Systemic Endothelial Dysfunction in Adults With Cyanotic Congenital Heart Disease

Erwin Oechslin, MD; Wolfgang Kiowski, MD; Ruth Schindler, RN; Alain Bernheim, MD; Barbara Julius, MD; Hans Peter Brunner-La Rocca, MD

Background—Secondary erythrocytosis results in increased shear stress in cyanotic congenital heart disease (CCHD), which may modify the balance between vasodilators and vasoconstrictors and affect systemic endothelial function. Because no data are available on systemic vasomotion, systemic endothelial function and nitric oxide (NO) availability were investigated in CCHD patients.

Methods and Results—Responses to arterial endothelium-dependent (acetylcholine [Ach]) and -independent (sodium nitroprusside [SNP]) vasodilation, NO synthase blockade (Nω-monomethyl-L-arginine [L-NMMA]), endothelin-1 (ET-1), and ET-1 receptor blockade by BQ-123 in 11 CCHD patients (O₂ saturation < 90%; mean ± SD, 79 ± 1%; mean ± SD age, 39 ± 2 years) were compared with those in 10 age-matched healthy referents by using forearm venous occlusion plethysmography. Resting forearm blood flow (FBF) was lower in CCHD patients than in referents (2.4 ± 0.2 versus 3.5 ± 0.4 mL · min⁻¹ · 100 mL⁻¹ of forearm volume [FAV], P < 0.05). Although the response to SNP was similar in both groups (CCHD, 2.0 ± 0.3 to 8.3 ± 1.0; referents, 3.6 ± 0.7 to 11.9 ± 1.2 mL · min⁻¹ · 100 mL⁻¹ of FAV; P > 0.1), the response to Ach was markedly reduced in CCHD (maximal increase in FBF, 2.8 ± 0.8 versus 37.5 ± 4.4 mL · min⁻¹ · 100 mL⁻¹ of FAV; P < 0.0001). L-NMMA was less effective in CCHD (decrease in FBF, 25 ± 6% versus 40 ± 4%; P < 0.05). ET-1 caused less vasoconstriction in the CCHD group (−25 ± 9% versus −51 ± 7%, P < 0.05), but the response to BQ-123 was similar in both groups (32 ± 9% versus 27 ± 9%).

Conclusions—Systemic endothelial dysfunction is evident in CCHD patients as shown by strikingly reduced endothelial vasodilation to Ach. The response to exogenous ET-1 is reduced, possibly because of elevated endogenous ET-1 levels, but the effects of endogenous ET-1 on arterial tone are not enhanced, as indicated by the similar response to ET-1 blockade. (Circulation. 2005;112:1106-1112.)

Key Words: heart defects, congenital cyanosis endothelium microcirculation hemoglobin
TABLE 1. Characteristics of CCHD Patients

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Diagnoses</th>
<th>Pulmonary Arterial Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, 51</td>
<td>VSD</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Female, 38</td>
<td>DILV, VSD, PDA</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Female, 42</td>
<td>DILV, I-TGA, VSD</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Female, 46</td>
<td>PA, large MAPCAs</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Female, 29</td>
<td>Complete d-TGA, VSD, PDA</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Female, 32</td>
<td>VSD, PDA</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Female, 33</td>
<td>Repaired TA, VSD/ASD closure, MAPCAs, residual ASD and VSD</td>
<td>Severe pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Female, 36</td>
<td>Univentricular connection, left AV atresia, ASD, VSD, d-TGA</td>
<td>Eisenmenger syndrome</td>
</tr>
<tr>
<td>Male, 43</td>
<td>DILV, VSD, d-TGA</td>
<td>Large right-to left shunt, normal pulmonary artery pressure</td>
</tr>
<tr>
<td>Female, 43</td>
<td>DILV, VSD, pulmonary artery banding</td>
<td>Severe pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Female, 32</td>
<td>PA, VSD, MAPCAs, occluded Waterston anastomosis, other surgical central aortopulmonary shunt</td>
<td>Severely restricted pulmonary blood flow, pulmonary artery pressure unknown</td>
</tr>
</tbody>
</table>

VSD indicates nonrestrictive ventricular septal defect; DILV, double-inlet left ventricle; PDA, nonrestrictive patent ductus arteriosus; I-TGA, I-transposition of the great arteries; PA, pulmonary atresia; MAPCAs, major aortopulmonary collateral arteries; d-TGA, d-transposition of the great arteries; TA, truncus arteriosus type 1; ASD, atrial septal defect within the fossa ovalis; and AV, atrioventricular.

complete for the first study day. The characteristics of the CCHD patients are presented in Table 1. The majority of patients (n=9) had severe pulmonary arterial hypertension. Because the study results for patients with and without pulmonary hypertension did not differ, they were pooled and are reported for the entire group of CCHD patients. The protocol was approved by the local Ethics Committee, and informed consent was given by all participants before the study.

All participants abstained from coffee and smoking for at least 12 hours before the study. Forearm volumes (FAVs) were measured by water displacement, using Archimedes’ principle. A 3F catheter was inserted into the brachial artery of the nondominant arm, under local anesthesia, for drug administration, blood sampling, and continuous recording of arterial blood pressure. A similar catheter was inserted into the brachial vein of the same arm for blood sampling. Heart rate and blood pressure were monitored during the entire study period.

A venous occlusion technique was used to measure forearm blood flow (FBF) in both arms with a mercury-in-Silastic strain-gauge plethysmograph, as described previously.12 Plethysmograph recordings were analyzed with the use of a digitized board and a suitably programmed computer. The mean value of 4 recordings obtained within 1 minute was taken for analysis. FBF measurements on the dominant arm served as controls to determine potential systemic drug effects. Control values for the respective intervention were obtained from the experimental arm preceding each intervention. In addition to FBF, forearm vascular resistance (FVR) was calculated by dividing FBF by mean arterial pressure (arbitrary units). All studies and analyses of plethysmographic recordings were done by a single observer (R.S.).

Arterial blood was taken to determine hematologic parameters and blood gases. Baseline measurements were performed after a resting period of 30 minutes on both days. Then, the following drugs were administered on study day 1 into the experimental brachial artery: (1) the endothelium-dependent vasodilator acetylcholine (Ach) in 5 ascending doses at 2.5, 10, 40, 80, and 160 µg/min per 100 mL of FAV for 5 minutes each, followed by a washout period of 30 minutes; (2) the NOS blocker N’-monomethyl-L-arginine (L-NMMA) at a dose of 200 µg/min per 100 mL of FAV for 5 minutes; (3) L-arginine at a dose of 850 µg/min per 100 mL of FAV for 7 minutes to reverse the effects of L-NMMA, followed by a waiting period of 60 minutes; and (4) norepinephrine at 8 and 40 ng/min per 100 mL of FAV for 5 minutes each.

On study day 2, the following drugs were administered in the same manner: (1) the endothelium-independent vasodilator sodium nitroprusside (SNP) at a dose of 0.6 µg/min per 100 mL of FAV for 15 minutes, followed by a washout period of 30 minutes; (2) BQ-123, an ET-1 type A receptor antagonist, at 6.1 µg/min per 100 mL of FAV for 30 minutes, followed by a waiting period of 45 minutes; and (3) ET-1 in 4 ascending doses of 2.6, 18, and 50 ng/min per 100 mL of FAV for 5 minutes each. FBF was measured after each dose.

These drug dosages were chosen because they have been shown to affect only regional, but not systemic, blood flow.12 Administration of these drugs was performed with constant-speed infusion pumps (Perfusor Secura FT, B. Braun) with volume rates between 30 and 90 mL/h.

Measurement of ET-1 and Big ET-1(1–38)

ET-1 plasma levels were determined by an extraction-free human ET-1 chemiluminescent immunoassay (R&D Systems, QuantiGlo QET00). This assay uses the quantitative sandwich enzyme immunoassay technique. The measuring range of the assay is 0.32 to 1000 pg/mL. The antibodies used in the kit cross-react with human ET-1 (100%), human big ET-2 (0.01%), human big ET-3 (0.019%), human ET-3 (7.8%), and human ET-2 (27.4%).

Big ET-1 plasma levels were determined by an extraction-free human big ET-1 ELISA (Biomedica, BI-20072). The measuring range of the assay is 0.05 to 15.6 fmol/mL. The antibodies that were used in the kit cross-react with human big ET-1 (1–38, 100%), human big ET-1 (22–38, <1%), ET-1 (1–21, <1%), ET-2 (1–21, <1%), and ET-3 (1–21, <1%).

Statistical Analysis

The SPSS statistical software package, version 11.5, was used for analysis (SPSS Inc). Results are represented as mean±SEM. Baseline characteristics were compared by Student’s t test, the Mann-Whitney U test, and Fisher’s exact test, as appropriate. Spearman rank correlation was used to test relations of continuous variables. Because the results of the FBF responses were normally distributed in each group, the parametric general-linear model for repeated measures was used to test the responses to infusions and to compare the responses between the 2 groups. Bonferroni’s adjustment for multiple comparisons was used where appropriate. Analysis of FVR was done after logarithmic transformation. Because there were small differences in the sex distribution between the 2 groups, all calculations were repeated, after adjustment for sex as a covariate. Because this did not influence the results at all, only unadjusted results are presented.

Power calculation was performed before the study, based on pooled data from various studies investigating healthy control subjects and our own previous data from 45 patients with endothelial dysfunction due to general atherosclerosis (authors’ unpublished data) and assuming similar endothelial dysfunction in CCHD patients. Thus, we assumed a 4 times larger response to the second largest dose of Ach in healthy referents compared with CCHD patients (SD of the response in referents was 300%; power >0.80, α
TABLE 2. Baseline Characteristics of Patients With CCHD and of Healthy Referent Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CCHD</th>
<th>Referent Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>39±2</td>
<td>40±3</td>
<td>0.70</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>2/9</td>
<td>4/6</td>
<td>0.36</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57±2</td>
<td>69±3</td>
<td>0.003</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164±2</td>
<td>173±2</td>
<td>0.004</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.60±0.03</td>
<td>1.81±0.04</td>
<td>0.0006</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21±1</td>
<td>23±1</td>
<td>0.04</td>
</tr>
<tr>
<td>FAV, mL</td>
<td>700±43</td>
<td>855±47</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78±5</td>
<td>65±2</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>117±9</td>
<td>115±4</td>
<td>0.86</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>79±1</td>
<td>96±0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P50, mmol/L</td>
<td>6.0±0.2</td>
<td>11.4±0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pco2, mmol/L</td>
<td>5.0±0.1</td>
<td>5.4±0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Base excess, mmol/L</td>
<td>−0.9±1.1</td>
<td>−1.5±0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>183±8</td>
<td>123±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>56±2</td>
<td>36±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean corpuscular volume, fl</td>
<td>86±3</td>
<td>87±1</td>
<td>0.78</td>
</tr>
<tr>
<td>Ferritin, μg/L</td>
<td>56±23</td>
<td>43±14</td>
<td>0.62</td>
</tr>
<tr>
<td>Leukocytes, 10³/μL</td>
<td>6.2±0.4</td>
<td>5.4±0.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Platelet count, ×10⁹/μL</td>
<td>132±20</td>
<td>267±24</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text. Values are mean±SD.

<0.05). According to this power calculation, 10 subjects in each group were needed to adequately address the primary aim of the study. A value of P<0.05 was considered to indicate statistical significance.

Results

Baseline characteristics are presented in Table 2. Height, weight, body surface area, body mass index, and FAV were lower in CCHD patients. These differences persisted only when women were considered (data not shown). Heart rate was higher in the CCHD patients. As per definition, O₂ saturation was lower in the CCHD patients, leading to marked erythrocytosis. Microcytosis was not present in the CCHD patients, and blood ferritin values did not differ from those of healthy subjects. Platelet count was lower in CCHD patients.

Arterial concentrations of plasma ET-1 were similar in both groups (0.19±0.02 for CCHD versus 0.20±0.03 fmol/mL in referents). Venous concentrations were slightly though not significantly higher in CCHD patients (0.40±0.07 versus 0.33±0.04 fmol/mL, P>0.1). Plasma big ET-1 levels were almost identical in arterial and venous blood but tended to be higher in CCHD patients (7.6±2.1 and 7.2±2.0 fmol/mL in arterial and venous blood, respectively, versus 4.3±1.2 and 4.2±1.1 fmol/mL, P=0.08 and P=0.06).

FBF at rest without drug infusions was lower in CCHD patients compared with referents (average of all measurements, 2.4±0.2 versus 3.5±0.4 mL · min⁻¹ · 100 mL⁻¹ FAV, P=0.03). The response to intra-arterial infusion of Ach was strikingly reduced in CCHD patients compared with the referents (Figure 1). The response of FVR to Ach was equally reduced in CCHD patients (P<0.0001; maximal reduction, 2.4±0.4 versus 14.6±1.7 times). There was a significant correlation between O₂ saturation and the maximal response to Ach in CCHD patients (r=0.67, P=0.03) but not in referents (Figure 2). There was no correlation between plasma ET-1 levels and the response to Ach in both groups.

In contrast, endothelium-independent vasodilation did not differ between the 2 groups (Figure 3; maximal increase of FBF, 6.6±1.1 versus 7.5±1.2 mL · min⁻¹ · 100 mL⁻¹ FAV, P=0.23; FVR in CCHD, 50.0±9.7 to 9.9±1.4; referents, 29.8±8.7 to 8.0±1.3 arbitrary units; P=0.70 between groups). The NOS blocker L-NMMA caused a smaller reduction in FBF (−0.7±0.2 versus −1.5±0.2 mL · min⁻¹ · 100 mL⁻¹ FAV; Figure 4) and a smaller increase in FVR in the CCHD patients (35.0±3.2 to 47.7±6.1 versus 25.2±3.3 to 45.6±6.4 arbitrary units; P=0.04 between groups), indicating reduced NO bioavailability. L-Arginine restored baseline FBF in both groups.

ET-1 infusion at a low dose (eg, 2 and 6 ng · min⁻¹ · 100 mL⁻¹ FAV) caused a small, nonsignificant increase in blood flow (7±16% versus 9±22%, P=0.20; Figure 5) and a corresponding reduction in FVR in both groups. This increase was correlated with venous ET-1 levels (r=0.82, P<0.01), the arteriovenous difference of ET-1 (r=0.90, P<0.001), and
the ratio of ET-1 to big ET-1 \((r=0.90, P<0.001)\) in CCHD patients. There was no such correlation in the referent group. At higher doses (eg, 18 and 50 ng \cdot min^{-1} \cdot 100 mL^{-1} FAV), exogenous ET-1 caused significant vasoconstriction. This vasoconstriction was reduced in CCHD patients \((0.7\pm0.3 \text{ versus } 2.3\pm0.5 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ mL}^{-1} \text{ FAV}; \text{Figure 5}; \text{increase in FVR, } 1.6\pm0.2 \text{ versus } 2.6\pm0.5 \text{ times, } P=0.04)\). No significant correlation existed between the response to high-dose ET-1 infusion and levels of ET-1 and big ET-1. The ET-1 type A receptor blocker BQ-123 caused significant but similar vasodilation in both groups \((0.7\pm0.3 \text{ versus } 1.0\pm0.5 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ mL}^{-1} \text{ FAV}; \text{Figure 6}; \text{equal reduction in FVR}). \text{The response to BQ-123 in CCHD patients was inversely related to venous ET-1 levels \((r=-0.78, P=0.02)\), the arteriovenous difference of ET-1 \((r=-0.75, P=0.03)\), and the change in the ratio of ET-1 to big ET-1 \((r=-0.70, P=0.04)\). In referent subjects, these correlations failed to reach statistical significance. Infusion of norepinephrine caused significant vasoconstriction \((P<0.0001)\). This response was similar in both groups (data not shown).

**Discussion**

The present study documents marked vasodilator dysfunction of the systemic vascular bed in adults with CCHD, as evidenced by the striking impairment of endothelium-dependent vasodilation to the endothelial agonist Ach. The reduced response to the NOS inhibitor L-NMMA also implies reduced basal bioavailability of NO. This may be the result of reduced production or release of NO at rest despite hemoconcentration and increased shear stress, which should increase NO release. Reduced production of NO as an important cause
is supported by the downregulation of endothelial NOS expression in cardiac tissues of patients with CCHD.14

There are several possible explanations for these findings. In response to prolonged episodes of hypoxia, endothelial cells exhibit a characteristic pattern of responses that can be considered either adaptive or pathological, depending on the circumstances.15 Hypoxia shifts the endothelial phenotype toward one in which anticoagulant properties are diminished, permeability and leukoadhesivity are increased, and proinflammatory features dominate the endovascular milieu.16 Thus, it is conceivable that a chronic hypoxic environment in CCHD patients leads to alterations in endothelial function.17 In our study, CCHD patients with the lowest arterial O2 saturation had the most markedly reduced response to Ach, suggesting a direct effect of chronic hypoxia on the endothelium in the peripheral arterial vasculature. It is difficult to ascribe the impaired Ach response to cyanosis, secondary erythrocytosis, or pulmonary hypertension.18,19 Cyanosis may be an important pathogenetic factor (Figure 2), although secondary erythrocytosis may also impair endothelial function.10,20 The Ach-mediated vasodilator response in patients with polycythemia rubra vera might help to elucidate the different pathogenetic roles of cyanosis and erythrocytosis, but this was not tested in this study. Furthermore, a potential increase in the release of NO as a result of increased shear stress1 is obviously not enough to compensate for the effects of chronic hypoxia, as suggested by the present study.

Abnormalities of endothelial NOS activity and NO have been found previously in the pulmonary circulation of patients with pulmonary hypertension and CCHD.11,21,22 Endothelium-dependent vasodilation of the pulmonary circulation was significantly reduced in children with congenital heart disease and abnormal pulmonary hemodynamics.22 The number of patients without pulmonary hypertension was small in our study. Thus, the potential effect of pulmonary hypertension on peripheral endothelial function cannot be assessed in our patients with certainty, although, on average, there was no difference between patients with and without pulmonary hypertension. Interestingly, NO production may change during progression of the disease, as described in experimental models of right-to-left shunt lesions,10,23 wherein increased endothelial NOS activity at an early stage was postulated as a compensatory mechanism.10 In our patients with CCHD and hypoxia for years, systemic endothelial dysfunction was invariably strikingly reduced.

Increased shear stress and mechanical pressure may also negatively influence other endothelial functions. These factors were found to increase the release of plasma von Willebrand factor, a marker of endothelial dysfunction, and ET-1.24,25 Release of factors contributing to endothelial dysfunction in the pulmonary circulation may affect the systemic circulation if released in sufficient amounts. In theory, it is conceivable that increased levels of ET-1 produced within the pulmonary circulation in CCHD may contribute to endothelial dysfunction in the systemic vascular bed.3,26 In our study, however, we did not find elevated circulating ET-1 levels, arguing somewhat against this hypothesis. Also, the vascular response to blockade of endogenous ET-1 did not differ between patients with CCHD and healthy referent subjects. However, we found a reduced vasoconstrictive response to high doses of locally administered ET-1, indicating desensitization or downregulation of ET-1 type A receptors. This was most likely caused by chronic overstimulation by increased tissue ET-1 levels, which may be higher than suggested by its plasma concentration because of its predominantly abluminal release.27 This is consistent with increased ET-1 protein levels in the vascular wall and reduced vascular response to ET-1 and big ET-1 in transgenic mice with erythropoietin-induced excessive erythrocytosis.20 In contrast, ET-1 type B receptors did not seem to be downregulated in this population of CCHD patients, because the vasodilator response to low-dose ET-1 considered to be due to NO release1 was preserved in CCHD.

It is not clear whether our findings are clinically relevant, but it is conceivable that severe endothelial vasodilator dysfunction may be involved in the development of cardiovascular events in CCHD patients. Adults with CCHD have an increased risk of cerebrovascular events (ie, 1/100 patient-years). Rheological problems, eg, microcytosis, and “traditional” risk factors, like hypertension and atrial fibrillation, are believed to contribute to this increased risk.28 Our findings are compatible with the contention that abnormal vascular regulatory mechanisms may also contribute to the increased risk for ischemic complications, because NO is not only a potent vasodilator but also a powerful antiaggregatory agent.29

Interestingly, a reduced forearm vasodilator response to Ach predicted cardiovascular events in hypertensive patients and in patients with acute coronary syndromes.30,31 A reduced Ach response of coronary resistance vessels predicted coronary events in patients with and without coronary atherosclerosis.32 On the basis of these reports and on our finding of a profoundly impaired Ach-induced endothelial response to FBF, one might expect an increased incidence of atherosclerosis and coronary events in adults with CCHD. This, however, contrasts with the low prevalence of coronary artery disease in adults with CCHD.33 Factors like low cholesterol levels, hyperbilirubinemia, and thrombocytopenia may account for the apparent discrepancy.34 Whether, in addition to differences in antiatherogenic factors, this low prevalence reflects a fundamental difference in the importance of the NO system (or endothelium-derived hyperpolarizing factors) in the coronary vascular bed in the pathogenesis of atherosclerosis in patients with CCHD remains speculative.

Limitations

Some limitations apply to the present study. First, the number of patients included was relatively small. However, endothelial function differed strikingly between the 2 groups, making a false-positive finding extremely unlikely.

Second, we studied a heterogeneous population, but the majority of CCHD patients had severe pulmonary hypertension. Thus, it is difficult to determine whether cyanosis, secondary erythrocytosis, or pulmonary hypertension was the primary underlying cause of systemic endothelial dysfunction or whether there is a complex interplay among these different pathogenetic factors. The impaired response to the endothelium-dependent vasodilator Ach was seen in patients both
with and without pulmonary hypertension, giving some hint that secondary erythrocytosis may be the more important factor.

Third, Ach infusions were used to assess endothelial vasodilator function by forearm venous occlusion plethysmography, which is a test of microcirculatory rather than conduit-artery endothelial function. Whether larger conduit arteries would show similar differences has not been investigated.

Fourth, it is well known that only a fraction of the vasodilation after Ach infusion is caused by the effects of NO. Endothelial responses to endothelial agonists (eg, Ach, bradykinin, substance P, serotonin) encompass several mechanisms other than generation of NO, such as endothelium-derived hyperpolarizing factors and prostaglandins. Without coinfusion of Ach and an NOS inhibitor such as L-NMMA, we cannot rule out the possibility that other pathways (eg, blunted release of NO or endothelium-derived hyperpolarizing factor) account for the strikingly depressed endothelial response to Ach. However, the reduced basal response to L-NMMA makes it tempting to speculate that the impaired response to Ach also entails reduced bioavailability of NO.

Fifth, circulating ET-1 levels in the systemic circulation were lower in our CCHD patients than previously reported in the pulmonary circulation. This may have limited our ability to determine the role of ET-1 in the development of systemic endothelial dysfunction.

Finally, as expected in chronically ill patients, weight, height, and body mass index of patients with CCHD were significantly lower than those of the referents. Importantly, infusions of vasoactive substances was corrected for differences in FAV to overcome this difference.

Conclusions

This study has demonstrated that endothelial dysfunction is evident in the systemic circulation of adults with CCHD, based on a strikingly impaired vasodilator response to Ach. It is tempting to speculate that systemic endothelial dysfunction may play a role in the increased rate of cerebrovascular events in this population, but further studies are needed to test this hypothesis.

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References


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