ORIGINAL ARTICLE

Long-term influence of antihypertensive treatment on arterial stiffness assessed by ambulatory measurement of the QKD interval

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An increase in arterial stiffness is an important risk factor for cardiovascular events. However, there are few data on the long-term evolution of arterial stiffness in treated hypertensives. We evaluated the progression of arterial stiffness in 120 initially untreated hypertensive patients whose arterial stiffness was assessed by the ambulatory monitoring of the QKD interval measured at baseline and then more than 1 year later. The ambulatory method produced an isobaric index of arterial stiffness, the QKD₁₀₀₋₆₀. Out of these patients, 30 with white coat hypertension did not receive any treatment, and over a mean follow-up period of 5 years their QKD₁₀₀₋₆₀ was unchanged. The 90 other patients received antihypertensive treatment (average of 2.5 classes of drug) over a mean period of 6 years. In this population, the mean 24 h blood pressure (BP) was significantly reduced (−9 mm Hg for systolic BP, −6 mm Hg for diastolic BP) and the QKD₁₀₀₋₆₀ was prolonged (+3.5 ms, $P < 0.05$). The presence of type 2 diabetes in 17 of these patients was the sole factor negatively correlated with the improvement in QKD₁₀₀₋₆₀. An initial reduction in QKD₁₀₀₋₆₀ appeared to be a factor of resistance to the BP-lowering action of the medication. Antihypertensive treatment has a long-term action on arterial stiffness. The existence of diabetes appeared to have a negative influence on this improvement. Furthermore, an increase in arterial stiffness may be a factor of resistance to the action of antihypertensive medication.

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INTRODUCTION

There are few data on the long-term progression (1 year and above) on arterial stiffness in treated hypertensives.^{1–5} Furthermore, the available data are based on the measurement of the pulse wave velocity⁶ (PWV), which is highly dependent on the blood pressure (BP) at the time of the measurement. A simple decrease in BP for any reason will reduce the PWV by a purely mechanical effect, and this technique cannot easily evaluate alterations in the intrinsic stiffness of the arterial system. Ambulatory measurement of the QKD⁷ coupled with the ambulatory measurement of BP produces indices of arterial stiffness. The main advantages of this method are that it is completely automatic, that it takes account of instantaneous variations in BP and heart rate (HR) and that it provides a reproducible isobaric index of arterial stiffness.^{8,9} This index has an independent prognostic value in the hypertensive patient^{10–12} and represents a marker of severe progression in systemic sclerosis.¹³ During the follow-up of the Bordeaux cohort of initially untreated hypertensives, we evaluated progression in patients who had benefited from at least two ambulatory measurements of BP and QKD separated at least by a 1 year interval.

METHODS

Population

Patients were recruited from the Bordeaux cohort of hypertensive patients. They had all been referred to our center before receiving antihypertensive treatment and were selected according to the following criteria:

- Office systolic BP (SBP) >140 or diastolic BP (DBP) >90 mm Hg on at least two determinations measured with a mercury sphygmomanometer by a physician after 10 min sitting or lying.
- Absence of cardiovascular complications or any pathology that might affect the prognosis
- High quality ambulatory measurements of BP and QKD
- Absence of left bundle branch block on the ECG, absence of known thyroid pathology.

All patients gave informed consent for participation in this survey, which was approved by our local ethics committee (Comité de protection des personnes Sud-Ouest et Outre Mer III). After the examination that included the ambulatory measurement of BP, electrocardiogram (ECG) and a full laboratory work-up, the patients were given antihypertensive treatment and followed up by their family physicians who were kept unaware of the QKD results. Some of these patients were not treated as they had normal ambulatory values (daytime

Figure 1 Twenty-four hours ambulatory monitoring of BP and QKD in a patient. The device measures systolic and diastolic BP, HR and QKD every 15 min. From a total of 96 measurements, the software calculates automatically the multiple linear regression of QKD as a function of SBP and HR. The QKD₁₀₀₋₆₀ is calculated as a value of QKD for an SBP of 100 mmHg and HR of 60 b.p.m. from the linear regression equation. The software also calculates the theoretical normal value of QKD₁₀₀₋₆₀ according to height from data on a population of normal healthy individuals (<40 years): QKD₁₀₀₋₆₀=0.73*height (cm)+91. The QKD₁₀₀₋₆₀ is thus expressed as a percentage of this theoretical normal value: height-predicted QKD₁₀₀₋₆₀=100*observed QKD₁₀₀₋₆₀/height-predicted QKD₁₀₀₋₆₀. BP, blood pressure; HR, heart rate.

SBP <135 mmHg, those with isolated office hypertension or white coat hypertension) in the absence of associated risk factors (diabetes or hypercholesterolemia). Smokers were strongly encouraged to quit. We included in this analysis only those patients, treated or not, who benefited from a second ABPM more than 1 year after inclusion in the cohort.

Ambulatory measurement of BP and QKD interval (Figure 1)

All patients benefited from ambulatory measurement of BP along with QKD interval. The apparatus (Diasys 200RK, later Diasys Integra, Novacor, France) uses the auscultatory method for measuring BP and determines during each measurement the QKD interval: time between the QRS wave on the ECG and detection of the last Korotkoff sound during deflation of the arm-band. This time is the sum of the pre-ejection time and the time of transmission of the pulse wave from the aortic valves to the microphone placed on the brachial artery. This interval was measured every 15 min along with BP over a period of 24 h. From each recording, out of the 96 or so measurements, the software determines automatically, from the multiple linear regression of QKD according to SBP and HR, the value of the QKD₁₀₀₋₆₀, namely the theoretical value of the QKD for a systolic pressure of 100 mmHg and a HR of 60 b.p.m. This index minimizes the influence of the pre-ejection time and enables comparison between patients at a given level of SBP. The value of this parameter is inversely related to PWV and arterial stiffness. The value of QKD₁₀₀₋₆₀ is influenced by the distance between the heart and the point of measurement on the arm and thus by the individual's height. To compare patients and patient groups, the QKD₁₀₀₋₆₀ was expressed as a percentage of the value predicted by height in a population of young normal individuals.¹⁴

Only patients with at least 80 validated measurements over 24 h and a negative relationship between QKD and DBP were included in the analysis. A positive relationship between QKD and DBP, found in less than of 5% of the patients, was indicative of poor detection of Korotkoff sounds by the microphone.

Statistics

Data were analyzed with SPSS 11.5 software and shown as mean $\pm$ s.d. The patient groups were compared using Student's *t*-test, and the differences between the value on entry and over follow-up were analyzed by paired *t*-tests. A study of the factors linked to mean 24 h QKD and QKD₁₀₀₋₆₀ evolution was conducted by multiple linear regression including the following variables: age, SBP, DBP, mean HR, and gender, smoking, hypercholesterolemia and diabetes as dummy variables.

RESULTS

We included in this study 120 patients, of whom 30 had a white coat hypertension and were left untreated. Their main characteristics are listed in Table 1. The patients with white coat hypertension were on average younger and had a lower ambulatory BP than those with

Table 1 Baseline characteristics of population studied

	WCH	Sustained HT	P-value
N	30	90	
Male/female	15/15	57/33	NS
Age (years)	46 $\pm$ 14	52 $\pm$ 14	0.04
Weight (kg)	70 $\pm$ 12	72 $\pm$ 13	NS
Height (cm)	170 $\pm$ 8	170 $\pm$ 10	NS
Smoker (Y/N)	5/25	24/66	NS
Diabetes (Y/N)	0/30	10/80	NS
Hypercholesterolemia (Y/N)	0/30	17/73	0.03
Office SBP (mm Hg)	149 $\pm$ 10	160 $\pm$ 19	0.004
Office DBP (mm Hg)	95 $\pm$ 7	94 $\pm$ 14	NS
Office HR (b.p.m.)	73 $\pm$ 13	72 $\pm$ 13	NS
Day SBP (mm Hg)	126 $\pm$ 8	144 $\pm$ 16	<0.001
Day DBP (mm Hg)	86 $\pm$ 6	91 $\pm$ 15	NS
Day HR (b.p.m.)	82 $\pm$ 12	78 $\pm$ 13	NS
Night SBP (mm Hg)	110 $\pm$ 11	124 $\pm$ 17	<0.001
Night DBP (mm Hg)	74 $\pm$ 7	78 $\pm$ 14	NS
Night HR (b.p.m.)	66 $\pm$ 9	66 $\pm$ 10	NS
24 h SBP (mm Hg)	120 $\pm$ 8	137 $\pm$ 16	<0.001
24 h DBP (mm Hg)	82 $\pm$ 6	87 $\pm$ 15	0.07
24 h HR (b.p.m.)	76 $\pm$ 11	74 $\pm$ 12	NS
24 h QKD (ms)	202 $\pm$ 17	190 $\pm$ 18	0.002
QKD ₁₀₀₋₆₀ (ms)	216 $\pm$ 16	206 $\pm$ 19	0.009
Height-predicted QKD (%)	101 $\pm$ 8	96 $\pm$ 9	0.004

Abbreviations: BP, blood pressure; DBP diastolic BP; HR, heart rate; HT, hypertension; N, no; NS, not significant; SBP, systolic BP; WCH, white coat hypertension; Y, yes.

sustained hypertension. There were few risk factors in this group, which contained only five smokers. All of them stopped smoking during follow-up. Their QKD₁₀₀₋₆₀ was significantly longer than that of the true hypertensive, and when expressed as a percentage of the height-predicted value it was normal (100%). The follow-up period was comparable for both groups (5 and 6 years respectively). Table 2 lists the changes in BP and HR over 24 h, mean 24 h QKD and QKD₁₀₀₋₆₀. In the untreated group, we observed a significant increase in mean 24 h SBP and DBP with no significant change in QKD₁₀₀₋₆₀. The hypertensive patients received on average 2.5 classes of antihypertensive medication. There was a significant reduction in BP in this group. The mean 24 h QKD increased significantly by 7 ms, and this increase was significantly and independently correlated with the decrease in mean 24 h HR ($r=-0.38$, $P<0.001$) and the decrease in

Table 2 BP and QKD changes at follow up

	WCH, N=30	P-value	Sustained HT, N=90	P-value	P-value, WCH vs. SHT
Follow up (years)	5 ± 4		6 ± 4		
24 h SBP change (mm Hg)	+5 ± 9	0.007	−9 ± 18	<0.001	0.04
24 h DBP change (mm Hg)	+3 ± 8	0.03	−6 ± 11	<0.001	NS
24 h HR change (b.p.m.)	−1 ± 7	NS	−4 ± 10	<0.001	NS
24 h QKD change (ms)	−1 ± 13	NS	+7 ± 13	<0.001	NS
QKD ₁₀₀₋₆₀ change (ms)	0 ± 14	NS	+3.5 ± 16	<0.05	NS

Abbreviations: BP, blood pressure; DBP, diastolic BP; HR, heart rate; NS, not significant; SBP, systolic BP; WCH, white coat hypertension.

Table 3 Comparison of diabetics and non-diabetic sustained hypertensives

	Diabetic		Non-diabetic	
	Baseline	Follow up (7 ± 4 years)	Baseline	Follow up (6 ± 4 years)
N	17		73	
Male/female	13/4		44/29	
Age (years)	57 ± 11		50 ± 14	
Weight (kg)	78 ± 10		71 ± 13	
Height (cm)	171 ± 9		169 ± 10	
Smoker (Y/N)	5/12		19/54	
Hypercholesterolemia (Y/N)	6/11		11/62	
Office SBP (mm Hg)	170 ± 23		156 ± 18	
Office DBP (mm Hg)	92 ± 17		94 ± 14	
24 h SBP (mm Hg)	138 ± 12	−11 ± 18	137 ± 17	−9 ± 18
24 h DBP (mm Hg)	82 ± 11	−8 ± 8	88 ± 15	−6 ± 11
24 h HR (b.p.m.)	70 ± 13	−4 ± 11	74 ± 11	−4 ± 10
24 h QKD (ms)	184 ± 17	+3 ± 13	191 ± 18	+8 ± 14
QKD ₁₀₀₋₆₀ (ms)	203 ± 19	−5 ± 13	207 ± 19	+5 ± 16
Height-predicted QKD ₁₀₀₋₆₀ (%)	94 ± 9		96 ± 9	

Abbreviations: BP, blood pressure; DBP, diastolic BP; HR, heart rate; N, no; SBP, systolic BP; Y, yes.

mean 24 h SBP ($r=0.29$, $P<0.001$). The QKD₁₀₀₋₆₀ increased significantly (+3.5 ms), but without reaching the values of the group with white coat hypertension. The change in QKD₁₀₀₋₆₀ was not correlated with the change in mean 24 h SBP or HR. The only factor negatively correlated with the increase in QKD₁₀₀₋₆₀ was the presence of diabetes ($r=-0.236$, $P<0.01$). Seventeen patients in this group had type 2 diabetes in the follow-up period (10 on inclusion and 7 new cases during follow-up). Table 3 compares the diabetic hypertensives with the non-diabetic ones, but in view of the small number of patients involved, no statistical tests were run. The diabetic patients had a lower QKD₁₀₀₋₆₀ than did the non-diabetics, and despite a reduction in mean 24 h BP that aligned their values with those of the non-diabetics, their QKD₁₀₀₋₆₀ decreased even lower during the follow up period. Table 4 shows the data of the treated hypertensives as a function of initial value, with normal or initially reduced QKD₁₀₀₋₆₀. Normal arterial stiffness was defined as baseline QKD₁₀₀₋₆₀ exceeding 95% of the height-predicted value. The baseline mean 24 h SBP was comparable in both groups, although the mean 24 h DBP was significantly lower in the group with reduced QKD₁₀₀₋₆₀, indicative of higher pulse pressure. The reduction in mean 24 h SBP was lower in the group with enhanced arterial stiffness despite the similar antihypertensive treatment. The QKD₁₀₀₋₆₀ increased by 6 ms in the group

Table 4 Comparison of patients with normal or reduced baseline QKD₁₀₀₋₆₀

	Normal baseline QKD ₁₀₀₋₆₀	Reduced baseline QKD ₁₀₀₋₆₀	P-value
N=	47	43	
QKD ₁₀₀₋₆₀ (ms)	219 ± 13	191 ± 12	<0.001
Height-predicted QKD ₁₀₀₋₆₀ (%)	102 ± 5	88 ± 5	<0.001
Male/female	27/19	29/14	NS
Age (years)	46 ± 13	58 ± 12	<0.001
Weight (kg)	72 ± 14	73 ± 13	NS
Height (cm)	169 ± 8	170 ± 10	NS
Smoker (Y/N)	14/32	10/33	NS
Diabetes (Y/N)	7/39	10/33	NS
Hypercholesterolemia (Y/N)	6/40	11/32	NS
Office SBP (mm Hg)	161 ± 21	157 ± 17	NS
Office DBP (mm Hg)	99 ± 13	88 ± 13	<0.001
24 h SBP (mm Hg)	137 ± 17	137 ± 15	NS
24 h DBP (mm Hg)	91 ± 14	81 ± 13	<0.001
24 h HR (b.p.m.)	76 ± 12	71 ± 11	0.02
Follow up (years)	6 ± 4	6 ± 4	NS
Antihypertensive class (n)	2.5	2.5	NS
24 h SBP change (mm Hg)	−13 ± 20	−5 ± 14	<0.05
24 h DBP change (mm Hg)	−9 ± 11	−3 ± 9	<0.01
24 h HR change (b.p.m.)	−3 ± 10	−4 ± 9	NS
24 h QKD change (ms)	+5 ± 13	+10 ± 13	NS
QKD ₁₀₀₋₆₀ change (ms)	+1 ± 15	+6 ± 17	NS

Abbreviations: BP, blood pressure; DBP, diastolic BP; HR, heart rate; N, no; NS, not significant; SBP, systolic BP; Y, yes.

with increased arterial stiffness and did not change in the other group, although the difference between the two groups was not significant.

DISCUSSION

Our study showed that the white coat hypertensives had a normal arterial stiffness that was significantly lower than that of the sustained hypertensives. Some studies¹⁵ based on measuring PWV have shown a significant increase in PWV of white coat hypertensives with respect to normotensives. That is not altogether surprising as the PWV is highly dependent on the value of the BP at the time of its measurement, and under these conditions the PWV and BP will both be elevated in the presence of the physician making the measurement. Ambulatory measurement of the QKD interval not only enables measurement in the absence of a physician, but also provides from a calculation of the QKD₁₀₀₋₆₀ an isobaric index of arterial stiffness whose prognostic value has been shown, independently of the mean 24 h BP and traditional risk factors.¹¹ This method should not be viewed as the

measurement of stiffness in a muscular artery, but indeed as an estimation of the stiffness in the aorta. The pulse transmission time included in the QKD corresponds to the travel of the pulse wave on an arterial segment, which includes the ascending aorta, transversal aorta (as the device is usually placed on the left arm), subclavian artery and part of the brachial artery. The ascending aorta plays a major role in buffering left-ventricular ejection, and another point of interest in this method is the exploration of this important part of the aorta 'unseen' by the carotid-femoral PWV. As the compliance of muscular arteries such as the brachial artery is unchanged (or even improved) in hypertension, the last part traveled by the pulse is unlikely to explain the reduction of QKD in hypertensive patients and its relationship to cardiovascular events. The QKD interval was shown to be significantly correlated to aortic PWV.^{16–18} These were not very high correlations ($r=0.37–0.55$), as the QKD interval is influenced by the pre-ejection time and the arterial segments studied by the two methods are not exactly the same. The main interest in the monitoring of QKD is the calculation of QKD_{100–60}. This index allows not only a reduction in the influence of the pre-ejection time but also provides an isobaric index of arterial stiffness that is difficult to compare with PWV, which remains strongly dependent on BP and HR at the time of measurement. In a recent study, Levi *et al.*¹⁹ have shown in 147 diabetic patients that QKD_{100–60} and carotido-femoral PWV were significantly correlated ($r=0.31$, $P<0.001$). In this study, QKD_{100–60} was more strongly correlated with age than PWV, which was influenced by a white coat effect, but QKD_{100–60} was not.

After around 5 years, the mean 24 h SBP of the white coat hypertensives increased on average by 5 mm Hg, confirming the need to monitor these patients if they were not receiving any antihypertensive treatment. In this population with a mean age of 46 years, arterial stiffness did not increase significantly over 5 years, but the sample size was probably too small to show a small change. In a population of 237 normotensive subjects aged 65 years, we observed a significant reduction in QKD_{100–60} (–2 ms) over a period of only 2 years.²⁰

Antihypertensive treatment was administered to all patients presenting high BP confirmed by ambulatory measurements. With a follow-up of 6 years, these patients received on average 2.5 different antihypertensive agents. The decline in mean 24 h BP was significant (–9 mm Hg for SBP, –6 mm Hg for DBP). The increase in mean 24 h QKD was significantly correlated with the decrease in HR, reflecting the influence of the pre-ejection time on the QKD.²¹ and on the decrease in SBP reflecting, at least in part, the mechanical reduction in PWV secondary to the decrease in BP. The QKD_{100–60} increased significantly in this population, but its change was not significantly correlated with the reduction in BP. However, it was significantly affected by the presence of diabetes. Diabetes (type 1 or 2) is one of the factors identified as increasing arterial stiffness independently of BP.^{22–26} In our population, 17 of our patients had type 2 diabetes and did not improve their QKD_{100–60}. In fact, they exhibited a reduction despite the significant decrease in BP. This sample is too small to draw definitive conclusions, but this issue merits further investigation. To our knowledge, there are no published studies on the long-term progression of arterial stiffness of diabetics receiving antihypertensive treatment. In the short term (6 months), some studies have shown a significant reduction in PWV with treatment, especially with agents inhibiting the renin-angiotensin system.²⁷ A comparison of the hypertensives having a normal or reduced QKD_{100–60} on inclusion in the study showed that those whose arterial stiffness was increased had less lowering of SBP under treatment. This suggests that increased arterial stiffness may be a factor of resistance to the action of

antihypertensive agents as hypothesized by Pickering.²⁸ Under treatment, patients whose arterial stiffness was raised improved their QKD_{100–60} significantly, although it did not return to normal. There have been few studies on the long-term progression of arterial stiffness in hypertensive patients. With determinations every 3 months, Ichihara *et al.*¹ observed a significant reduction in PWV over 1 year that was independent of the decrease in BP in 71 untreated non-diabetic hypertensives (target BP < 130/85 mm Hg). A similar observation, but over a period of 5 years, was described by Bellido *et al.*² in 66 initially untreated hypertensives. In the study of Asmar *et al.*,⁵ the reduction in PWV over 1 year was comparable in the groups treated with perindopril/indapamide or atenolol, and it could not be attributed to any factor other than the decrease in BP. The study of Mitchell *et al.*⁴ in 300 patients with coronary artery disease and preserved ejection fraction compared treatment with trandolapril to placebo over a period of 5 years. The carotido-femoral PWV was measured in treated patients, but not at baseline, and was lower in the trandolapril than in the placebo group. Analysis after adjustment for the change in BP was in favor of an action on the PWV independent of the decrease in BP. Only 11% of 152 patients randomly allocated to the trandolapril group were diabetic. However, in all these studies on PWV, it is hard to discriminate the influence of the decrease in BP from that of a more direct action on the structure of the arterial wall. Ambulatory measurement of the QKD interval produces automatically an isobaric index (referred to 100 mm Hg SBP) of arterial stiffness and thus avoids any *a posteriori* data processing. Our data, along with other published studies, are in favor of long-term improvement in the arterial stiffness of hypertensive patients receiving antihypertensive medication, although without return to normal values.

Limitations of the study

Our patients were recruited from a cohort whom we have followed up for several years but who are not subject to any therapeutic trial. In these patients, the antihypertensive and antidiabetic treatments were chosen and adjusted by their family physicians. It is unlikely, however, that this influenced our results greatly as the QKD findings were not communicated to their doctors. We could not determine whether any particular class of BP-lowering agent had any better efficacy than another on arterial stiffness. Moreover, we do not know the optimal duration of follow-up to show a therapeutic influence on arterial stiffness. In the short term (< 6 months), it is unlikely that treatment would have any significant effect on the structure of the arterial wall, and modifications observed on arterial stiffness assessed by PWV are most likely linked to the simple reduction in distension of the artery. But in the long-term, as here, the effect of treatment competes with the aging process.²⁹ and may have minimized the improvement we observed especially in the diabetic patients.

Conclusions

An increase in arterial stiffness is an important factor for cardiovascular events.^{30–34} Our study indicates that a long-term action on this factor may be obtained by antihypertensive treatment. Other interventions and especially the optimal control of all risk factors, especially diabetes, are doubtless required to slow vascular aging and reduce arterial stiffness, but increased arterial stiffness *per se* appears to be a factor limiting the efficacy of BP reduction. The limited data in patients with renal insufficiency indicate that improvement in arterial stiffness can improve the prognosis.³⁵ Ambulatory measurement of the QKD interval is of value as it provides an indication of arterial stiffness that is independent of the BP at the time of its measurement.

CONFLICT OF INTEREST

None of the authors have any conflict of interest in relation with this manuscript.

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