CLIN. AND EXPER. HYPERTENSION, 19(5&6), 793–811 (1997)

V. LARGE ARTERIES & TARGET ORGANS

INFLUENCE OF GENDER ON THE LEVEL OF PULSE PRESSURE : THE ROLE OF LARGE CONDUIT ARTERIES

ASMAR R, BRISAC AM, COURIVAUD JM, LECOR B, LONDON GM, SAFAR ME
From Department of internal Medecine, Institut de Recherche et Formation Cardio-vasculaire, and INSERM (U 337), Broussais hospital, 96, rue Didot 75674 - Paris - Cedex (France)

KEYWORDS: Hypertension, Large arteries, Gender, Ambulatory, Pressure monitoring, Pulse pressure

ABSTRACT

The blood pressure curve may be divided into two components: a steady component represented by the mean arterial pressure, and a pulsatile component represented by the pulse pressure. Whether the contribution of either these two components may be different in men and women was not yet investigated.

The present study used 24 hours ambulatory brachial blood pressure monitoring and determination of casual carotid and radial pulse pressure by applanation tonometry to investigate 320 subjects (199 men and 121 women) with normal or elevated blood pressure.

Address corespondence to Professor Michel Safar.

With ambulatory blood pressure monitoring, there was no gender influence on the mean values of mean and diastolic blood pressure, but men were characterized by a significantly higher systolic and pulse pressure ($P<0.001$). In women, pulse pressure was strongly and positively correlated with systolic (and not diastolic) blood pressure. In men, pulse pressure was positively correlated with systolic blood pressure and negatively with diastolic blood pressure ($P<0.001$). In the overall population (men plus women), brachial ambulatory pulse pressure was positively correlated with body height and mean arterial pressure ($P<0.001$) but the latter correlation was stronger in women. Applanation tonometry indicated that, whereas carotid pulse pressure was identical in men and women, men had a significantly higher radial systolic blood pressure, indicating a gender difference in pressure wave transmission.

The study provides evidence that men and women did not differ in terms of mean arterial pressure, but rather in terms of pulse pressure and pressure wave transmission, indicating that large (and not only small) arteries modulate the gender difference in the level of blood pressure. This finding may have important implications for the diagnosis and the clinical management of subjects with hypertension.

INTRODUCTION

Hypertension is a cardiovascular risk factor, generally attributed to the reduction in the caliber or number of small arteries or arterioles with a resulting increase in peripheral resistance and mean blood pressure (MBP). MBP refers to steady phenomena, considering a linear model of the circulation which does not take into account that blood pressure (BP) fluctuates during the cardiac cycle. In clinical practice, pressure is defined in terms of systolic (SBP) and diastolic (DBP) blood pressure, which refers to a pulsatile phenomenon,. The most modern and realistic approach is to consider that blood pressure has a steady component (MBP), and a pulsatile component (PP) (1). MBP is the pressure for the distribution of steady flow to the tissues and organs. The pulsatile component of BP is the consequence of the intermittence of ventricular ejection, and its determinants are the elastic properties of arterial walls (arterial stiffness), and the timing and intensity of arterial wave reflections.

Because hypertension is usually defined in terms of brachial systolic and diastolic blood pressure independent on age and gender, the hemodynamic differences between men and women have been minimized for a long time. However, when hypertension is analyzed in terms of mean arterial pressure and pulse pressure, substantial particularities may be considered. Firstly, women and men differ significantly in their arterial geometry, namely arterial cross-sectional area and length (1). Secondly, brachial pulse pressure is lower in women, which suggests particular alterations of ventricular ejection and arterial function (2). Finally, brachial pulse pressure is an independent cardio-vascular risk for cardiac mortality (3) and myocardial infarction (4), but the implications of these findings were shown to predominate in women (3).

The purpose of the present study was to show that, in women: (i) the status of the arterial system plays a substantial role in the hemodynamic factors governing the level of blood pressure, and (ii) the transmission of pulse pressure from central to peripheral arteries differs in women significantly from that of men. Ambulatory blood pressure monitoring and casual applanation tonometry were used as noninvasive markers to investigate the respective contribution of mean and pulse pressure.

MATERIAL AND METHODS

PATIENTS:

Three hundred and twenty subjects (199 males and 121 females) consulting at the cardio-vascular prevention center (Broussais Hospital, Paris) participated to the study. On the basis of auscultatory method as

described below, brachial diastolic blood pressure was in all subjects between 52 and 144 mmHg. Age range was between 16 and 82 years. Mean weight and height was respectively 76 ± 10 kg (± 1 standard deviation) and 175 ± 7 cm in males, and 61 ± 11 kg and 162 ± 6 cm in females. All subjects were never treated or have stopped their treatment at least 4 weeks before the investigation day. No subject had coronary ischemic heart disease, congestive heart failure or any renal or cerebral complication on the basis of a complete clinical and biological examination. Written consent, based on a detailed description of the procedure, was obtained from all patients after approval by Ethical Committee. Casual brachial blood pressure was measured in the supine position after 10 minute rest; thereafter casual carotid and radial pulse pressure was measured using applanation tonometry; then patients underwent brachial blood pressure monitoring according to the methodology described below.

CASUAL BRACHIAL BLOOD PRESSURE MEASUREMENTS :

Casual blood pressure was measured after 10 minutes rest in the supine position according to the WHO recommendations and using a mercury sphygmomanometer and an appropriate cuff. An average of three measurements was taken for each patient. The Korotkoff noise phase I was used for the determination of systolic blood pressure. Phase V was used for the evaluation of diastolic blood pressure. Mean blood pressure was calculated as the sum of diastolic blood pressure plus one third of the pulse pressure, and pulse pressure as the difference between systolic and diastolic blood pressure.

CASUAL CAROTID AND RADIAL PULSE PRESSURE MEASUREMENTS :

To improve the accuracy of non invasive recording of the arterial pressure wave contour at the site of the carotid and the radial arteries, we used a pencil-type probe incorporating a high-fidelity strain-gauge tranducer (Millar instruments, Houston, TX) (5,6). The instrument uses the principle of applanation tonometry as it is used in ocular tonometry for registration of intraocular pressure: flattening (applanation) of a curved surface that is subject to internal pressure allows direct measurement of the pulse pressure within the structure. The use and the accuracy of the tonometer were previously studied and validated on the exposed canine femoral artery and percutaneously on the human radial artery (5). In addition, in 16 subjects undergoing catheterisation, pulse pressure was measured simultaneously by two methods invasively at the site of the aortic arch and noninvasively at the site of the common carotid artery. A significant positive correlation ($r=0.93$, $p<0.0001$) was observed with a slope equal to 1.05 and an intercept that was not significantly different from zero (0.4 mmHg) (6). In another study in 105 subjects, we measured brachial pulse pressure by conventional sphygmomanometry and radial pulse pressure by applanation tonometry. The two measures were strongly correlated: $r=0.97$; slope 0.98; intercept 1.4 mmHg (7). Because the tonometer transducer is small relative to the size of the artery, the positioning of the tranducer over the site of the artery was found to be an important consideration for clinical investigation. Difficulty arising for these measurements and the way to correct them have been described elsewhere (5-7). Intra-observer variability of the pulse pressure measurement was 4.7 ± 2.5 % and inter-observer variability was 6.1 ± 3.5 % (6,7). Such levels of reproducibility can be achieved after four to six weeks use of the probes (5). In this study, one observer (RA) was involved in the tonometer measurements.

AMBULATORY BRACHIAL BLOOD PRESSURE MONITORING :

Automated blood pressure monitoring was carried out in each patient using a Novacor apparatus (model Diasys 200 R, Rueil-Malmaison, France) to measure and record brachial blood pressure and heart rate over a full 24 h period. The reliability of this method has been published in detail elsewhere (8). Recordings were performed every 15 minute during the 24 h. Ambulatory monitoring was undertaken for a full active day; the patient worked as usual during the day and then went home as usual in the evening. Each full day recording was divided into an activity (diurnal) period (7:00 a.m. to 10:00 p.m.) and a non-activity (nocturnal) period (10:00 p.m. to 7:00 a.m.). On the basis of patients' diaries, this classification corresponded adequately to awake and asleep categories.

STATISTICAL ANALYSIS (9):

Statistical analysis was performed with the software NCSS (Kaysville, USA). Values are expressed by means ± 1 standard deviation. Comparison of the mean values between two populations was performed using unpaired t-student test. Simple and stepwise multiple regression analysis populations were performed according to classical techniques. The significance level was fixed at 0.05.

RESULTS:

Ambulatory brachial blood pressure monitoring **: Table I (left side) shows that men and women differed in terms of weight, height, systolic blood pressure and pulse pressure, which were lower in women than in men ($P < 0.001$). There was no difference in the mean value of mean and diastolic blood pressure between men and women. Age did not influence such findings (Table I; right side). Heart rate was significantly higher ($p < 0.001$) in females, particularly below 50 years.**

Table II indicates the values of the simple correlation coefficients relating systolic, diastolic, mean and pulse pressure (in men, in women and in the totality of the population) with the various clinical and hemodynamic variables.

In men, systolic, diastolic and mean pressure were positively correlated with age ($p < 0.001$) and body weight ($P < 0.001$), but not with body height. Pulse pressure was shown to exhibit only two strong correlations: one positive correlation with systolic blood pressure ($P < 0.001$) and one negative correlation with diastolic blood pressure ($P < 0.001$). Pulse pressure did not correlate with mean pressure, or body height, and was slightly correlated with body weight ($P < 0.05$).

In women, pulse pressure was positively correlated with age ($P < 0.05$), weight ($P < 0.05$), height ($P < 0.05$), systolic blood pressure ($P < 0.001$) and mean blood pressure ($P < 0.001$). Pulse pressure did not correlate with diastolic blood pressure.

Figure 1 illustrates a positive correlation between pulse pressure and mean arterial pressure. Although the correlation was significant in the totality of the population ($r=0.20$; $P<0.001$), it was stronger in women

Table I: Clinical characteristics of the population according to gender and age

Men and women are statisticaly compared on the left of the table.
The role of age is indicated by the study on the right of the table

	Men (n=199)	Women (n=121)	p value	Men Age ≥ 50 years (n=81)	Men Age < 50 years (n=118)-	Women Age ≥ 50 years (n=53)	Women Age < 50 years (n=68)
Age (years)	46 ± 14	48 ± 13	NS	59 ± 7	37 ± 9	59 ± 8	39 ± 8
Weight (Kg)	76 ± 10	48 ± 13	0.001	76 ± 11	77 ± 10	61 ± 8	60 ± 7
Height (cm)	175 ± 7	162 ± 6	0.001	174 ± 7	177± 7	161 ± 5	163 ± 6
24 ^{h} SBP (mmHg)	129 ± 13	121 ± 14	0.001	133 ± 14	126 ± 11	122 ± 6	120 ± 14
24 ^{h} DBP (mmHg)	80 ± 11	82 ± 9	NS	84 ± 10	78 ± 10	81 ± 8	83 ± 9
24 ^{h}MBP (mmHg)	97 ± 10	95 ± 10	NS	101 ± 10	94 ± 9	95 ± 9	95 ± 10
24 ^{h} PP (mmHg)	48 ± 11	38 ± 11	0.001	49 ± 11	48 ± 10	40 ± 12	36 ± 9
24 ^{h} HR (h/mn)	76 ± 10	79 ± 10	0.001	75 ± 10	76 ± 10	76 ± 10	82 ± 8

± 1 Standard deviation

Table II :Simple correlation coefficient analysis

Correlations	Age (years)	Weight (kg)	Height (cm)	24 H SBP (mmHg)	24 H DBP (mmHg)	24 H MBP (mmHg)	24 H PP (mmHg)	24 H HR (b/mn)
Total								
24 H SBP(mmHg)	0.21 ***	0.27***	0.24 ***	——	0.58 ***	0.84 ***	0.70 ***	0.07
24 H DBP(mmHg)	0.28 ***	0.12*	- 0.076	0.57 ***	——	0.92 ***	- 0.17 **	0.18 ***
24 H MBP(mmHg)	0.29 ***	0.20 ***	0.06	0.84 ***	0.92 ***	——	0.21 ***	0.15 **
24 H PP(mmHg)	0.004	0.22 ***	0.34***	0. 70 ***	-0.17 **	0.20***	——	-0.08
24 H HR (b/mn)	-0.12 *	- 0.05	- 0.14 **	0.07	0.18 ***	0.15 ***	- 0.08	——
Men								
24 H SBP (mmHg)	0.27 ***	0.12	0.04	——	00.61 ***	0.84 ***	0.60 ***	0.12
24 H DBP (mmHg)	0.38 ***	0.30 ***	0.003	0.61 ***	——	0.94 ***	- 0.26***	0.11
24 H MBP (mmHg)	0.38 ***	0.25 ***	0.01	0.84***	0.94 ***	——	0.07	0.12
24 H PP (mmHg)	- 0.05	- 0.16 *	0.04	0.60 ***	- 0.26 ***	0.07	——	0.02
24 H HR (b/mn)	- 0.02	0.07	- 0.05	0.12	0.11	0.12	0.02	——
Women								
24 H SBP (mmHg)	0.19 *	0.15	0.10	——	0.68 ***	0.89 ***	0.78 ***	0.15
24 H DBP (mmHg)	0.05	0.02	-0.09	0.68 ***	——	0.93 ***	0.08	0.30 ***
24 H MBP (mmHg)	0.12	0.09	- 0.005	0.89 ***	0.93 ***	——	0.43 ***	0.25 **
24 H PP (mmHg)	0.21 *	0.18 *	0.22 *	0.78 ***	0.08	0.43 ***	——	- 0.06
24 H HR (b/mn)	- 0.34 ***	0.03	0.01	0.15	0.30 ***	0.25 **	- 0.06	——

P value: * <0.05 **<0.01 ***< 0.001

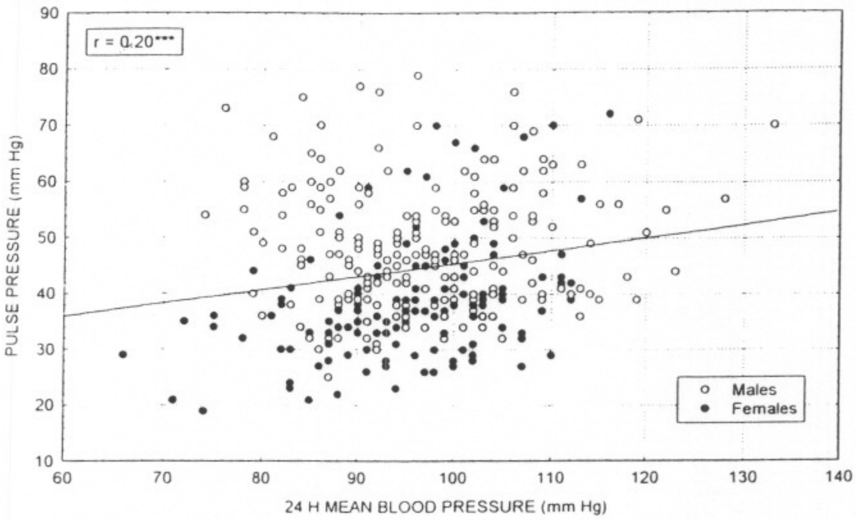

Figure 1:

Simple linear correlation between the mean blood pressure and the pulse pressure measured over 24 hours in men and women.

***** : < 0.001**

A significant correlation was observed only in females.

(r=0.43; P<0.001). As shown in table III, in women, a significant positive correlation was observed both in older (³ 50 years) or younger (² 50 years) subgroups. In men, the correlation was negative in younger subjects and positive in older subjects (P=0.04), but did not reach the statistical significance (Table III).

Figure 2 shows that, whereas pulse pressure was poorly correlated with body height in men (r=0.03), a significant positive correlation was observed in women (r=0.22; P<0.05) as in the totality of the population (r=0.34; P<0.001).

Table III: Correlation coefficients of the 24 ^{H} PP vs 24 ^{H} MBP relationships according to age and gender

PP/MBP	Men	Women	p value (gender effect)
Age < 50 years	r = -0.08	r = 0.42	0.001
Age ^{3} 50 years	r = 0.21	r = 0.49	0.07
p value (age effect)	0.04	0.60	

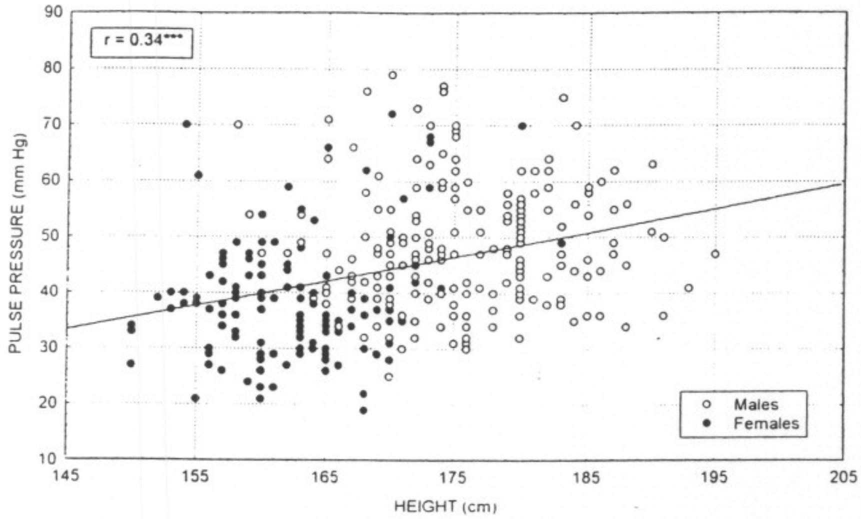

Figure 2:

Simple linear correlation between brachial pulse pressure measured over 24 hours and body height in men and women.

***: < 0.05**

Table IV: Multiple regression analysis of ambulatory brachial pulse pressure (PP)

	MEN			WOMEN		
	Beta	B	p value	Beta	B	p value
Age (years)	- 0.06	0.08	0.4	0.17	0.14	0.06
Weight (kg)	- 0.35	- 0.37	0.001	0.04	0.04	0.67
Height (cm)	0.23	0.36	0.012	0.23	0.41	0.012
MBP (mmHg)	0.18	0.18	0.02	0.43	0.47	0.001
HR (b/mn)	0.04	0.04	0.6	- 0.11	- 0.12	0.20

B: Regression coefficient

Beta: Standardized regression coefficients

MBP: mean blood pressure

Regression summary for dependent variable: 24^{H} PP :

Men: R = 0.29; R2 = 0.28; F (5.193) = 3.5; p<0.004

Women: R = 0.53; R2 = 0.28; F (5.115) = 9.2; p<0.001

Table IV indicates the factors which on the basis of multiple regression analysis, influence brachial pulse pressure in men and women. In men, pulse pressure was influenced by three parameters: body weight (beta:-0.35; P <0.001), body height (beta: 0.23; P <0.012), and mean blood pressure (beta: 0.18; P <0.02). In women, only body height (beta: 0.23; P <0.001) and mean blood pressure (beta: 0.43; P <0.001) influenced pulse pressure.

All the findings observed with ambulatory monitoring were calculated from 24 hours brachial blood pressure. Results did not differ whether diurnal or nocturnal blood pressure measurements were used (data not shown).

•On the basis of *Applanation tonometry*, casual measurements of radial and carotid pulse pressure were obtained. As previously described (1,2,5-7), the values approximate those obtained with brachial casual measurements using mercury manometer but are indeed lower than those obtained with ambulatory monitoring. Accepting these observations, radial pulse pressure was significantly higher in men than in women (67 ± 20 versus 63 ± 21 mmHg; P< 0.05). Carotid pulse pressure was similar: 58 ± 22 versus 56 ± 24 mmHg (NS).

DISCUSSION

Two major results were obtained from the present study. Firstly, ambulatory brachial blood pressure measurements showed that, whereas men and women did not differ in terms of mean and diastolic blood pressure, systolic and hence pulse pressure were significantly higher in men. The finding was not influenced by age or the circadian profile of the

recording. Secondly, based on tonometry, because carotid pulse pressure was identical in men and women whereas radial pulse pressure was different, the results point to a gender-difference in pressure wave transmission.

- Gender-difference in brachial pulse pressure:

As we mentioned in the introduction, the blood pressure curve may be divided into two components: mean arterial pressure and pulse pressure. Whereas mean arterial pressure in influenced exclusively by cardiac output and total vascular resistance, pulse pressure is influenced by three independent hemodynamic factors: the pattern of ventricular ejection, the degree of arterial stiffeness and the timing of reflected waves. Although cardiac output (measured in absolute value: ml/min) is known to be undoubtly lower in women than in men, it seems likely that the product of cardiac output by vascular resistance, i.e., mean arterial pressure, was not influenced by gender. This finding might indicate that the behaviour of small arteries and arterioles is not substantially different in men and women.

The present study shows important differences in the behaviour of large arteries and ventricular ejection in men and women. Because stroke volume is lower in women than in men (1), a decrease in ventricular ejection might explain the reduced pulse pressure observed in women. In the present study, the finding that, in women, pulse pressure was positively correlated with systolic blood pressure but not with diastolic blood pressure is consistent with this possibility.

In men, pulse pressure was positively correlated with systolic blood pressure but negatively with diastolic blood pressure. This result indicates

that decreased ventricular ejection cannot explain exclusively the difference in the levels of pulse pressure in men and women. Changes in the function of large conduit arteries should be associated. Indeed, a simultaneous increase in systolic blood pressure and decrease in diastolic blood pressure for a given mean arterial pressure requires significant changes in arterial stiffness, in waves reflections, or a combination of both (1). In the literature on clinical hypertension, there are two arguments in favour of this latter interpretation. Firstly, whereas systolic blood pressure and pulse wave velocity, a classical marker of arterial rigidity, increase markedly with age, diastolic blood pressure remains almost constant and even decrease above 70 years of age (1). Secondly, in large populations of normotensive and hypertensive subjects, cross-sectional studies have shown that aortic pulse wave velocity is positively correlated with systolic blood pressure and negatively with diastolic blood pressure (10). Finally the group of London (2) has recently pointed out that large arteries differ significantly in men and women not only in term of their geometry (i.e. length and cross-sectional area) but also in terms of their function: (i) aortic pulse wave velocity is significantly higher in men below 50 years of age, but, after menopause, tends to be equal in men and women; and (ii) the timing of reflected waves is quite different in men and women, making the reflected wave returning earlier during systole in women.

- **Gender-difference in pressure wave transmission:**

It is widely accepted that, in a given population, a strong positive correlation is expected between mean arterial pressure and pulse pressure according to the classical formula: mean arterial pressure equals diastolic blood pressure plus one third pulse pressure. The present report strongly

suggests that such an assumption cannot be longer maintained. Indeed, in our investigation, a positive correlation was noticed between mean arterial pressure and pulse pressure but such a correlation was much more pronounced in women than in men. Because this finding refers exclusively to blood pressure monitoring and therefore is restricted to pulse pressure measurements at the site of the brachial artery, the result should be interprated cautiously as indicated below.

Pulse pressure is a complex parameter which is known to increase from central to peripheral arteries whereas mean arterial pressure remains nearly constant or even slightly decreases along the arterial tree. Thus changes in peripheral (radial or brachial) pulse pressure should be interprated adequately only in the presence of a concomitant determination of central (aortic) pulse pressure (1,2,7). In this report, using applanation tonometry, we showed that, both in men and in women, carotid pulse pressure, a widely accepted index of aortic pulse pressure, was nearly identical in both sexes. In contrast, radial pulse pressure was significantly different.Thus, it is likely that the difference in radial pulse pressure between men and women results mainly from a change in pressure wave transmission along the arterial tree as previously reported (2).

Several previous investigations have shown that two main factors are susceptible to amplify the pressure wave transmission of the forearm : the rapidity of ventricular ejection and the length of the arterial tree. Reduced ejection duration is strongly associated with an amplification of the pressure pulse from the carotid to the brachial artery (11,12) Increased heart rate and activation of the autonomic nervous system may be

responsible for this finding (13). However, in the present study, brachial pulse pressure did not correlate with heart rate. On the other hand it is obvious that the amplification of pressure pulse will be greater when the length of the arterial tree is augmented. In this study, the multiple regression analysis clearly indicated that this latter factor should be mainly considered. Indeed, the length of the arterial tree is augmented when body height is increased, resulting in a positive relationship between brachial pulse pressure and body height (Fig 2) (Tableau IV). Several epidemiological studies (14,15) have similarly reported that the ratio between ankle and brachial systolic blood pressure is increased in proportion of body height.

In conclusion, the present study has shown that there are important differences between the level of brachial systolic and pulse pressure in men and women. These differences cannot be explained on the exclusive basis of a difference in behaviour of resistant arterioles. A significant contribution of large conduit arteries is also involved. It is so suggested that the interpretation of brachial pulse and mean arterial pressure may have significant implications in the management of subjects with hypertension.

ACKNOWLEDGMENT

This study was performed with a grant from the Institut National de la Santé et de la Recherche Médicale (INSERM-U337), Paris. We thank Mrs Anne-Safar for her contribution and Mrs Christiane Kairati for the secretary assistance.

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