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Prediction of Future Hypertension by Casual Blood Pressure or Invasive Hemodynamics? A 30-year Follow-up Study

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Blood pressure elevation in young age is associated with a risk of developing hypertension. However, not all subjects will progress to clinical hypertensives in need of pharmacological therapy. In younger subjects, there is essential to find clinical or experimental characteristics to predict the future risk of hypertension. In the present study, the long-term relationship between casual blood pressure measurement and future hypertension has been examined. The initial study group consisted of 20-year-old men ($n = 44$) with mild blood pressure elevation and a normotensive male control group ($n = 29$). After 30 years, we re-examined 32 (72%) of the subjects with previous mild blood pressure elevation and 21 (73%) of the controls. We further analyzed possible associations between blood pressure level at follow-up and anthropometric data, and invasively measured hemodynamic variables at baseline. After 30 years, 38% in the group with blood pressure elevation at baseline had developed hypertension, as compared to 10% in the control group. There was a significant positive relationship between baseline systolic blood pressure ($r = 0.56$; $p < 0.001$) and diastolic blood pressure ($r = 0.36$; $p < 0.01$) and systolic blood pressure 30 years later. In further regression analyses, there were no associations between cardiac output, vascular resistance or anthropometric data at baseline and blood pressure at follow-up. In conclusion, casual blood pressure measurements predict the risk of future hypertension, whereas invasive hemodynamic and anthropometric measurements do not in young men with mild blood pressure elevation. *Key words: body mass index, cardiac output, hypertension, vascular resistance, waist/hip ratio.*

INTRODUCTION

In several cross-sectional studies, a hyperkinetic circulation and an increased cardiac output has been demonstrated in borderline hypertension and in young individuals with slightly elevated blood pressure [1–3]. An enhanced cardiac output is related to an increased activity of the sympathetic nervous system, whereas the amplified vascular resistance depends on both sympathetic tone and hypertrophy of pre-capillary resistance vessels [3–6]. With increasing age, the cardiac output often normalizes, while the total peripheral resistance rises [4–9]. As a result, the blood pressure elevation is maintained. Subsequently, the adaptive mechanisms in the peripheral vessels are further augmented. This augmentation will eventually cause sustained hypertension [2, 10].

The period with hyperkinetic circulation has been suggested as a pre-hypertensive stage [1, 11]. However, an alternative interpretation may be the inclusion of tense anxious individuals in examined hyperkinetic groups, showing increased heart rate and cardiac output during invasive procedures. In previous communications, we have reported that young men with mild blood pressure elevation had increased cardiac output and arteriolar hypertrophy [3, 11]. Whether these individuals had increased risk to develop hypertension has been largely unknown.

It is well established that young subjects with mild blood pressure elevation have an increased risk of developing hypertension in the future [12–14]. In particular, blood pressure response to psychological stress [15] or physical stimuli [16, 17] have been shown to predict development of hypertension.

For most patients with mild blood pressure elevation, current guidelines recommend lifestyle advice and regular blood pressure controls [18]. In particular, the latter may cause worries for the individual and costs for the healthcare system. The problem is particularly unresolved in younger subjects. Obviously, there is an urge to find clinical or experimental characteristics to predict which patients are at risk and who may be in need of therapy.

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In the present study, blood pressure results from invasive hemodynamic evaluations and anthropometrical data have been assessed in order to analyze if the pre-hypertensive characteristics in these young men with mild blood pressure elevation were predictive of sustained hypertension and signs of target organ damage 30 years later.

SUBJECTS AND METHODS

The present study was initiated in 1970 [3]. The subjects were recruited in a military enlistment center, which all healthy men aged 19–22 years from western Sweden attended.

Eighty-six men presented with a casual systolic blood pressure $\geq$150 mmHg and a diastolic blood pressure $\geq$90 mmHg, when seen in the afternoon. If the blood pressure level was verified the subsequent morning, the subject could be included. Additional criteria for inclusion were systolic blood pressure $\geq$140 mmHg on two subsequent visits at our Hypertension Clinic [19]. Men with cardiovascular abnormalities or signs of secondary hypertension were not included in the study.

A control group consisted of 24 healthy men recruited from the same enlistment center health examination. All had blood pressure $\leq$130/80 mmHg at the screening and in the following visit at the Hypertension Clinic. In addition, five healthy male blood donors, aged 19–22 years, fulfilling the same blood pressure criteria, were included in the control group.

Thus, the total study group includes a group of men with blood pressure elevation, in whom blood pressure levels were above the 98th percentile in the blood pressure distribution of all the examined men, and a control group with blood pressure levels in the range between 50th and 75th percentile of the blood pressure distribution.

Subjects with mild blood pressure elevation and controls were examined with invasive central and regional hemodynamics [3, 9]. Forty-four of the 86 subjects with mild blood pressure elevation (51%) and all the 29 controls were examined hemodynamically.

Central and regional hemodymaic investigations have been previously described [3, 8, 9]. Cardiac output was determined by dye-dilution (indocyanine green) using a cuvette and a densitometer (Cardiognost, Atlas Werke, Germany) [20]. Total peripheral resistance was calculated from the mean arterial pressure and the cardiac output. Hemodynamic variables were corrected for body surface area, and the cardiac index, stroke volume index and total peripheral resistance index were derived. Vascular resistance at maximal dilatation was assessed following ischemic hyperemia, caused by a 5-min occlusion of the brachial artery, and calculated from blood flow, determined by plethysmography, and simultaneous intra-arterial blood pressure [8, 9]. Height, weight and waist/hip ratio were measured using standard methods. Body mass index (BMI) was calculated from body weight and height.

Thirty years after the initial study, all subjects were located. All men were contacted, except one man in the blood pressure elevation group who had died in an accident. Thirty-two of 44 (73%) in the group with blood pressure elevation and 21/29 (72%) in the control group agreed to be examined again.

Assessments were made in the subjects' everyday environment, mainly at home. Auscultatory blood pressure was measured three times after 5 min of rest in the sitting position. The mean blood pressure of the latter two measurements was used. Men with suspected hypertension were further examined in our outpatient clinic according to our standard routines [19]. Four consecutive blood pressure readings were performed before therapy was started.

The study was approved by the Ethical Committee at the University of Göteborg. All men gave informed consent to participate in the study.

Statistical analysis

Means, standard deviations and correlation coefficients were calculated according to standard methods. Differences in means between groups were tested with Student's *t*-test. For longitudinal changes within groups, Student's *t*-test for paired observations were used. The χ^2 test was used to compare relative changes in subgroups of patients and multiple regression analysis was used to evaluate variables related future stable hypertension.

RESULTS

Thirty-two (73%) subjects with mild blood pressure elevation out of the 44 in the initial screening were re-examined. Their baseline anthropometric and follow-up characteristics are given in Table I. Twelve of these (38%) had a blood pressure repeatedly exceeding 140/90 mmHg; two were already on antihypertensive therapy. Twenty-one normotensive subjects (72%) of the 29 in the initial screening were re-examined (Table I). Two of them (10%) had developed a blood pressure above 140/90 mmHg. These fourteen patients had developed clinical hypertension and were subsequently put on drug therapy.

Blood pressure over time in subjects with mild blood pressure elevation and normotensive controls are shown in Table I. Diastolic blood pressure was increased from 79 ± 7 to 86 ± 8 mmHg ($p < 0.04$) and from 73 ± 8 to 82 ± 10 mmHg ($p < 0.005$) in subjects with mild blood pressure elevation and normotensive subjects, respectively. Mean systolic blood pressure did not change significantly among subjects with mild blood pressure

Table I. *Body mass index (BMI), body weight, and waist/hip (W/H) ratio, systolic lood pressure (SBP) and diastolic blood pressure (DBP) in subjects with mild blood pressure elevation and normotensive subjects at baseline ($_0$) and after 30 years ($_{30}$)*

	Normotensive controls ($n = 21$)	BP elevation group ($n = 32$)	p
BMI_0	21 ± 2	22 ± 3	<0.03
BMI_{30}	26 ± 3	26 ± 4	n.s.
$Weight_0$	66 ± 7	74 ± 10	<0.005
$Weight_{30}$	83 ± 9	88 ± 5	<0.05
W/H $ratio_{30}$	0.91 ± 0.06	0.95 ± 0.08	<0.06
SBP_0	117 ± 8	140 ± 9	<0.0001
SBP_{30}	124 ± 14[a]	140 ± 11	<0.0009
DBP_0	73 ± 7	79 ± 9	<0.0001
DBP_{30}	82 ± 10[b]	86 ± 10[c]	<0.05

Values are mean ± SD.
[a]SBP_0–SBP_{30} ($p < 0.03$).
[b]DBP_0–DBP_{30} ($p < 0.005$).
[c]DBP_0–DBP_{30} ($p < 0.04$).

elevation over the observational period but in the normotensive group systolic blood pressure increased from 117 ± 11 to 124 ± 14 mmHg ($p < 0.03$).

The mean systolic blood pressure in subjects with mild blood pressure elevation initially was significantly increased after 30 years (140 ± 11 vs 124 ± 14 mmHg; $p = 0.0009$), compared with normotensive subjects (Table I). The diastolic blood pressure at follow-up was also higher in the group with higher baseline values (86 ± 10 vs 82 ± 10; $p < 0.05$). The mean blood pressure in patients who were diagnosed as hypertensive at follow-up was 148/96 mmHg.

Anthropometrical data over time are shown in Table I. At baseline, subjects with mild blood pressure elevation were heavier and had higher BMI. At follow-up, there were no differences between the groups with regard to BMI, whereas body weight and the waist/hip ratio were higher among men with higher blood pressure level at baseline.

There was a significant correlation between systolic blood pressure at baseline and at follow-up (Table II). In further regression analyses, no relationship was found between values from the invasive hemodynamic examination at baseline, i.e. data on cardiac index and total peripheral resistance, or BMI and change in blood pressure or achieved blood pressure (Table II). There was a significant correlation between systolic blood pressure and waist/hip ratio ($r = 0.61$, $p < 0.03$) in the re-examination with all participants included.

DISCUSSION

In the present 30-year follow-up of 18–19-year-old men with mild blood pressure elevation at baseline, we could confirm that hypertension may develop in a large proportion of individuals. We were not able to confirm the generally adopted hypothesis linking hemodynamic or metabolic characteristics to increasing blood pressure. In fact, no clinical finding except blood pressure *per se* could predict the development of increasing blood pressure or hypertension in these young men representative of the population of western Sweden.

In this follow-up study, we were able to contact and re-examine 73% and 72% of controls and individuals with mild blood pressure elevation, respectively. We could confirm that all except one individual from the originally recruited group were alive and they were all contacted and responded. The re-examined individuals were evenly allocated in the original blood pressure distribution and none of those with the 10 highest blood pressures were missed for follow-up. It is therefore fair to assume that selection errors to a large extent were avoided.

The blood pressure in the group of normotensive young individuals increased over the 30-year period to an extent that was expected. Among subjects with mild blood pressure elevation, diastolic blood pressure increased less and systolic blood pressure was virtually unchanged. Increasing blood pressure to hypertensive levels over time was observed in 38% of subjects with mild blood pressure elevation but in only 7% of the control group. These findings corroborate previous reports indicating a substantial risk of developing hypertension in adolescents and young individuals with slightly elevated blood pressure. Hence, Widimsky & Jandowa found that 53% of young borderline hypertensive patients had become hypertensive during 20 years of follow-up [12]. Moreover, Paffenbarger *et al.* have reported a 20% incidence of hypertension in subjects aged 22–31 years with systolic blood pressure in the range 140–149 mmHg and diastolic blood pressure 90–99 mmHg during a 19-year follow-up

Table II. *Regression coefficients for relationships between suggested pre-hypertensive clinical and experimental observations and blood pressure 30 years later*

	SBP30		DBP30	
	r	p	r	p
SBP	0.56	0.001	0.14	0.32
DBP	0.26	0.07	0.22	0.11
CI	0.18	0.21	0.04	0.79
Rmin	0.12	0.36	0.06	0.67
BMI_0	0.17	0.23	0.063	0.63
BMI_{30}	0.16	0.26	0.12	0.41

SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, cardiac index; Rmin, vascular resistance during maximal vasodilatation; BMI, body mass index.

period [13]. In addition, Julius *et al.* found a 26% incidence in a study on 20-year-old subjects followed for 20 years [14]. Thus, the observed proportion of 38% hypertensive individuals at follow-up in the present study is in agreement with other observations. In our observation, subjects were recruited from a population sample and not from clinical healthcare routines. Obviously, these subjects yield the same risk for progress from mild blood pressure elevation to sustained hypertension.

Hyperkinetic circulation with increased sympathetic tone to the heart causing increased heart rate and cardiac output is a well-established characteristic of borderline hypertension [1–3]. This circulatory feature was also shown in the present group of young men with mild blood pressure elevation in the initial investigation 30 years ago [3, 9]. Total peripheral resistance was not increased, but inappropriately high allowing for increased blood pressure [3, 9]. There was evidence that hypertrophy of precapillary resistance vessels was present already in this early stage of blood pressure elevation [3, 8]. It has been suggested that increased heart rate and cardiac output could be signs of adrenergic hyperactivity as a starting phase of sustained essential hypertension – at least in subjects susceptible to daily life stress [12–14].

Increasing peripheral resistance, the typical hemodynamic abnormality of hypertension, should follow with time [9].

In the present study, no correlation between cardiac index and blood pressure at follow-up was observed. This indicates that subjects with hyperkinetic circulation were not prone to develop hypertension. Moreover, there was no correlation between vascular resistance during maximal vasodilatation and subsequent blood pressure level. Thus, higher peripheral resistance or arteriolar hypertrophy may not be indicators of forthcoming risk of developing hypertension. Furthermore, in the 12 subjects with blood pressure exceeding 140/90 mmHg cardiac output, calculated peripheral resistance and resistance during hyperemia was not significantly different from the normotensive control group.

To predict future hypertension and plan a strategy in young subjects with blood pressure elevation is still difficult and lacks scientific grounds. In the present report, we have used invasive and elaborate methods that would hardly be successful in daily clinical routines. The most important predictor of the forthcoming risk of becoming hypertensive in our study was casual blood pressure measurement. Stress tests have been used to predict the development of hypertension [15–17]. Based on a follow-up study over 28 years, Kasagi found that the cold pressor test was not as effective a predictor of hypertension as resting blood pressure [16]. However, when adjusting for baseline, resting systolic and diastolic blood pressure's systolic response to cold was found to be an independent and significant predictor, whereas diastolic response was significant only when resting diastolic blood pressure was also considered [16].

Casual blood pressure measurement is a simple and inexpensive method, while invasive hemodynamic evaluations are complicated and costly. The cold pressor test is less expensive and more straightforward. However, other data may be even more available and less expensive. Several years ago, Borghi *et al.* demonstrated that intralymphocytic sodium content was a good predictor of future hypertension in borderline subjects during a 5-year follow-up study [21]. More recently, a 15-year follow-up by Borghi *et al.* showed that serum cholesterol levels is an independent predictor for the development of hypertension [15].

Perhaps the most important finding of the present study is the negative finding that hemodynamic measurements at baseline did not predict the rise in blood pressure. It is obvious that the study may be undersized to detect a small influence of early hemodynamic changes on the future blood pressure level. However, the follow-up is long, which makes the observation of an association between casual blood pressure measurement at youth and the risk of future hypertension most interesting. Thus, the observations clearly indicate that invasive, complicated and costly investigations cannot be justified in the management of young subjects with mild blood pressure elevation.

In conclusion, in the present re-examination of young subjects with mild blood pressure, elevation in a military health screening casual blood pressure was the only significant variable predictive of hypertension 30 years later. We were not able to identify any invasive hemodynamic measure to be of significance for later hypertension. The clinical relevance should be that among young men with borderline hypertension, a high proportion may develop hypertension and be considered for drug treatment later in life.

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