Increased blood pressure variability in menopause

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Abstract. – Blood pressure variability represents an independent risk factor for cardiovascular diseases. To detect possible blood pressure variability changes from fertile to menopausal status, we enrolled consecutively 219 women: 104 fertile women (46.6 ± 3.4 years) and 115 menopausal women (53.9 ± 3.98 years). We evaluated for each patient the body mass index (BMI), 24 h, daytime, night-time systolic and diastolic mean blood pressure values and blood pressure variability data by means of an Ambulatory Blood Pressure Monitoring device. We found a significant higher mean age, body mass index, systolic and diastolic 24 h, day and night-time blood pressure variability in menopausal women when compared to fertile women. Age and BMI were significantly correlated to most blood pressure variability data with the Spearman Rank test. The multivariate logistic regression with dichotomic variables showed that the menopausal status is independently correlated to 24 h systolic ($p < 0.0005$) and diastolic ($p < 0.05$) variability, systolic ($p < 0.05$) and diastolic ($p < 0.05$) daytime pressure variability and systolic night-time pressure variability ($p < 0.05$). Furthermore, we found independent correlations between age 24h systolic ($p < 0.05$) and night-time diastolic blood pressure variability ($p < 0.05$), while the BMI was indepentently correlated to BMI 24h diastolic ($p < 0.01$), daytime systolic ($p < 0.01$) and diastolic ($p < 0.05$) blood pressure variability. These data show a significant increase of blood pressure variability in menopausal women when compared to fertile women, even after exclusion of confounding factors, such as aging and BMI. Menopausal status, aging and BMI increase may all, independently, contribute to the enhanced blood pressure variability we found in menopausal women.

Key Words:

Hypertension, Blood pressure variability, Woman, Menopause.

Introduction

There is growing evidence that blood pressure variability (BPV) represents an independent risk factor for cardiovascular diseases. In fact, the degree of hypertension-related end organ damages, such as left ventricular hypertrophy[1], atherosclerosis[2], cerebrovascular disorders with cognitive decline[3], microalbuminuria and progressive renal failure[4], reflects both daily life mean blood pressure levels and 24-hour BPV as assessed by a 24 hour Ambulatory Blood Pressure Monitoring (ABPM) device[5].

Determinants of BPV are not fully understood. Many reports suggest that alterations in sympathetic regulative functions may predispose individuals to abnormal high blood pressure fluctuations[5,6].

One possible explanation is a baroreflex dysfunction, due to an atherosclerotic arterial wall stiffening, that unables the cardiovascular system to smoothen stress-induced blood pressure oscillations[7]. Recent experimental studies, in fact, show how carotid sinus denervation has long-term detrimental effects on blood pressure variability[8].

The steep rise of cardiovascular morbidity and mortality in menopause, in particular of coronaric atherosclerotic disease and stroke[9,10], is probably due to the appearance of major cardiovascular risk factors such as dyslipidemia, diabetes, obesity and hypertension[10,11].

In fact, the dramatic decrease of estrogen production in menopause interferes with many metabolic pathways leading to insulin resistance, increased body mass index (BMI) and dislypidemia[10,12]. Moreover, some experimental studies show direct protective effects of estrogens on the arterial wall like vasodilation[12] and inhibition of the smooth muscle cell proliferation[13], modulating

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thereby the response to injury. Estrogen deprivation seems the major determinant of the higher prevalence of hypertension in menopausal women when compared to fertile women: in experimental studies estrogens show calcium antagonist-like effects on the smooth muscles of the arterial wall[14]; furthermore, the administration of hormonal therapy in menopausal women causes a slight, but significant, decrease of blood pressure values[15].

Recent reports show how the stress response of menopausal women involve higher cathecolamine spillover[16], and a greater sympathetic drive when compared to premenopausal women[17]. It is known that estrogen replacement therapy reduces sympathetic activity[18], with a significant decrease of the sympathetic response to mental or physical stress[19,20] and that estrogen administration blunts the norepinephrine-induced vasoconstriction in menopausal women[18,21].

Whether these menopausal changes of sympathetic haemodynamic regulation lead to enhanced blood pressure variability is not clear.

Our purpose was the detection of possible BPV changes from fertile to menopausal status.

Materials and Methods

222 women referring to the Hypertension Center of our Teaching Hospital were enrolled consecutively. Every patient, aware of the aims and methods of the study, gave written consent to participate to the study. We excluded patients affected by ischemic heart disease or cardiac insufficiency, diabetes mellitus, secondary or malignant hypertension, major renal, pulmonary or neurological diseases such as uremia, chronic obstructive pulmonary diseases or Parkinson's disease.

Other exclusion criteria were age less than 42 and more than 58, smoke habits, surgical menopause, pharmacological treatment affecting blood pressure.

The study was approved by our Institutional Ethical Committee.

Every patient underwent clinical investigations (visit, laboratory exams, echocardiography and renal ultrasound scan) to assess blood pressure values, possible end organ damages and comorbidities. Patients were subdivided into two groups: fertile women (FW) (106 individuals, mean age 46.71 ± 3.37 years) and menopausal women (MW) (116 subjects, mean age 53.97 ±

3.97 years). Women were considered in menopause if menses ceased at least two years before enrolment, while women having regular menses were considered fertile.

No menopausal woman was on estrogen replacement therapy.

According to the JNC VII classification, 60% of the FW and 51% of the MW were classified as hypertensive subjects. Hypertensive women were not on pharmacological antihypertensive treatment.

For each patient we detected 24 h, daytime (from 7.00 a.m. to 10.00 p.m.), night-time systolic and diastolic blood pressure (BP) mean values and BPV data by means of a ABPM device (Spacelabs 90207, Spacelabs Inc., Richmond, Washington, USA) performed within 5 days from enrolment. The cuff was placed on the non dominant upper arm, and the suitable cuff size (24-32 cm or 32-42 cm) was selected after measuring the arm circumference of each patient. BP readings were obtained every 15 minutes.

If less than 85% of the BP readings were considered reliable, ABPM was performed another time within 5 days. BPV data were obtained considering the standard deviations of (SD) 24 h-, day- and night-time mean BP values[22].

Moreover, we calculated the BMI of each patients using the formula weight (kg)/height^2 (m^2)[23].

Age, BMI, mean BP and BPV data of menopausal and fertile women were compared using the Student's t-test.

We performed the Spearman Rank test in order to assess possible correlations between age, mean BP and BPV data and between BMI, mean BP and BPV data. Furthermore, in order to assess if age, BMI and menopausal status are independently correlated to mean BP and to BPV data we used a logistic regression with dichotomic variables: all subjects were subdivided into two groups (high or low age, high or low BMI compared to the median value, menopausal o fertile status) and the multivariate comparison was performed between all six subgroups and every single mean BP value and every single BPV value.

Data are expressed as mean value ± SD.

Results

104 fertile women and 115 menopausal women were included in the study after the ABPM. 21 fertile women and 16 menopausal

women had to perform ABPM twice, and only 2 fertile women and 1 menopausal woman were excluded from the study because of the unreliability of both ABPM.

The Student's t-test showed a significant higher mean age (53.89 ± 3.98 years vs 46.62 ± 3.42 years, $p < 0.00001$) and significant higher mean BMI (26.79 ± 3.97 kg/m^2 vs 24.86 ± 3.56 kg/m^2, $p < 0.001$) in the menopausal group when compared to the fertile women.

We found significant lower 24h-, day- and night-time mean diastolic blood pressure values in the MW when compared to the FW (Table I).

Menopausal women showed similar day-night systolic and diastolic blood pressure differences to the fertile group. As regards BPV data, we found significant higher systolic and diastolic 24 h, day- and night-time BPV in MW when compared to FW (Table I).

The Spearman Rank test showed that age was significantly correlated to BMI ($p < 0.05$), and to some of the mean blood pressure values, in particular to 24h-, day and night-time mean diastolic blood pressure values ($p < 0.005$, $p < 0.005$, $p < 0.05$ respectively). As regards BPV data, age was significantly correlated to 24h systolic ($p < 0.005$), daytime systolic ($p < 0.05$), daytime diastolic ($p < 0.01$) and night-time diastolic ($p < 0.01$) blood pressure variability.

BMI was significantly correlated to all BPV data. In particular we found correlations with systolic 24h-, daytime and night-time blood pressure variability ($p < 0.005$, $p < 0.001$, $p < 0.005$ respectively) and to diastolic 24h, daytime and night-time blood pressure variability ($p < 0.001$, $p < 0.001$, $p < 0.005$ respectively). No correlations between mean blood pressure data and BMI were found.

The multivariate logistic regression with dichotomic variables showed that the menopausal status is independently correlated to 24 h, day and night-time mean diastolic blood pressure, and, as regard BPV data, to 24 h systolic and diastolic variability, systolic and diastolic daytime variability and systolic night-time variability (Table II).

Furthermore, the multivariate analysis showed that some of the correlations between age and BPV data we found using the Spearman Rank test failed to reach statistical significance. Only 24h systolic and night-time diastolic BP variability were correlated to age (Table II).

Finally, the multivariate analysis confirmed some of the correlations between BMI and BPV data we found using the univariate analysis. In particular BMI was significantly correlated to 24h diastolic, daytime systolic and daytime diastolic BPV (Table II).

Discussion

Our data show a significant increase of BPV in MW compared to FW. 24 hour BPV partly reflects haemodynamic response to exogenous

Table I. Comparison of blood pressure values (mmHg) and blood pressure variability data (mmHg) between fertile and menopausal women with Student's t test. All data are expressed in mean value ± SD.

Haemodynamic data	Fertile women	Menopausal women	Significance
24h SBP*	133.57 ± 12.66	131.00 ± 14.36	n.s. ‡
24h DBP†	86.19 ± 8.71	81.22 ± 10.13	$p < 0.0005$
24h SBP variability	14.14 ± 2.82	15.75 ± 3.69	$p < 0.0005$
24h DBP variability	12.86 ± 2.55	13.96 ± 3.04	$p < 0.005$
Daytime SBP	139.45 ± 12.51	137.41 ± 14.82	n.s.
Daytime DBP	92.15 ± 8.46	87.43 ± 10.83	$p < 0.0005$
Daytime SBP variability	12.55 ± 2.58	14.23 ± 3.33	$p < 0.00005$
Daytime DBP variability	11.26 ± 2.56	12.86 ± 3.04	$p < 0.00005$
Night-time SBP	124.89 ± 14.18	121.78 ± 15.71	n.s.
Night-time DBP	77.64 ± 10.26	72.26 ± 10.22	$p < 0.0005$
Night-time SBP variability	10.38 ± 2.55	11.53 ± 3.64	$p < 0.01$
Night-time DBP variability	8.81 ± 2.09	9.61 ± 2.96	$p < 0.05$

*SBP: systolic blood pressure; †DBP: diastolic blood pressure; ‡n.s.: not significant.

Table II. Independent correlations between menopausal status, age, body mass index (BMI) and every single mean blood pressure value (mmHg) and blood pressure variability data (mmHg) obtained with the multivariate logistic regression analysis.

Haemodynamic data	Menopausal status	Age	BMI
24h SBP*	n.s.‡	n.s.	n.s.
24h DBP†	$p < 0.05$	n.s.	n.s.
24h SBP variability	$p < 0.0005$	$p < 0.05$	n.s.
24h DBP variability	$p < 0.05$	n.s	$p < 0.01$
Daytime SBP	n.s.	n.s	n.s.
Daytime DBP	$p < 0.05$	n.s.	n.s.
Daytime SBP variability	$p < 0.05$	n.s.	$p < 0.01$
Daytime DBP variability	$p < 0.05$	n.s.	$p < 0.05$
Night-time SBP	n.s.	n.s.	n.s.
Night-time DBP	$p < 0.01$	n.s.	n.s.
Night-time SBP variability	$p < 0.05$	n.s.	n.s.
Night-time DBP variability	n.s.	$p < 0.05$	n.s.

*SBP: systolic blood pressure; †DBP: diastolic blood pressure; ‡n.s.: not significant.

stimuli[24], and increased BPV may indicate enhanced stress induced and sympathetic mediated cardiovascular responses in MW. Many reports, in fact, show increased haemodynamic response to stress[25] in MW. The loss of estrogen protective activity seems to be involved in such sympathetic menopausal hyperactivity, since estrogen replacement therapy reduces sympathetic outflow[26] and blunts the enhanced cardiovascular response to stress[27]. These results suggest a direct influence of estrogens on sympathetic activity.

Increased BPV may also reflect impaired baroreflex function. Menopausal induced dyslipidemia, obesity, hypertension or diabetes may lead to arterial stiffening and consequent decreased baroreflex sensitivity[28,29]. On the other hand, some reports show direct influence of estrogens on this buffering system, since hormonal replacement therapy seems to increase baroreflex sensitivity[30] and reduce BPV[31].

Aging is an important confounding factor: older subjects show higher blood pressure oscillations than younger individuals[32]. Whether these differences reflect higher blood mean blood pressure values or progressive baroreflex maladaptation[28,33] in older individuals is debatable. According to these reports, using the univariate regression model we found higher BPV data in older individuals than in younger ones, even if some of these data failed to reach statistical significance in the multivariate analysis.

The comparison between MW and FW automatically involves the comparison between older and younger individuals. To exclude the influence of aging, we performed the multivariate analysis showing that the increase of BPV data is correlated to the menopausal status independently of age.

Another possible confounding factor is represented by the BMI, since obesity, in particular visceral obesity, seems to affect cardiovascular autonomic regulation[34,35].

Interestingly, we found a significant correlation between all BPV data and BMI using the Spearman Rank test. Most of these correlations were confirmed with the multivariate logistic regression analysis.

Some studies indicate that BMI increase induces sympathetic hyperactivity[36]. Hyperinsulinemia is a known trigger of sympathetic hyperactivity[37], and since adipose tissue enhances insulin resistance, hyperinsulinemia may be responsible for imbalanced autonomic cardiovascular regulation[38], hence for increased BPV in obese women. Moreover, some studies show a depressed baroreflex sensitivity in obese subjects[39], that may lead to broader blood pressure fluctuations than in lean subjects.

Another possible link between obesity and sympathetic hyperactivity is an elevation of leptin serum levels[40].

According to previous studies[41], we found a slight but significant increase of BMI in MW when compared to the fertile group.

In addition, it is known that MW show a higher prevalence of visceral adipose tissue distribution than FW[42], and visceral fat is known to influence sympathetic activity[43], probably inducing greater insulin resistance than peripheral fat[44].

This BMI increase and, hypothetically, the adipose tissue redistribution may contribute to the overall BPV increase in MW we found in our study group. On the other hand the multivariate analysis showed an independent correlation between menopausal status and BPV increase, even after exclusion of the BMI variable.

Finally, BPV is known to increase with mean blood pressure levels. Hypertensive subjects show broader blood pressure fluctuations than normotensive subjects[45]. The enhanced BPV of hypertensive individuals is probably caused by an autonomic dysregulation[46] and, in particular, by a baroreflex decreased sensitivity[47].

In this study the influence of mean blood pressure levels on BPV seemed to be overwhelmed by other factors, like menopausal status or BMI, since we found significant higher BPV, despite lower mean diastolic blood pressure values, in the menopausal group compared to the fertile group. The lower diastolic mean pressure levels of MW probably depends on the lower prevalence of hypertensive individuals in our menopausal study group than in the fertile group. On the other hand, we found no significant differences regarding mean systolic blood pressure values between the two groups. This slight increase of the pulse pressure in menopause, regardless the mean pressure values, is consistent with results of previous reports[48] and may reflect beginning of age-dependent arterial stiffening.

In conclusion, this study shows a significant increase of BPV in MW when compared to FW, even after exclusion of confounding factors such as age and BMI.

Menopausal status, aging, BMI increase and, hypothetically, adipose tissue redistribution may all independently contribute to the significant BPV increase in MW we found.

Further studies are required to confirm the influence of menopausal status on BPV and to find out whether these haemodynamic changes are expression of baroreflex impairment due to menopausal atherosclerosis, or represent the cardiovascular response to centrally induced sympathetic hyperactivity.

Also, longitudinal studies may evaluate the importance of BVP as risk factor for the development of target organ damages in MW.

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