmHg)	59±7	69±9[c]	61±8	70±10[c]
R_d (mm)	1.96±0.21	1.74±0.27[b]	2.21±0.27[**]	1.84±0.32[c]
$10^5 \times K_{rel}$ (dyn × cm^{-5})	9.7±2.6	13.7±3.7[c]	7.1±2.1[***]	12.2±4.5[c,**]
$10^5 \times K_{in}$ (dyn × cm^{-5})	10.9±5.0	10.8±3.2	10.3±4.4	10.6±4.6
$10^6 \times E_{in}$ (dyn × cm^{-2})	3.47±1.61	2.74±1.09[b]	3.98±1.73[*]	2.90±1.25[c]
RVR [mmHg/(mL × 100 mL^{-1} × min^{-1})]	57.1±28.8	84.8±29.8[c]	38.1±19.0[***]	74.1±25.0[c,*]
Arterial inflow (mL × 100 mL^{-1} × min^{-1})	1.84±1.02	1.35±0.61[c]	2.71±1.20[***]	1.61±0.83[c,**]
RH (mL × 100 mL^{-1} × min^{-1})	8.3±4.0	9.8±5.0	12.8±5.7[***]	11.9±5.3[**]
Venous outflow (mL × 100 mL^{-1} × min^{-1})	30.3±10.4	26.8±8.0	40.7±10.7[***]	34.4±8.3[b,***]
Venous capacity (mL × 100 mL^{-1})	1.69±0.58	1.57±0.58	2.24±0.71[***]	2.20±0.74[***]

Note. [*,**,***] $P \le 0.05$, 0.01, 0.001 (Mann-Whitney or *t*-test, difference between sexes); [b,c] $P \le 0.01$ and 0.001 *vs.* arm (Wilcoxon or paired *t*-test). HR: heart rate; P_d, P_s, P_m, P_p: diastolic, systolic, mean, and pulse blood pressures; R_d: effective inner diastolic radius of arteries; K_{rel}: elastic resistance of the relaxed arterial wall; K_{in}: elastic resistance of the intact wall; E_{in}: bulk modulus of elastic resistance of intact arteries; RVR: regional vascular resistance; RH: reactive hyperemia.

Effect of AtPr

There were neither differences in physiological parameters among AtPr tertiles nor any significant correlation with pressure levels in the arms and legs of women. Consequently, further analysis was conducted for male parameters. E_{in} only showed a weak correlation (r=0.15, P=0.035) in the legs after controlling for age, but several variables were found to be pressure-dependent in the arms. Arm E_{in} and K_{in} showed a linear association with AtPr. The partial coefficients were 0.25 (P=0.001) and 0.15 (P=0.025), respectively. The association for K_{rel} was inverse (r=-0.19, P=0.01), whereas AIF levels showed a U-shaped association. For both limbs, AtPr-associated differences in distensibility parameters were not followed by alterations in HR, blood pressure, RVR, or R_d (Table 2).

Delayed Physiological Responses to Changes in AtPr

Based on suggestions that physical sensations and hemodynamic parameters in cardiovascular patients are dependent upon AtPr changes rather than the pressure itself[2], the next step in analysis was to examine the delayed effects of barometric stimuli. In contrast to previous studies, our investigations of parameters associated with male upper extremities demonstrated that no physiological variables exhibited any statistically reliable correlation with mean daily AtPr levels measured 1 and 2 days prior to the examination day, and that there were no differences between days 0, 1 (AtPr0-AtPr1, Delta1), and 2 (Delta 2).

Age as a Predictor of Barometric Responsiveness

Given the importance of age in the initial analysis, we determined whether the AtPr effects were similar across age groups. Variable/AtPr ratios were computed and plotted against age. The AIF/AtPr index revealed an inverted "V-shaped" age dependence that was visibly different from the almost

Table 2. Hemodynamic Variables and Parameters of Brachial Artery Wall Distensibility in the Left Arms of Hypertensive Men and Their Dependence on Atmospheric Pressure

Parameter	Atmospheric Pressure Tertiles			*P* #
	≤749	750-754	≥755	
	742±4	752±2	761±4	
n	63	65	66	
Age, years	56.1±9.4	56.3±9.4	55.9±9.3	
Heart rate	72±11	70±11	73±10	
P_d	87±4	88±6	89±6	
P_s	147±13	152±14	145±12˜	
P_m	106±6	108±8	108±8	
P_p	60±12	63±14	58±12	
R_d	2.18±0.21	2.20±0.27	2.25±0.31	
$10^5 \times K_{rel}$	8.4±1.5	7.5±2.5	6.8±2.3*	0.044
$10^5 \times K_{in}$	10.3±3.3	11.7±5.6	12.2±4.0	0.095
$10^6 \times E_{in}$	3.74±1.17	4.29±1.75	4.89±1.48*	0.017
RVR	38.5±19.9	45.1±21.9	37.3±19.3	
Arterial inflow	2.80±1.00	2.42±0.93*	2.94±1.14˜	0.066
Reactive hyperemia	12.5±6.1	13.9±6.4	13.5±5.3	
Venous outflow	38.0±12.8	42.9±16.6	41.1±13.1	
Venous capacity	2.14±0.60	2.60±1.10	2.24±0.57	

Note. *$P \leq 0.05$ *vs.* 1st tertile, ˜$P \leq 0.1$ *vs.* 2nd tertile, *post-hoc* Bonferroni test; #Kruskal-Wallis test. For units of measurements see Table 1. HR: heart rate; P_d, P_s, P_m, P_p: diastolic, systolic, mean, and pulse blood pressures; R_d: effective inner diastolic radius of arteries; K_{rel}: elastic resistance of relaxed arterial wall; K_{in}: elastic resistance of intact wall; E_{in}: bulk modulus of elastic resistance of intact arteries; RVR: regional vascular resistance.

linear associations observed with the other physiological variables. As can be seen in Figure 1, there was a general position association between the AIF score and age until approximately 46 years of age, at which point the evident positive association in the younger group was replaced by a negative association in the older group. The regression coefficients from the respective linear equations for the 2 age groups differed, which was indicated by a transgression analysis of confidence intervals (P<0.05):

$AIF/AtPr_{(35\text{-}46\ years)}$=-5.395+0.217 (95% CI, -0.002, 0.448) × age; (P_{model}=0.064, n=36, r=0.31, P_r=0.032), and

$AIF/AtPr_{(47\text{-}75\ years)}$=5.282–0.030 (95% CI, -0.059, -0.005) × age; (P_{model}=0.036, n=158, r=-0.17, P_r=0.018).

As might be expected, the forearm AIF itself displayed similar age dependence with a turning point at approximately 46 of age. These distinct changes in physiological parameters between the younger and older groups may help explain the lack of association between AIF and AtPr for the total sample (Table 2). In any case, this effect led us to conduct subsequent analysis separately with the 2 age groups divided at approximately 46 years of age. The associations disappeared in the older group whereas they became stronger in the younger group (Table 3, Figure 1).

Our analyses revealed consistent differences between younger and older men for the upper limb: P_s (145.0±14.3 mmHg *vs.* 152.0±17.6 mmHg, P=0.048), R_d of the radial artery (2.12±0.23 mm *vs.* 2.23±0.27 mm, P=0.024), AIF (3.02±1.36 *vs.* 2.62±1.03 mL × 100 $mL^{-1} \times min^{-1}$, P=0.015), and K_{in} (11.80±4.85 × 10^{-5} *vs.* 9.93±4.23 × 10^{-5} dyn × cm^{-5}, P=0.025). Among the younger group, high AtPr linearly increased vascular resistance in the forearm muscles without any changes in HR. Systolic, mean, and pulse blood pressures showed a U-shaped association with ambient pressure. On days of high pressure, there was a pronounced fall in K_{rel} and an increase in K_{in} and

Table 3. Hemodynamic Variables and Brachial Wall Distensibility Parameters in the Left Arms of Hypertensive Men Younger than 47 Years of Age and Their Dependence on Atmospheric Pressure

Parameter	Atmospheric Pressure Tertiles			$P^{\#}$
	≤749	750-754	≥755	
n	13	12	14	
HR	72±10	71±10	73±10	
P_d	87±2	93±6	89±4	
P_s	143± 8	149±12$^{\wedge}$	139±5^{a}	0.083
P_m	104± 2	112±10*	105±6^{a}	0.068
P_p	55± 6	57±7	50±4$^{\wedge}$	0.069
R_d	2.08± 0.18	2.06±0.28	2.19±0.24	
$10^5 \times K_{rel}$	8.11±1.67	7.04±2.11	5.20±1.65$^{***\,a}$	0.003
$10^5 \times K_{in}$	8.16±3.10	12.90±5.61*	14.90±3.10***	0.001
$10^6 \times E_{in}$	3.20±1.18	3.53±1.51	6.74±0.83$^{***\,c}$	0.001
RVR	28.4±15.3	40.0±16.4	47.0±20.1*	0.049
Arterial inflow	3.70±1.32	2.83±1.33	2.55±1.26$^{\wedge}$	0.051
Reactive hyperemia	11.40±3.50	14.10±7.55	13.80±4.97	
Venous outflow	50.5±9.7	40.6±12.4$^{\wedge}$	43.3±11.2	
Venous capacity	2.46±0.44	2.38±0.77	2.00±0.14$^{\wedge}$	

Note. $^{\wedge, *, ***}P$≤0.1, 0.05, 0.001 *vs.* 1st tertile; $^{a, c}P$≤0.05, 0.001 *vs.* 2nd tertile, *post-hoc* Bonferroni test. $^{\#}$Kruskal-Wallis test. For units of measurements see Table 1. R_d: effective inner diastolic radius of arteries; K_{rel}: elastic resistance of relaxed arterial wall; K_{in}: elastic resistance of intact wall; E_{in}: bulk modulus of elastic resistance of intact arteries; RVR: regional vascular resistance.

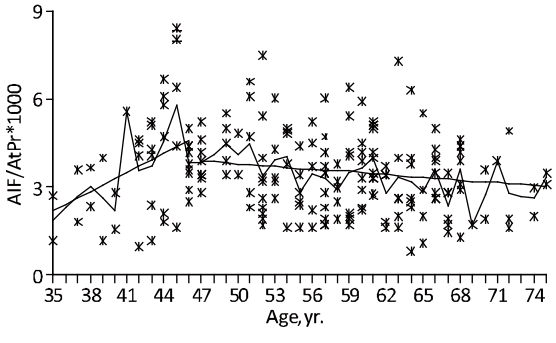

Figure 1. Scatterplot, mean values (broken line), and linear regression lines for the arterial inflow in men's forearm/atmospheric pressure ratio by age. Absent data for mean values were linearly interpolated.

E_{in}. Despite there being fewer participants in the younger group, the differences in physiological variables among the AtPr strata were more pronounced and the correlations were stronger in this group than in the older group. In the latter group, no correlations approached significance (data not shown).

Finally, combined effects of AtPr and age were detected using GLM. The forearm muscle AIF and E_{in} of the radial artery were the only characteristics for which the interaction term AtPr × age was significant, indicating that associations among AtPr, AIF, and E_{in} may vary across age groups (Table 4). For AIF, the positive interaction term indicated that the greater the age, the higher the negative influence of AtPr on AIF. Similarly, for E_{in}, the negative B for the interaction showed that the direct influence of AtPr on E_{in} decreased with age. Comparison of Eta-squared values indicated that the contribution of AtPr to the total variance of E_{in} (0.053) was 1.6 times higher than that of age (0.034) and AtPr × age (0.034).

For men younger than 47 years of age, VC showed a delayed response to ambient pressure stimuli. An inverse linear association was evident for VC in relation to differences in the magnitude of AtPr on days 0, 1, and 2; that is, the greater the increase in AtPr , lower VC. Conversely, decreases in AtPr were followed by proportional elevation of VC with a delay of 1-2 days. The respective Spearman correlation coefficients between VC and AtPr were -0.42 for

Delta 1 (*P*=0.01) and -0.43 for Delta 2 (*P*=0.008).

Impact of Hypertension and Season

Our final questions related to associations between hypertension and hemodynamic metrics and between season and outcomes. We expected that associations between parameters of arterial compliance and AtPr levels would be dependent on hypertension status, i.e., the degree of vascular wall distension. Correlation analysis revealed bivariate associations with coefficients ranging from 0.15 to 0.36 for each pairing of the 3 indices of distensibility (K_{rel}, K_{in}, and E_{in}) from one side and the 4 indicators of blood pressure (diastolic, systolic, mean, and pulse pressures) from the other side. P_d showed the strongest associations, and this variable was thus further examined by GLM analysis (Table 4). The relaxed artery was the only distensibility parameter to demonstrate a significant AtPr × P_d interaction. The negative coefficient for this term meant that the effect of AtPr on K_{rel} depended upon the degree of hypertension, namely the greater the diastolic pressure (i.e., the more distended the artery), the weaker the inverse association between AtPr and K_{rel}. Arteries that were permanently more distended seemed to be less susceptible to the effects of high AtPr on K_{rel} of the wall in its relaxed state.

Finally, prior data on seasonal variations in clinical symptoms of cardiovascular diseases prompted us to assess the influence of season on hemodynamics and parameters of arterial distensibility. For the younger male group, a comparison revealed seasonal differences in arm K_{in} (cold season $11.1\pm4.8\times10^{-5}$ *vs.* warm season $9.0\pm3.3\times10^{-5}$ dyn/cm^5, *P*=0.050) and E_{in} (cold season $4.16\pm1.75\times10^{-6}$ *vs.* warm season $3.68\pm1.65\times10^{-6}$ dyn/cm^2, *P*=0.048). Differences in leg measurements were less marked and displayed an acceptable 5% probability of error for K_{rel} (*P*=0.024) and K_{in} (*P*=0.038).

In order to compare the contribution of season and AtPr to the total variance in the physiological variables, multiple regression analysis for brachial E_{in} was performed (Table 5). In univariate models for men of all ages, season as a fixed factor had a marginal effect (*P*=0.080), whereas AtPr had a more pronounced effect (*P*=0.001). In the mixed model, the joint effect of AtPr and season as well as the distinct effect of season became insignificant, whereas the influence of AtPr remained reliable, suggesting that the impact of AtPr is independent of seasonally varying environmental factors. The disappearance of the seasonal effect in the multivariate model suggests that any association between season and clinical parameters is primarily a consequence of AtPr influences.

Table 4. Results from Multiple Regression Analysis (GLM) of Arm Physiological Variables and Influencing Factors for Men of all Ages

Parameter	Type III Sum of Squares	*P*	Partial Eta Squared	B
AIF				
Model	20.4	0.004	0.090	
Intercept	10.7	0.003	0.049	140.9
AtPr	9.0	0.006	0.042	-0.171
Age	9.2	0.005	0.043	-2.299
AtPr × Age	7.9	0.010	0.037	0.003
E_{in}				
Model	55.7	0.000	0.111	
Intercept	23.6	0.004	0.051	-200.1
AtPr	24.9	0.003	0.053	0.276
Age	15.4	0.018	0.034	2.925
AtPr × Age	15.7	0.017	0.034	-0.004
K_{rel}				
Model	67.9	0.001	0.095	
Intercept	15.7	0.047	0.024	-313
AtPr	16.1	0.044	0.024	-0.422
P_d	21.5	0.020	0.032	4.618
AtPr × P_d	21.2	0.021	0.032	-0.006

Note. K_{rel}: elastic resistance of relaxed arterial wall; E_{in}: bulk modulus of elastic resistance of intact arteries; AIF: arterial inflow; P_d: diastolic blood pressure; B: regression coefficient; *P*: level of significance.

Table 5. Results from Multiple Regression Analysis of arm E_{in} (Dependent Variable), Atmospheric Pressure (Predictor), and Season (Fixed Factor) for Men of all Ages

Parameter	Type III Sum of Squares	*P*
Model	9.1	0.080
Intercept	2426	0.000
Season	9.1	0.080
Model	30	0.001
Intercept	25	0.004
AtPr	30	0.001
Model	31	0.014
Intercept	17	0.014
Season	0.2	0.788
AtPr	21	0.007
Season × AtPr	0.2	0.792

The Eta-squared values suggested a small contribution of both predictors to the total variance of E_{in} from 1.8% for season to 5.9% for AtPr. A comparison of sums of squares (9.1 for season and 30 for AtPr) yielded about a 3-fold preponderance of AtPr over the effects of season upon E_{in}. Physiological characteristics of younger men seemed to show more adjustments to seasonal influences than those of older men.

DISCUSSION

In this study, the hypothesis that enhanced AtPr decreases arterial wall distensibility was examined. The key findings concern differences in the barosensitivity of vessels in relation to sex, age, hypertensive status, and season. We also assessed the implications of our findings with regard to the circulatory mechanisms underlying barometric susceptibility, age and sex differences, and the susceptibility of different measurement sites.

Previous studies involving high altitude, baric chambers, submarines, and aircraft cabins have suggested an association between cardiovascular variables and ambient pressure. One study showed that arterial and venous functions in cat gastrocnemius muscle preparations exposed *in vivo* are associated with stepwise changes in tissue pressure over a wide range[20]. Exposure of cultured human aortic smooth muscle cells to high AtPr leads to about a 4-fold increase in cell proliferation[21]. This effect in co-cultured endothelial cells/smooth muscle cells is mediated by nitric oxide synthase activity followed by hyperplasia of the intima–media complex and increased wall thickness and stiffness[22]. In view of the findings of our study, it appears that pressure-induced modifications of arterial distensibility can occur without concurrent changes in their inner radius.

Overall, the existing data and our findings suggest that several circulatory mechanisms are responsible for the barometric susceptibility of an organism. Changes in AtPr result in compression/decompression of the pleural cavity and the production of intestinal gas bubbles, which are then followed by alterations in intrathoracic pressure and pulmonary blood flow. External forces are important modulators of cellular functions, especially in the cardiovascular system. Mechanically induced arterial wall deformations are known to lead to the production of a variety of vasoactive mediators such as nitric oxide and prostacyclin. The expression of these mediators may be regulated at the transcription level in endothelial cells[23]. External pressure within the range 140-200 mmHg induces an acceleration of DNA synthesis in endothelial cells in a pressure-dependent manner *in vitro*[24]. Other data regarding ambient pressure-induced pain in rats[25] and humans[26] have shown that the physiological mechanisms underlying the effects of pressure on the circulation and arterial distensibility may be attributed, in part, to nerve-mediated pathways. Low AtPr leads to an increase in neuronal activity in the rat spinal trigeminal nucleus, which is considered a possible animal correlate of headaches[27]. Barometric stimulation of the sympathetic nervous system[28] can also be considered to be involved in the determination of arterial mechanical function. Thus, there is evidence that increased sympathetic tone reduces distensibility by contracting smooth muscles in the arterial wall[29].

A recent intriguing study by Mammam et al.[30]. clearly showed that stimulation of vestibular nerves can cause partial entrainment of muscle sympathetic nerve activity, which was shown to be involved in AtPr-dependent regulation of vascular tone when the ambient pressure modified the function of the vestibular apparatus[31].

Sex differences have been found in resting cutaneous blood flow, which responds to mental stress. Basal hand and finger blood flows are greater in men than in women. Skin blood perfusion is 3-fold greater in men than in women. Mental stress and deep inspiration decrease peripheral blood flow in

men but increase peripheral blood flow in women due to differences in sympathetic tone[32]. Men appear to be more susceptible than women to weather changes occurring 72 h prior to an aneurysmal subarachnoid hemorrhage, and there is a greater seasonal variation in the incidence of aneurysm among men compared with women[10].

The loss of arterial wall barometric responsiveness in aging men is suggested here as a likely mechanism for their weather sensitivity. With advancing age, progressive accumulation of connective tissue in the walls of major vessels leads to decreased vascular distensibility[33]. As a result, vascular pressure-volume relations are altered so that mild increases in vascular volume are associated with substantial increases in pressure. A clinically relevant consequence of physiologically impaired arterial compliance is increased blood pressure[14], as was observed in the present study. Although the absence of previous studies precludes explanation at this point, the apparent existence of a turning point and age boundary around age 46 for blood flow and wall stiffness is intriguing and requires further interpretation.

Comparing limbs, one can conclude that parameters of distensibility in the leg are less evidently impacted by AtPr, whereas those for the arm show greater impacts. The difference in E_{in} between AtPr tertiles was more pronounced for shoulder-than shank-based measurements. Regarding these inter-regional differences, the higher the location of an artery, the more sensitive the wall pressure. Although further studies are required to confirm these findings, an extension of this logic suggests that the cerebral vasculature is the most susceptible to changes in AtPr since the intracranial cavity is a stiff closed apical space. The lack of sufficient space to permit blood vessels to increase their volume in response to external pressure challenges may help explain why publications describing ambient pressure-associated clinical circulative disturbances are increasingly focused on intracranial circulation and cerebral pathological symptoms[34].

Adamopoulos et al.[35] reported that exposure to low environmental temperature in Athens is related to decreased aortic pulse pressure but not to altered carotid-radial and carotid-femoral pulse wave velocity (i.e., to indices of arterial distensibility), which is consistent with the fact that the seasonal effect on E_{in} is not attributable to temperature influences, but rather monthly variations in AtPr.

The maximum annual pressure amplitude in Novosibirsk is about 60 mmHg (720-780 mmHg). This difference corresponds to 82 cm H_2O and about 600 metres in altitude. The additional external mechanical force and compression that occur in winter are probably minimal for the stiff and distended vessels of aged and hypertensive persons, but they appear to be sufficiently high for the arterial walls of young individuals who respond to passive or active constriction, and increased RVR or decreased AIF. In these conditions, a higher transmural/pulse pressure is necessary to increase the volume of the vessels, which is manifested as elevated arterial stiffness.

Overall, our results may partially explain why hypertensive patients show spastic responses and report feeling bad on days with high AtPr. In this study, arterial distensibility increased RVR in the forearm in association with increased AtPr. In these conditions, conduit arteries appear and function like rigid vessels with robust mechanical properties. If cardiac function remains unchanged, these alterations must be followed by increased aortic pressure, thus further increasing the already elevated intracranial perfusion pressure. Conversely, the redistribution of blood flow in favor of cerebral circulation may lead to a better feeling in hypotensive patients during episodes of high AtPr. Such an interpretation is consistent with animal findings under hyperbaric conditions. Compression in cats[36] and rats[37] at an ambient pressure of 5-30 bar elevates cerebral and total myocardial blood flows and pulse pressure, but does not change arterial pressure, HR, or cardiac output. Risberg and Tyssebotn[38] reported that in rats kept at an ambient pressure of 5 bar, blood flow was increased in the adrenal glands and liver and decreased in the skeletal muscles.

Limitations and Concluding Remarks

Although the current data represent a useful contribution to the understanding of how AtPr is associated with changes in blood flow, the following limitations deserve mention. First, the generally weaker and more scattered associations among women are problematic. The findings in our study may reflect the smaller number of women included in the study, and the conclusion about sex differences should be considered tentative and requires confirmation. Second, this was not a repeated measures study and our data cannot exclude other interpretations. Alternately, whereas

artificial experimental modification of pressure in a barometric chamber might not reproduce the entire set of conditions accompanying natural changes in AtPr, it may be a useful supplementary approach. Third, the associations between AtPr and hemodynamic outcomes are modest and explain no more than 20% of the observed variance. Previous studies have noted that weather is weakly associated with health outcomes[39], presumably because the influences of non-meteorological regulatory factors are more important for blood circulation. However, the effects of AtPr exceed those of age, degree of hypertension and season. Consequently, although the impacts are modest, conduit and probably resistive arteries can be useful *in vitro* and *in situ* models for studying the effects of AtPr in humans and animals.

In summary, the findings of the present study suggest that muscle conduit arteries are sensitive to even small changes in ambient pressure, and that their wall can be considered a distributed "baroreceptor" of the human body. Associations among AtPr, peripheral circulation parameters, and arterial wall distensibility are evident in men, but not women, are more evident in middle-aged than older men, and apply to arm rather than leg arteries. Arteries appear to lose with age their ability to adjust their mechanical properties in response to changes in AtPr. Such a loss appears a likely mechanism underlying the particular barometric susceptibility of aging individuals. Similarly, the lack of responsiveness in the vessels of women explains why they are more sensitive to and more often suffer from meteorological perturbations. These findings raise the question of what are the health implications of the association between AtPr and arterial distensibility. They will be useful for aircraft and submarine crews, divers and undersea workers, air passengers with health problems, medical personnel in emergency departments, and specialists providing professional services for the selection and examination of individuals who work under such conditions.

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