Persistent Macrovascular and Microvascular Dysfunction in Patients With Malignant Hypertension

Alena Shantsila, Girish Dwivedi, Eduard Shantsila, Mehmood Butt, D. Gareth Beevers, Gregory Y.H. Lip

Abstract—Endothelial dysfunction is characteristic of patients with essential hypertension, but only limited data are available on different aspects of endothelial function in patients with malignant-phase hypertension. We investigated myocardial perfusion using real-time quantitative myocardial contrast echocardiography with concurrent assessment of macrovascular and microvascular endothelial damage/dysfunction in patients with previous malignant hypertension (but now in stable phase), who were compared with patients with treated “high-risk” hypertension (hypertension) and healthy controls. We measured flow (hyperemia)-mediated dilation and response to glyceryl trinitrate of brachial artery (ultrasound), microvascular (forearm) response to acetylcholine and sodium nitroprusside (laser Doppler), pulse wave velocity, circulating endothelial and endothelial progenitor cells in 15 patients with malignant hypertension, 40 matched patients with hypertension, and 40 healthy controls. Patients with malignant hypertension had impaired endothelial-dependent response to acetylcholine ($P<0.001$, but not to sodium nitroprusside) compared with hypertension and impaired reaction to both stimuli compared with healthy subjects ($P<0.001$). Patients with malignant hypertension had increased circulating endothelial cells ($P=0.001$), endothelial progenitors ($P=0.008$), and stiffness ($P=0.003$). Both hypertensive groups had impaired response to hyperemia and glyceryl trinitrate when compared with healthy controls ($P<0.05$). Both hypertensive groups had similar myocardial perfusion, which was significantly lower than in healthy controls. There were no significant differences in hyperemia and endothelium-independent stimuli between the 2 hypertensive groups. In conclusion, despite fairly well-controlled blood pressure, malignant hypertension patients had more pronounced abnormalities of macrovascular and microvascular function (which seem to be both endothelium dependent and endothelium independent) compared with patients with hypertension and healthy controls. (Hypertension. 2011;57:00-00.)

Key Words: malignant hypertension ■ flow-mediated dilatation ■ arterial stiffness ■ endothelial progenitor cells ■ endothelial dysfunction ■ myocardial contrast echocardiography

Hypertension predisposes to all major forms of cardiovascular diseases, and distinctive structural and functional small vessel changes accompany many forms of hypertension. Malignant-phase hypertension (MHT) is the most severe form of hypertension and, at least until recently, was associated with poor prognosis. Indeed, previous studies have shown that 80% of patients with untreated MHT die within 2 years of diagnosis.1 However, with the advent of effective and tolerable antihypertensive drugs, the prognosis of MHT has greatly improved.2 Despite the vast range of antihypertensive agents and, thus, effective blood pressure control, MHT continues to remain an important clinical entity. In the largest prospective analysis of 446 MHT patients with a total of $>5700$ person-years of observation and a median follow-up of 103.8 months, the demography and number of new cases of MHT have not been shown to change substantially more than the past 40 years.2,3

It is well known that endothelial dysfunction and increased arterial stiffness exist in essential hypertension subjects and portend adverse prognosis. Similarly, impaired myocardial blood flow (MPF) reserve (MBFR) has been shown to have prognostic implications in hypertensive and diabetic patients without overt coronary artery disease.4 However, limited studies are available in literature on the pattern of arterial elasticity and endothelial function in patients with MHT.5–7 Myocardial contrast echocardiography, which uses contrast agents that are entirely intravascular, has been shown in experimental models and humans to be accurate in assessing myocardial perfusion both at rest and during stress.8–10 To the best of our knowledge, there is no study that has interrogated myocardial perfusion in MHT patients.

In this study, we hypothesized that macrovascular and microvascular (dys)function would still be present in patients with previously diagnosed MHT but with good blood pressure control at present. To test this hypothesis, we studied macrovascular and microvascular function in patients with previous MHT and compared the results with patients having high-risk hypertension (HHT, but non-
MHT, as “disease controls”) and normotensive healthy controls (HC).

Methods
We recruited consecutive eligible consenting subjects with a confirmed previous diagnosis of MHT. MHT was clinically defined as the presence of severe hypertension in association with bilateral retinal hemorrhages, cotton wool spots, or exudates with or without papilledema (on fundoscopy and retinal photography). For the MHT group we identified 101 potentially suitable patients with MHT from our MHT database. Of these, 40 patients under regular outpatient follow-up were invited to take part in the study, because others had 1 or more exclusion criteria. Of these, 15 patients consented to take part (given the intensity of the study protocol and the various exclusion criteria; see below) and were recruited, which fulfilled our a priori power calculation (see below; n=15 needed in the MHT group).

All of the MHT patients were clinically stable and treated (>3 months, average time since diagnosis: 144±108 months; range: 12 to 353 months) before recruitment and under regular outpatient follow-up. Patients with MHT were compared with 40 age and consecutively recruited sex-matched patients with treated HHT as disease controls and 40 healthy normotensive subjects (“healthy controls”). HHTs were defined as those patients with treated known hypertension (but not MHT) with 2 or more cardiovascular risk factors: left ventricular hypertrophy (using Sokolow-Lyon or Cornell voltage criteria on ECG11); age >55 years; peripheral vascular disease; or with a known family history of coronary artery disease. All of the healthy control participants were recruited accompanying relatives/carer of patients attending our outpatient clinics and colleagues working in hospital who were all defined as “healthy” by careful history, clinical examination, baseline blood tests, 12-lead ECG, and transthoracic echocardiography.

We excluded patients with coronary artery disease, valvular heart disease, left ventricular dysfunction (ejection fraction <50%), diabetes mellitus, liver disease, serum creatinine >200 μmol/L, or malignancy and those with recent (<3 months) arterial or venous thromboembolic disease, active infections, and/or a history of inflammatory or connective tissue disorders. Ethical approval was granted by local research ethics committee, and written informed consent was obtained from all of the participants.

All of the study subjects abstained from smoking, alcohol, tea, and coffee for 24 hours before the study. Hypertensive subjects were advised to omit their medications on the study day, because prolonged treatment omission was deemed unethical. All of the scans were performed in a quiet, darkened, temperature-controlled room after patient rested for 15 to 20 minutes. Blood pressure measurement and baseline venous blood sampling were performed before any scanning, from the left and right arm, respectively, while subjects were rested in supine position.

Myocardial Contrast Echocardiography
An intravenous echocontrast, Sonovue (Bracco Research SA), was administered IV at the rate of 0.7 to 1.0 mL/min using a Vueject (BR-INF 100, Bracco Research SA) infusion pump. Quantitative myocardial contrast echocardiography was performed offline. Standard commercial software (Q-Laboratory, Philips Medical Systems) was used to quantify myocardial replenishment for 15 frames after bubble destruction by placing the region of interest across the entire thickness of the myocardium, excluding the high-intensity endocardial and epicardial borders. Segments with inadequate visualization were excluded from analysis, and basal segments (of the 16 segment left ventricle model) were not quantified because of concerns about signal attenuation. Frames showing wide variation in contrast intensity were also discarded to minimize errors in the analysis. Plateau myocardial contrast intensity (representing MBF-volume), the rate of rise of signal intensity (representing mean MBF velocity), and their product, MBF, were measured at rest and after stress. The MBFR was then calculated as the ratio of MBF at rest and MBF at stress for each segment. For stress, 0.56 mg/kg of dipyridamole (Perisant ampoules, Boehringer Ingelheim) was administered through an IV cannula for >4 minutes, followed by 4-, 2-, and 3-chamber images acquisition. The mean values of MBFR were then calculated in each patient. This technique has been validated in our laboratory (n=10), with <10% and interobserver and intraobserver variability.

Laser Doppler Flowmetry
Assessment of microvascular endothelial function has been performed using scanning laser Doppler flowmetry (Periscan system PM II, Perimed AB, 780 nm red laser) with iontophoresis (0.1 mA for 60 seconds) of 2% acetylcholine (to evaluate endothelial-dependent response) and 1% sodium nitroprusside (to evaluate endothelium-independent response). The current was delivered through 2 drug delivery chambers (Model LI 611, Perimed) placed on the ventral aspect of the right upper forearm 5 cm apart and were connected to a current intensity-regulated generator (Perilont, Perimed AB). Three baseline scans were taken before each drug was iontophoresed followed by pulse scanning (each scan for 38 seconds) for a minimum of 7 minutes. Mean baseline perfusion, mean maximum perfusion, and maximum percentage change in perfusion were calculated. This technique was validated in our laboratory, and interobserver and intraobserver variabilities (n=10) were calculated at 6.3% and 8.0%, respectively.

Flow-Mediated Dilatation and Echocardiography
All of the images were acquired with a GE Vingmed System 5 or Philips iE33 ultrasound system using a hand-held 10-MHz vascular ultrasound probe in accordance with international guidelines. High-resolution ultrasound scanning of the right brachial artery was performed 3 to 5 cm above the antecubital fossa while patients lying flat with the probe stayed in the same position during the study. Anterior-to-posterior wall diameters (leading edge to leading edge) were recorded simultaneously with synchronization by R-wave on ECG. For every stage the artery diameter was calculated as an average of 5 measurements of 3 consecutive cardiac cycles. Endothelium-dependent dilatation was assessed by response to flow-mediated hyperemia. The phymgonomomaneter cuff placed around the right upper arm was inflated to 30 to 40 mm Hg above the systolic blood pressure for 5 minutes, followed by prompt deflation and recording of brachial artery image for 5 minutes. Once the baseline brachial artery diameter and flow restored, endothelium-independent dilatation was assessed 3 minutes. After administration of 0.1 mg of glyceryl trinitrates (Nitrolingual). Endothelium-dependent and endothelium-independent responses were estimated as the percentage of the brachial diameter changes compared with baseline levels. Interobserver and intraobserver variabilities for the technique in our laboratory (n=10) were 2.7% and 1.9%, respectively.

Pulse Wave Velocity and Aortic Augmentation Index
Pulse wave velocity and aortic augmentation index were measured using a SphygmoCor device (SphygmoCor, Atcor Medical). Carotid arterial waveforms were recorded noninvasively over 10 seconds using a high-fidelity hand-held application tonometer to measure the aortic augmentation index.

Aortic pulse wave velocity was recorded by making sequential ECG-gated tonometer recordings at the carotid and femoral arteries. The straight-line distances between the sternal notch and both waveform measurement sites were determined, and path length was taken as the difference between the 2 distances. This technique was validated in our laboratory, and interobserver and intraobserver variabilities (n=10) were 10.0% and 5.1%, respectively.

Flow Cytometry
A venous blood sample was taken from the right antecubital vein and was collected into EDTA Vacutainers. Quantification of endothelial progenitor cells (EPCs) and circulating endothelial cells (CECs) was performed using flow cytometry (FACS Caliber, Becton Dickinson) within 3 hours of sampling. Full blood count was obtained using a hematoanalyser (Advia, Bayer). Whole EDTA-anticoagulated ve-
uous blood (200 μL) mixed with 500 μL of PBS was incubated with fluorochrome-labeled monoclonal antibodies anti-CD45-PerCP (Becton Dickinson), anti-CD34-PE (Becton Dickinson), anti-CD146-FITC (Biocytex) and KDR-PE (R&D) for 20 minutes in the dark at room temperature. The sample was then lysed by BD Lysing Solution (Becton Dickinson) and washed once in PBS. The resultant pellet was then resuspended in PBS before running for flow cytometric analysis. Acquired events were plotted according to their forward and side scatter characteristics and gated to include mononuclear cell events. EPCs were defined as CD34

\[ \text{events} \] and CECs as CD34

\[ \text{and} \] CD146

\[ \text{events} \]. A minimum of 1 million mononuclear cell events was analyzed per sample. Absolute count of EPCs and CECs was obtained using their proportion to CD45

\[ \text{leukocytes and leukocyte count from whole blood analysis.} \]

**Statistical Analysis and Power Calculation**

Data are expressed as mean±SD for normally distributed data or median and interquartile range for descriptive and/or nonnormally distributed data. Data among 3 groups (MHT, HHT, and healthy controls) were analyzed by 1-way ANOVA. Log transformation of nonnormally distributed variables was performed using a previous ANOVA. A post hoc Tukey test was performed to assess intergroup differences, where appropriate. A P value of <0.05 was considered statistically significant. SPSS 17 (SPSS, Inc) statistical software was used to perform the statistical analyses.

On the basis of our previous work using CECs, arterial stiffness, and indices of endothelial damage/dysfunction, we calculated that a sample size of ≥15 patients in each group would have an 80% power to detect a significant difference ≥0.5 SD.

**Results**

Study subjects were comparable in age, sex, and body mass index among the 3 groups (Table 1). Blood pressure was similar in the 2-hypertensive groups (MHT and HHT), both of which had significantly higher systolic blood pressure levels when compared with healthy subjects (P<0.05).

**Myocardial Contrast Echocardiography**

Values of various myocardial perfusion indices including MBFR in the 3 groups are provided in Table 2. MBFR was significantly (<0.001) attenuated in the MHT group (1.62±0.38) compared with the healthy controls (3.42±1.02). MBFR was not significantly different between the MHT and HHT groups (1.62±0.38 versus 1.76±0.91, respectively; P value not significant; Figure 1).

**Flow-Mediated Dilatation**

All 3 of the study groups had a similar baseline brachial artery diameter (Table 3). No significant differences were observed in endothelial-dependent (hyperemia-mediated) dilatation between MHT and HHT, but endothelial-independent (glyceryl trinitrate–mediated) dilatation of the brachial artery was significantly impaired in HHT subjects. The response to hyperemia was significantly lower in both hypertensive groups (MHT vs HC 0.001).

**Table 1. Demographic and Clinical Characteristics of the Study Groups**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Malignant Hypertension</th>
<th>High-Risk Hypertension</th>
<th>Healthy Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>53.1±12.9</td>
<td>48.6±11.2</td>
<td>47.1±8.26</td>
<td>0.17</td>
</tr>
<tr>
<td>Male, %</td>
<td>73</td>
<td>65</td>
<td>68</td>
<td>0.85</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.8±5.56</td>
<td>31.5±6.43</td>
<td>29.9±6.76</td>
<td>0.50</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>149±20.3†</td>
<td>151±20.5‡</td>
<td>135±15.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>87.7±10.5</td>
<td>85.2±9.32</td>
<td>81.6±9.60</td>
<td>0.077</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>40</td>
<td>42</td>
<td>35</td>
<td>0.83</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.05 (4.90 to 5.78)</td>
<td>5.00 (4.80 to 5.70)</td>
<td>5.10 (4.70 to 5.40)</td>
<td>0.78</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.9±1.09*</td>
<td>13.9±1.39</td>
<td>14.4±1.22</td>
<td>0.027</td>
</tr>
<tr>
<td>White blood cells, ×10⁶/mL</td>
<td>7.76±2.20</td>
<td>7.10±1.89</td>
<td>6.85±1.54</td>
<td>0.26</td>
</tr>
<tr>
<td>Platelets, ×10⁹/mL</td>
<td>264±101</td>
<td>245±74.7</td>
<td>225±56.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>118±39.9†</td>
<td>86.6±19.9</td>
<td>78.1±16.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>8.52±3.55†</td>
<td>5.64±1.73</td>
<td>5.19±1.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.84±0.79</td>
<td>5.06±1.04</td>
<td>5.49±1.07</td>
<td>0.063</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or median (interquartile range).

*P<0.05 between malignant hypertension and hypertension groups.

†P<0.05 between malignant hypertension and healthy controls groups.

‡P<0.05 between hypertension and healthy controls groups.

§None of the patients were chronic smokers (defined as ≥6 continuous months of smoking a minimum of 1 cigarette daily, as per the World Health Organization criteria). Casual smokers were allowed in the study, but they abstained from smoking for ≥24 hours before the examination. Pack-year data for individual patient was not captured.

**Table 2. Myocardial Perfusion Indices Using MCE in Study Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Malignant Hypertension</th>
<th>High-Risk Hypertension</th>
<th>Healthy Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBFR rest, db/s</td>
<td>26.4±9.04</td>
<td>32.5±12.8</td>
<td>42.8±14.9</td>
<td>&lt;0.001 MHT vs HC 0.003 HHT vs HC 0.04</td>
</tr>
<tr>
<td>MBF stress, db/s</td>
<td>42.1±13.7</td>
<td>53.7±25.4</td>
<td>137.0±38.5</td>
<td>&lt;0.001 MHT vs HC &lt;0.001 HHT vs HC &lt;0.001</td>
</tr>
<tr>
<td>MBFR</td>
<td>1.62±0.38</td>
<td>1.76±0.91</td>
<td>3.42±1.02</td>
<td>&lt;0.001 MHT vs HC &lt;0.001 HHT vs HC &lt;0.001</td>
</tr>
</tbody>
</table>

MBF rest indicates myocardial blood flow at rest; MBF stress, myocardial blood after the stress test.
and HHT) compared with healthy subjects ($P=0.02$ and $P<0.01$, respectively).

**Laser Doppler Flowmetry**
Parameters of baseline cutaneous perfusion were higher in MHT and HHT groups compared with controls ($P=0.018$ and $0.001$, respectively) but did not differ between the 2 hypertensive groups (Table 3). The response of cutaneous blood flow to iontophoresis of acetylcholine ($P=0.045$) but not of single-nucleotide polymorphism was significantly impaired in MHT compared with control hypertensive group. Both hypertensive groups reveal reduced responsiveness to single-nucleotide polymorphism compared with healthy individuals.

**Pulse Wave Velocity and Aortic Augmentation Index**
Progressive significant increment in pulse wave velocity was observed among the groups, from 5.64±0.91 m/s in healthy subjects to 6.03±1.35 m/s in patients with high-risk hypertension and, further, to 7.23±2.30 m/s in MHT ($P=0.027$ for both comparisons; Table 3). No differences in aortic augmentation index have been observed between the study groups.

**EPCs and CECs**
There were no statistically significant differences in EPCs and CECs between the HHT and healthy control groups (Table 3 and Figures 2 and 3). Both EPC and CEC counts were significantly increased in MHT patients ($P=0.007$ and $P<0.001$, respectively).

The blood pressure in MHT was generally well controlled, with the mean systolic and diastolic blood pressures during follow-up since the diagnosis of 138.1±10.1 and 88.0±6.2 mm Hg, respectively (average number of measurements analyzed being 9.7±4.6). Linear regression analysis did not reveal any statistically significant predictive value of the mean blood pressure during follow-up from the various parameters of endothelial/vascular function (all $P$ values not significant; Table 4).

**Discussion**
This study demonstrates for the first time the presence of significant macrovascular and microvascular damage/dysfunction (both endothelial dependant and endothelial independent) in patients with previously diagnosed MHT despite fairly well-controlled blood pressure. Of note, all of these patients were free of other confounding factors known to influence endothelial function. Moreover, to the best of our knowledge, this is the first study that has directly interrogated myocardial perfusion noninvasively in patients with MHT.

Evidence of endothelial dysfunction in human hypertension is well established.6 Endothelial dysfunction in hypertensive patients is associated with the development of coronary artery disease and predicts future cardiovascular events, but the prognosis can be significantly improved by effective antihypertensive treatment.6,15

In our study, we found significantly attenuated MBFR in MHT patients compared with the HC group. However, MBFR values were similar in the MHT and HHT groups. Despite the small size of the MHT group, the difference in the MBFR between the MHT and HC groups was so marked that the results were significant. Moreover, the above observations have great clinical implications as a number of previous

---

**Table 3. Parameters of Endothelial/Vascular Function in Study Groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Malignant Hypertension</th>
<th>High-Risk Hypertension</th>
<th>Healthy Controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD baseline, PU</td>
<td>0.70 (0.6 to 0.92)†</td>
<td>0.75 (0.60 to 0.83)‡</td>
<td>0.51 (0.34 to 0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>LD acetylcholine, %</td>
<td>21.8±10.2†</td>
<td>97.3±57.6‡</td>
<td>228±129</td>
<td>0.001</td>
</tr>
<tr>
<td>LD sodium nitroprusside, %</td>
<td>66.0±57.1†</td>
<td>103±41.1†</td>
<td>189±82.0</td>
<td>0.001</td>
</tr>
<tr>
<td>BA diameter, mm</td>
<td>4.29±0.61</td>
<td>4.52±0.76</td>
<td>4.24±0.68</td>
<td>0.21</td>
</tr>
<tr>
<td>BA FMD, %</td>
<td>8.23±3.82†</td>
<td>7.02±4.33‡</td>
<td>12.9±7.40</td>
<td>0.001</td>
</tr>
<tr>
<td>BA response to GTN, %</td>
<td>12.2±4.39</td>
<td>11.4±5.76‡</td>
<td>15.4±7.64</td>
<td>0.025</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>7.23±2.30†</td>
<td>6.03±1.35</td>
<td>5.64±0.91</td>
<td>0.003</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>24.2±14.4</td>
<td>25.1±16.3</td>
<td>27.9±15.8</td>
<td>0.59</td>
</tr>
<tr>
<td>EPC, mL</td>
<td>331 (149–447)*†</td>
<td>133 (62–190)</td>
<td>73 (36–212)</td>
<td>0.008</td>
</tr>
<tr>
<td>CEC, mL</td>
<td>313 (177–420)*†</td>
<td>85 (46–154)</td>
<td>79 (32–181)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or median (interquartile range). LD indicates forearm perfusion obtained with laser Doppler flowmetry; BA, brachial artery; FMD, flow-mediated dilatation; GTN, glycerol trinitrate; PU, perfusion units.

* $P<0.05$ between malignant hypertension and hypertension groups.

† $P<0.05$ between malignant hypertension and healthy controls groups.

‡ $P<0.05$ between malignant hypertension and healthy controls groups.
studies have demonstrated prognostic significance of reduced MBFR even in the presence of angiographically proven normal coronary arteries. We found no significant changes in flow-mediated dilation between patients with MHT and HHT, similar to previously made observations, which found no association between the degree of endothelial dysfunction and blood pressure values.

Several previous studies uniformly reported impaired cutaneous response to acetylcholine in patients with essential hypertension. In the present study, we show significant incremental reduction of endothelial-mediated microvascular response in patients with MHT compared with HHT subjects. Indeed, controversy exists in relation to microcirculatory endothelial-independent response in essential hypertension. Although some studies have shown its impairment, others did not reveal significant abnormalities. Generally, the responsiveness of microvascular beds to such stimuli depends on the presence of different concomitant factors, such as insulin and salt resistance, as well as background therapy (eg, successful inhibitors of the renin-angiotensin system can reverse vascular hypertrophy).

In the present study, however, both hypertensive groups show a reduced endothelial-independent response compared with healthy controls, as seen in previous work. Of note, prominent abnormalities in response to acetylcholine in MHT compared with HHT with similar responsiveness to single-nucleotide polymorphism in these 2 groups indicate that impairment of microvascular endothelium in MHT patients was not attributable to possible vasodilatory effects of background therapy. Experimental studies have shown that the endothelial cells exposed to a chronic elevation in arterial blood pressure age prematurely, their turnover is accelerated, and they are replaced by regenerated endothelial cells. However, the regenerated endothelium seems to be functionally impaired. CECs are a recognized marker of endothelial damage and are increased in patients with severe cardiovascular disorders, such as acute coronary syndromes, heart failure, and stroke. Our group has previously reported increased CEC levels in hypertensive patients admitted with acute ischemic stroke. In the present study, we have now observed a significant increase in CEC counts in MHT patients.

Results from several studies and the present study indicate that EPC counts were not significantly changed in well-controlled essential hypertension. Preservation of the circulating EPC pool is further contributed to by effective antihypertensive treatment. However, EPC levels have been shown to be reduced in resistant arterial hypertension compared with well-controlled arterial hypertension and normotensive subjects, and this reduction parallels the diminished flow-mediated dilatation. Although essential hypertension does not affect EPC counts, hypertension still remains a major independent predictor for impaired EPC function. In addition, there is accelerated EPC senescence in hypertensive patients. In the present study, we show for the first time that

### Table 4. Predictive Value of Average Blood Pressure During the Period of the Observation for Parameters of Vascular Function in Malignant Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B (95% CI)</th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD acetylcholine</td>
<td>−0.67 (−1.62 to 0.25)</td>
<td>−0.42</td>
<td>0.17</td>
</tr>
<tr>
<td>LD sodium nitroprusside</td>
<td>−0.68 (−9.1 to 7.8)</td>
<td>−0.05</td>
<td>0.86</td>
</tr>
<tr>
<td>BA FMD</td>
<td>−0.88 (−0.31 to 0.13)</td>
<td>−0.23</td>
<td>0.40</td>
</tr>
<tr>
<td>BA response to GTN</td>
<td>−0.17 (−0.41 to 0.07)</td>
<td>−0.40</td>
<td>0.14</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>0.08 (0.04 to 0.21)</td>
<td>0.37</td>
<td>0.18</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.47 (0.33 to 1.28)</td>
<td>0.33</td>
<td>0.23</td>
</tr>
<tr>
<td>EPC</td>
<td>−10.2 (−35.2 to 14.8)</td>
<td>−0.24</td>
<td>0.39</td>
</tr>
<tr>
<td>CEC</td>
<td>21.2 (−10.1 to 53.2)</td>
<td>0.37</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD acetylcholine</td>
<td>0.77 (−0.21 to 1.76)</td>
<td>0.46</td>
<td>0.11</td>
</tr>
<tr>
<td>LD sodium nitroprusside</td>
<td>8.81 (3.81 to 21.4)</td>
<td>0.42</td>
<td>0.15</td>
</tr>
<tr>
<td>BA FMD</td>
<td>0.11 (−0.26 to 0.47)</td>
<td>0.17</td>
<td>0.54</td>
</tr>
<tr>
<td>BA response to GTN</td>
<td>−0.01 (−0.44 to 0.41)</td>
<td>−0.14</td>
<td>0.96</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>0.11 (−0.10 to 0.33)</td>
<td>0.31</td>
<td>0.26</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>1.04 (−0.20 to 2.28)</td>
<td>0.45</td>
<td>0.09</td>
</tr>
<tr>
<td>EPC</td>
<td>−10.4 (−51.8 to 31.1)</td>
<td>−0.15</td>
<td>0.60</td>
</tr>
<tr>
<td>CEC</td>
<td>19.1 (−35.7 to 73.9)</td>
<td>0.20</td>
<td>0.47</td>
</tr>
</tbody>
</table>

B indicates unadjusted regression coefficient; β, adjusted regression coefficient; LD, forearm perfusion obtained with laser Doppler flowmetry; BA, brachial artery; FMD, flow-mediated dilatation; GTN, glycerol trinitrate.
EPC levels are significantly upregulated in MHT patients despite good blood pressure control.

Thus, we can conclude that, despite fairly good blood pressure control for an average of 144 months, patients with MHT still had features of abnormal macrovascular and microvascular function compared with HHT and healthy controls. Thus, the macrovascular and microvascular dysfunctions seen in MHT do not, therefore, return to normal with treatment. These persistent endothelial abnormalities may be associated with the etiology of MHT and could explain the tendency for MHT recurrence in some patients.32

Given the evidence of persistent endothelial abnormalities, MHT may well be a distinct pathophysiological entity rather than simply “very severe hypertension,” per se.

Limitations

This study is limited by its cross-sectional design and the limited number of patients with MHT because of the relative rarity of such patients, especially because of our exclusion of many patients with concomitant coronary artery disease, diabetes mellitus, and significant renal impairment (which is so typical among the MHT population). Such careful selection of the study patients was necessary to reduce any bias that could have been introduced by major clinical confounders known to adversely affect endothelial function; however, sufficient numbers of patients were recruited in the MHT group to fulfill our power calculation. Also, body mass index was not a selection criterion, and (high) body mass index of the HC group probably reflects the average weight of the population of the area. None of the MHT patients had undergone cerebral imaging in the 3 months before the study examinations, but none of the recruited patients had a previous history of cerebrovascular accident. Also, we did not have long-term blood pressure control data of the HHT group, because these patients were not being routinely followed up in a dedicated clinic (but rather, in diverse general practices within the catchment population of our hospital), unlike the MHT group, which has specific follow-up in our specialist hypertension service. In addition, techniques such as laser Doppler flowmetry could be sensitive to various biological and environmental factors and, thus, could potentially affect assessment of microvascular function, but in our study we strived to achieve highly standardized conditions to minimize their effects. Finally, it would be reasonable to expect reduction rather than an increase in EPC levels in MHT patients, and although the study results are statistically significant, there is a possibility that these findings are attributed to chance given the challenging nature of the rare event analysis.

Perspectives

Patients with MHT had significantly more pronounced abnormalities of macrovascular and microvascular functions (including myocardial perfusion) compared with patients with HHT and HC. These endothelial abnormalities that persist despite the length of time since the initial diagnosis strongly suggest that endothelial damage/dysfunction may be an integral part of the pathogenesis of MHT and the tendency for MHT to recur.

Sources of Funding

A.S. was supported by an International Research Fellowship from The Lancet.

Disclosures

None.

References


Persistent Macrovascular and Microvascular Dysfunction in Patients With Malignant Hypertension
Alena Shantsila, Girish Dwivedi, Eduard Shantsila, Mehmood Butt, D. Gareth Beevers and Gregory Y.H. Lip

Hypertension, published online January 24, 2011;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2011/01/24/HYPERTENSIONAHA.110.166314

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/