SCIENTIFIC LETTERS

Endothelial dysfunction in hypertensive patients and in normotensive offspring of subjects with essential hypertension

Essential arterial hypertension (EH) is an important risk factor for atherosclerosis. There is growing evidence that endothelial dysfunction is the earliest event in atherogenesis and also precedes morphological changes of the arterial wall in hypertensive patients.[1] One of the most widely recognised methods of determining the endothelial function is the dilation capability of arteries. Risk factors of atherosclerosis, including EH, probably decrease the production and increase the consumption of nitric oxide which plays a central role in the vasodilation.

Studies where venous occlusion plethysmography was used for measurement of changes in the blood flow demonstrated that patients with EH showed impaired endothelium dependent vasodilation of peripheral resistance arteries. On the other hand, there is only little evidence, albeit controversial, of the dilation capability of systemic conduit arteries in EH patients.[2–4]

The aim of the present study was to evaluate non-invasively whether flow-mediated dilation (FMD) of the brachial artery is also impaired, in spite of treatment in patients with EH, and to find whether these abnormalities precede clinical manifestations of elevated blood pressure and can therefore be detected in the normotensive offspring of subjects with EH (hypertensive familial trait (FT)).

The study encompassed four groups involving a total of 172 subjects. In the first group there were 46 patients (35 men and 11 women, mean age 49 years) with the EH documented for at least two years. Only hypertonics with well documented elevated blood pressure (⩾ 145/95 mm Hg in a sitting position in at least three different measurements before starting treatment) were included. The hypertensive subjects took their medication (either long acting calcium channel antagonists or angiotensin converting enzyme (ACE) inhibitors) 6–8 hours before haemodynamic measurements were performed. The second group of 44 healthy normotensive subjects (32 men and 12 women), matched with the patients in age and sex, served as controls. The third group comprised 41 subjects (23 men and 18 women, mean age 25 years), with a family history of essential hypertension in their first degree relatives (parents or siblings, or both). In the fourth control group there were 41 volunteers age and sex matched with FT subjects, and without a family history of hypertension. Both groups of young volunteers had recorded normal blood pressure at least three times in the year preceding the investigation. Information on blood pressure was obtained from family doctors and their medical records.

The dilation capability of the brachial artery was studied by high resolution ultrasound. The method of haemodynamic measurements was described elsewhere.[1] The relative flow increase during reactive hyperaemia was calculated as the maximum flow divided by the flow during rest. The FMD response was expressed as a change in the end diastolic diameter of the brachial artery during reactive hyperaemia compared to the baseline measurement, and used as a measure of endothelium dependent vasodilation. Endothelium independent vasodilation of the brachial artery was studied by way of the sublingual application of 0.5 mg glyceryl trinitrate (GTN).

The patients with EH had significantly higher systolic and diastolic blood pressure than the controls (140.76 (11.74) mm Hg *v* 122.52 (8.11) mm Hg, p < 0.00005) and a higher body mass index in comparison to the control group (28.60 (3.61) kg/m^2 *v* 25.05 (2.59) kg/m^2, p < 0.00005). Systolic and diastolic blood pressure, although in the normal range, was higher in the FT group than in the controls (121.95 (9.54) mm Hg *v* 114.88 (9.39) mm Hg, p = 0.001; 80.24 (6.22) mm Hg *v* 75.49 (5.57) mm Hg, p = 0.0005 respectively). Subjects with a family history of hypertension also had a higher body mass index than healthy controls (24.33 (3.72) kg/m^2 *v* 21.81 (2.45) kg/m^2, p = 0.0006).

The mean resting diameter of the brachial artery in EH patients and in subjects with FT was comparable to the control groups (4.5 (0.87) mm *v* 4.2 (0.68) mm, p = 0.085; 3.7 mm (0.69) *v* 3.6 (0.52) mm, p = 0.211, respectively). The mean hyperaemic flow increase observed after cuff deflation was lower in EH patients than in the control group (380 (128)% *v* 476 (180)%, p = 0.005), while mean flow increase during reactive hyperaemia was comparable between the FT group and the controls (476 (129)% *v* 444 (140)%, p = 0.099).

FMD in hypertonics was significantly less than in controls (fig 1), and GTN induced dilation as well (12.1 (4.3)% *v* 16.1 (4.6)%, p = 0.00007). FMD in hypertensive patients was also impaired when corrected for the GTN response (2.9 (3.0)% *v* 7.7 (2.4)%, p < 0.00005). In subjects with FT, FMD was also decreased in comparison to controls (fig 1); in contrast to hypertonics, the GTN induced dilation was comparable between the groups of young volunteers (14.0 (5.3)% *v* 15.7 (5.2)%).

In the group of older participants as a whole, the univariate analysis FMD was strongly inversely related to the systolic and diastolic blood pressure (p < 0.00005), to the duration of hypertension (p < 0.00005), the family history of hypertension (p < 0.00005), and the body mass index (p < 0.00005), yet weakly related to the age (p = 0.045). There was also a strong inverse relation observed between the dilation capability (flow and GTN mediated) and the baseline vessel diameter (p < 0.00005). In contrast, hyperaemic flow increase was not a significant predictor of FMD. Variables that were significant in the univariate analysis were included in different multiple regression models. Multivariate analysis with the highest predicting value showed that in patients with EH the FMD was related to the family history of hypertension (partial $r = -0.42$, p < 0.00005), the systolic blood pressure (partial $r = -0.43$, p < 0.00005), and the baseline vessel diameter (partial $r = -0.27$, p = 0.010). The model was significant (p < 0.00005) with a relatively high goodness of fit ($R^2 = 0.53$). Similar results were obtained when diastolic blood pressure was substituted for the systolic blood pressure.

In both groups of young subjects (FT plus controls), FMD was strongly negatively related to the family history of hypertension (p < 0.00005). FMD was also negatively related to the baseline vessel diameter (p = 0.002). Multivariate regression analyses including the family history of hypertension, the baseline vessel diameter, the body mass index (p < 0.00005), and the systolic blood pressure (p = 0.030), revealed that the family history of hypertension (partial $r = -0.42$, p = 0.0002) and the baseline vessel diameter (partial $r = -0.24$, p = 0.048) were the most important determinants of FMD ($R^2 = 0.37$, p < 0.00005).

The present study demonstrated that, in spite of treatment, hypertonics without cardiovascular events showed decreased FMD of the brachial artery as compared to the normotensive controls. This difference was also preserved after making correction

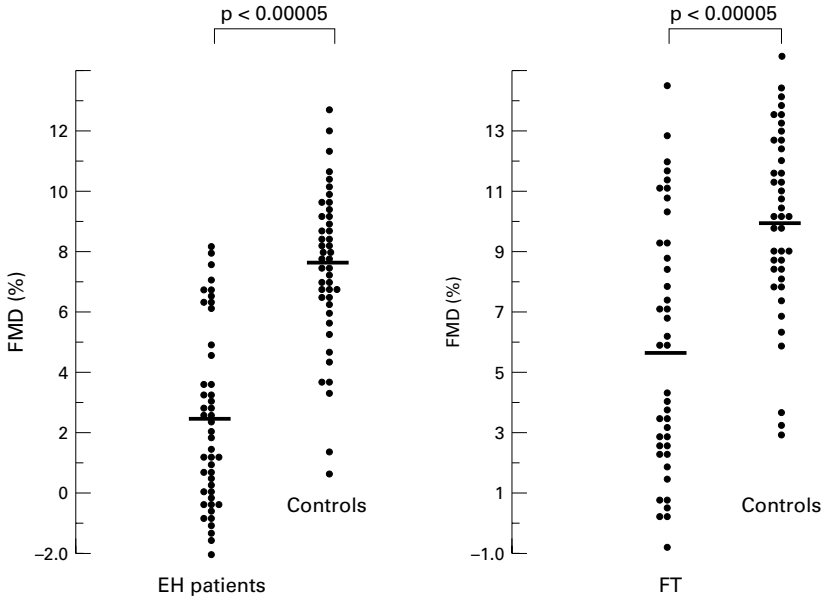

Figure 1 Flow mediated dilation (FMD) of brachial artery in patients with essential hypertension (EH), in subjects with hypertensive familial trait (FT), and controls.

for the GTN response, which could further decrease the vasodilatatory capability of the investigated vessels. The observed difference in FMD between subjects with and without hypertension does not appear to be the consequence of methodologic variation as the intraobserver variability only accounts for 0.9 (1.8)%. Moreover, it was shown that the consequence of differing flow challenges between the groups had no influence on FMD. Only few and conflicting results have been reported in the literature with respect to direct measurements of FMD of conduit arteries. Iiyama *et al*[2] and Schmieder *et al*[3] clearly showed that FMD of the radial artery in untreated hypertonics was blunted during an increased flow provoked by reactive hyperaemia or acetylcholine. On the other hand, Laurent *et al*[4] failed to demonstrate impaired FMD in hypertensive patients. A shorter period of occlusion (2 minutes) of the investigated arm than that in other studies (4–5 minutes), or too small groups may be responsible in the latter study for the inability to demonstrate decreased FMD in hypertonics.

The reduction of FMD in our study was shown to be related to the systolic and diastolic blood pressure. Multivariate analysis confirmed that the systolic and diastolic blood pressure had the strongest independent negative influence on the dilation capability of the brachial artery. Data from experimental studies showed that blood pressure, like any other risk factors of atherosclerosis, caused a decrease in bioavailability of nitric oxide (related to its decreased synthesis and/or release), probably through damage of endothelial cells.

Our study also showed that in normotensive subjects with FT the vasodilator response of the brachial artery was blunted, as compared to the controls, during reactive hyperaemia. In comparison to the controls, our FT subjects showed increased levels of blood pressure, yet these were still in the normal range and they had no other manifestation of hypertensive disease. Previous studies based on plethysmographic investigation showed that normotensive subjects with a family history of EH had higher levels of peripheral resistance than controls, which is probably a consequence of endothelium dysfunction of the small vessels.[5] These findings could imply that in subjects with FT a functional abnormality of endothelium may appear early in the life or may even be directly inherited.

Another important finding of our study is the decreased response to GTN in patients with EH compared to the controls, suggesting that hypertension, in addition to endothelial dysfunction, also causes dysfunction of smooth muscle cells. Until now, only a few studies have investigated the effects of hypertension on the functional properties of the smooth muscle cells of conduit arteries. Some investigators reported normal endothelium independent vasodilation of the systemic arteries in hypertensive patients, but Celermajer and colleagues[1] demonstrated a blunted response to GTN in subjects with different risk factors of atherosclerosis, as well as in hypertonics. The causes of the conflicting data may be related to the different methods applied, the duration of hypertension, and particularly to the treatment modalities and use of different drugs.

In summary, patients with EH had, in spite of undergoing medication, decreased FMD and, to some extent, also decreased GTN mediated dilation of the brachial artery. These findings indicate that hypertension is related to endothelial and smooth muscle cell dysfunction. Endothelial dysfunction precedes the manifestation of hypertension and is present in the offspring of subjects with EH.

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1 Celermajer DS, Sorensen KE, Gooch VM, *et al.* Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;**340**:1111–5.
2 Iiyama K, Nagano M, Yo Y, *et al.* Impaired endothelial function with essential hypertension assessed by ultrasonography. *Am Heart J* 1996;**132**:779–82.
3 Schmieder RE, Weihprecht H, Schobel H, *et al.* Is endothelial function of the radial artery altered in human essential hypertension? *Am J Hypertens* 1997;**10**:323–31.
4 Laurent S, Lacolley P, Brunel P, *et al.* Flow-dependent vasodilatation of brachial artery in essential hypertension. *Am J Physiol* 1990;**258**: H1004–H11.
5 Taddei S, Virdis A, Mattei P, *et al.* Endothelium-dependent forearm vasodilation is reduced in normotensive subjects with familial history of hypertension. *J Cardiovasc Pharmacol* 1992; **20**(suppl 12):S193–S5.

Quality of life in patients with silent atrial fibrillation

Atrial fibrillation (AF) is a common arrhythmia associated with substantial morbidity, mortality, and health care cost. Although AF is responsible for a variety of symptoms, at least one third of patients report no overt symptoms and are unaware of their arrhythmic condition.[1] This silent AF is diagnosed incidentally during routine physical or electrocardiographic examination. In some cases, asymptomatic AF is revealed only after complications such as stroke or congestive heart failure have occurred. Implantable pacemakers or defibrillators equipped with long term Holter memory function have shown that a very large proportion of patients (> 50%) have unsuspected episodes of silent AF.[2]

Silent AF is likely to be associated with morbidity and mortality rates similar to those in symptomatic AF, but its effect on quality of life (QoL) has not yet been established. We studied 154 patients with paroxysmal (60.5%) or persistent (39.5%) AF. Symptoms relevant for AF were selected from Bubien and Kay's symptom checklist, including palpitations, dyspnoea, dizziness, exercise intolerance, chest discomfort, and syncope. Thirty eight patients with the lowest quartile symptom scores (≤ 25.4) were considered asymptomatic or very mildly symptomatic (group 1); 118 patients in the other three quartiles (> 25.4) were considered symptomatic (group 2). Palpitations (68%), dyspnoea (60%), and fatigue (62%) were the most common symptoms reported by these patients. A control group consisted of 49 subjects (mean (SD) age 54 (14) years, 45% men) referred for routine health examination, without documented cardiovascular or any serious systemic disease. Symptom burden, as assessed by the symptom frequency and severity checklist, did not differ between normal subjects and group 1 patients, confirming that the latter were truly asymptomatic. Group 1 and group 2 patients did not differ with respect to age (58.6 (12.3) years *v* 57.6 (11.1) years), left ventricular ejection fraction (62.4 (14.1)% *v* 60.8 (16.1)%), left atrial dimension (4.3 (0.6) cm *v* 4.2 (0.6) cm), or New York Heart Association (NYHA) functional class I (91.7% *v* 87.9%). There was a significantly greater proportion of women among symptomatic compared to "asymptomatic" patients (32.5% *v* 13.2%, p = 0.022).

QoL was assessed by a generic health scale, the 36 item short form health survey (SF-36) with standardised scores ranging from 0–100 to measure eight health dimensions. Total functional capacity was measured by a modified Goldman specific activity scale, and the illness intrusiveness ratings scale was used to assess the lifestyle disruption attributable to illness. In addition, global life satisfaction was evaluated using a one item visual analogue scale ranging from 1 (worst possible life) to 10 (best possible life).

Patients with AF had substantially impaired QoL compared with healthy subjects (p < 0.003, table 1). Although the conventional "objective" measures of illness severity were similar in group 1 and group 2 patients, the latter reported significantly lower scores on all SF-36 scales (p < 0.005). Group 2 patients had a significantly increased illness intrusiveness compared with group 1 patients (39 (15) *v* 25 (10), p < 0.001). Total functional capacity and global life satisfaction were significantly lower in symptomatic patients compared to "asymptomatic" patients (p < 0.005).

NYHA class and symptom frequency and severity were related to SF-36 scores but accounted for only 7% of total variability of the latter (P Dorian, unpublished data).

Although most SF-36 scale scores did not differ much between normal subjects and "asymptomatic" AF patients, and total functional capacity was similar in both groups, the

Table 1 Comparison of quality of life in patients with silent (group 1), symptomatic (group 2), all atrial fibrillation (all AF), and healthy subjects (control)

	Control n=49	*Group 1 n=38*	*Group 2 n=116*	*All AF n=154*
SF-36 score				
Role-physical	88 (28)	83 (26)	35 (38)*†	48 (42)*
Vitality	71 (14)	63 (15)	42 (19)*†	49 (21)*
Physical functioning	89 (19)	89 (13)	61 (26)*†	68 (27)*
Social functioning	92 (14)	87 (23)	67 (27)*†	73 (27)*
Mental health	81 (11)	75 (15)	65 (18)*†	69 (18)*
Role-emotional	92 (24)	88 (22)	58 (43)*†	65 (41)*
Bodily pain	77 (15)	81 (14)	65 (19)*†	69 (20)*
General health	78 (18	63 (17*	51 (21)*†	55 (21*
Symptom burden (checklist)				
Symptom frequency	10 (6)	11 (5)	26 (8)*†	22 (10)*
Symptom severity	8 (5)	9 (3)	22 (6)*†	19 (8)*
Total functional capacity	93 (11)	90 (11)	71 (20)*†	75 (20)*
Global life satisfaction	8.0 (1.2)	7.3 (1.6)*	5.9 (1.9)*†	6.2 (1.9)*

Data presented as raw mean (SD) scores; *p < 0.003 compared with healthy controls; †p < 0.005 compared with group 1; AF, atrial fibrillation.

perception of general health was significantly poorer in the latter ($p < 0.003$). Global life satisfaction was significantly decreased in "asymptomatic" patients compared with normal subjects ($p < 0.003$).

This study suggests that the subjective effects of AF on isolated physical aspects or on social and emotional spheres may be subtle in patients with little or no symptoms, but the arrhythmia may significantly decrease the overall perception of well being in this population. Our data are consistent with the results of other studies evaluating QoL in patients with AF. In the Canadian trial of atrial fibrillation, 289 patients with paroxysmal or persistent AF reported better QoL and had significantly higher scores in physical functioning, vitality, mental health, and role emotional when they perceived themselves to be in sinus rhythm.[3] Complete atrioventricular node ablation in patients with refractory AF resulted in a remarkable improvement in general QoL. An improvement in QoL and a reduction of symptoms after ablation was significantly greater than after atrioventricular node modification, probably because of better control of the rate and regularity of the ventricular response.[4] Although a noticeable increase in QoL has been seen in ablation studies, these usually addressed highly symptomatic patients with poorly controlled AF; only in a small series of patients with permanent AF and a normal ventricular rate response, a similar significant improvement in symptom scores and in the perception of general health have also been achieved after atrioventricular node ablation.[5]

Even less is known about QoL in patients whose rhythm and/or rate are believed to be well controlled by antiarrhythmic drugs or in those who can be potential candidates for treatment with implantable atrial defibrillators. Although pharmacological treatment may prevent the arrhythmia recurrence, it often renders symptomatic AF to asymptomatic, and the assessment of QoL in these patients may have an impact on the risk-benefit ratio of antiarrhythmic drugs. A serious consideration should be given to QoL in atrial defibrillator recipients as this device may decrease a total symptom burden of AF but usually it does not affect the recurrence of arrhythmia, in particular, short, non-treated episodes which may be well tolerated or may be unrecognised by a patient as AF.[6]

The issue of long life anticoagulation also remains open in patients with AF in whom frequent, long lasting, highly symptomatic episodes have been suppressed by either kind of treatment but the arrhythmia has not been completely abandoned. This study indicates that several aspects of QoL may be reduced in patients with AF, even in the absence of symptoms of the arrhythmia. QoL should be assessed and treatment for the improvement of QoL should be considered in patients with "asymptomatic" AF.

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1 Kerr C, Boone J, Connolly S, *et al*. Follow-up of atrial fibrillation: the initial experience of the Canadian Registry of Atrial Fibrillation. *Eur Heart J* 1996;**17**(suppl C):48–51.
2 Defaye P, Dournaux F, Mouton E, for the Aida Multicenter Study Group. Prevalence of supraventricular arrhythmias from the automated analysis of data stored in the DDD pacemakers of 617 patients: the AIDA study. *PACE* 1998;**21**:250–5.
3 Paquette M, Roy D, Talajic M, *et al*, for the CTAF Investigators. Sinus rhythm at the time of assessment is associated with better quality of life than atrial fibrillation or flutter: results from the Canadian trial of atrial fibrillation [abstract]. *PACE* 1999;**22**:863.
4 Lee SH, Chen SA, Tai CT, *et al*. Comparisons of quality of life and cardiac performance after complete atrioventricular junction ablation and atrioventricular junction modification in patients with medically refractory atrial fibrillation. *J Am Coll Cardiol* 1998;**31**:637-44.
5 Natale A, Zimerman L, Tomassoni G, *et al*. Impact on ventricular function and quality of life of transcatheter ablation of the atrioventricular junction in chronic atrial fibrillation with a normal ventricular response. *Am J Cardiol* 1996;**78**:1431–3.
6 Timmermans C, Lévy S, Ayers GM, *et al*, for the Metrix Investigators. Spontaneous episodes of atrial fibrillation after implantation of the Metrix atrioverter: observations on treated and nontreated episodes. *J Am Coll Cardiol* 2000; **35**:1428–33.

IMAGES IN CARDIOLOGY

Unicuspid aortic valve

Transoesophageal echocardiography showed a unicuspid unicommissural valve in a 16 year old boy with severe aortic stenosis. In systole, a posteriorly situated eccentric orifice extending to the annulus was seen (O, eccentric orifice; LA, left atrium, AO, aorta). In diastole there was one lateral commissural attachment to the aorta posteriorly. The single commissure showed fibrosis and thickening. An aortic valve replacement was done.

The aortic valve develops from three tubercles that are converted into thin valve cusps and sinuses of Valsalva by a process of excavation. A unicuspid aortic valve is formed by fusion of all the three cusps. It may have a central opening (no true commissure) or an eccentric orifice (unicommissural) as in our patient. The free edge of the single leaflet originates from the single attachment. It then proceeds across the orifice without additional contact with the aorta. Then it bends on itself and returns to the point of origin. It is usually stenotic at birth.

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