Blood Vessels

Arterial Stiffness Is Regulated by Nitric Oxide and Endothelium-Derived Hyperpolarizing Factor During Changes in Blood Flow in Humans

Jeremy Bellien, Julie Favre, Michele Iacob, Ji Gao, Christian Thuillez, Vincent Richard, Robinson Joannides

Abstract—Cytochrome-derived epoxyeicosatrienoic acids may be important endothelium-derived hyperpolarizing factors, opening calcium-activated potassium channels, but their involvement in the regulation of arterial stiffness during changes in blood flow in humans is unknown. In healthy volunteers, we measured arterial pressure, radial artery diameter, wall thickness, and flow (NIUS02) during hand skin heating in the presence of saline or inhibitors of NO synthase (N\textsuperscript{G}-monomethyl-L-arginine), calcium-activated potassium channels (tetraethylammonium), and cytochrome epoxygenases (fluconazole). Arterial compliance and elastic modulus were calculated and fitted as functions of midwall stress to suppress the confounding influence of geometric changes. Under saline infusion, heating induced an upward shift of the compliance-midwall stress curve and a downward shift of the modulus-midwall stress curve demonstrating a decrease in arterial tone and stiffness when blood flow increases. These shifts were reduced by N\textsuperscript{G}-monomethyl-L-arginine and abolished by the combinations of N\textsuperscript{G}-monomethyl-L-arginine/tetraethylammonium and N\textsuperscript{G}-monomethyl L-arginine/fluconazole. In parallel, in isolated mice coronary arteries, fluconazole and tetraethylammonium reduced the relaxations to acetylcholine. However, fluconazole did not affect the relaxations to the openers of calcium-activated potassium channels of small- and intermediate-conductance NS309 and of large-conductance NS1619 excluding a direct effect on these channels. Moreover, tetraethylammonium reduced the relaxations to NS1619 but not to NS309, suggesting that the endothelium-derived hyperpolarizing factor involved mainly acts on large-conductance calcium-activated potassium channels. These results show in humans that, during flow variations, arterial stiffness is regulated by the endothelium through the release of both NO and cytochrome-related endothelium-derived hyperpolarizing factor. (Hypertension. 2010;55:674-680.)

Key Words: arterial stiffness • endothelium • NO • endothelium-derived hyperpolarizing factor • cytochrome epoxygenases

The mechanical properties of conduit arteries play a major role in maintaining an optimal arterial function, that is, allowing these arteries to propagate blood pressure and flow between the heart and arterioles, which lie at the junction of the capillary network, and to act as a cushion, transforming pulsatile flow at the level of ascending aorta into steady flow through the arterioles.\textsuperscript{1,2} A progressive alteration in the mechanical properties of elastic conduit arteries and, in particular, an increase in wall stiffness occur with aging, but this alteration is accelerated in many diseases with a high independent prognostic value.\textsuperscript{1,2} In fact, arterial stiffening induces an early return of arterial wave reflections, through an increase in pulse wave velocity, boosting systolic pressure while reducing pressure throughout diastole and, thus, increasing aortic pulse pressure.\textsuperscript{1,2} The functional consequences are the enhancement of left ventricular afterload and myocardial work, the reduction of coronary perfusion, and, at last, the increase in the fatigue effect of pulsatile stress exerted on the load-bearing elements of the arterial wall.\textsuperscript{1,2}

Regarding the regulation of arterial mechanics, increasing evidence shows that the vascular endothelium may play a crucial step through the control of arterial smooth muscle cell relaxation and contraction, which influence wall stiffness by modifying isometric tone.\textsuperscript{2,8} However, few results have been obtained in humans and, in particular, no data are available regarding the endothelial pathways involved in the adaptation of arterial mechanics during changes in blood flow. This is of crucial importance because this adaptation allows us to maintain an appropriate arterial conductance and ventricular vascular coupling under physiological conditions of flow variations and, in particular, during exercise.\textsuperscript{7,8} Under basal flow conditions, the role of endothelium-derived NO in the

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regulation of the elastic properties of conduit arteries, although somewhat controversial in aorta, is generally admitted. In addition, an endothelium-derived hyperpolarizing factor (EDHF), acting through the opening of vascular calcium-activated potassium ($K_{Ca}$) channels, might be also involved at this level, but its nature is undetermined. Of interest, epoxycystatrienonic acids produced by endothelial cytochrome epoxygenases may be important EDHFs in humans, notably at the level of conduit arteries. In this respect, we and others have demonstrated in vivo that NO and an EDHF produced by endothelial cytochrome epoxygenases account for two thirds of human conduit artery flow-mediated dilatation during prolonged hyperemic stimulation. Furthermore, despite this increase in diameter, which induces the recruitment of the peripherally stiffer elements through the vascular wall, we observed that heating is associated with a decrease in isometric tone and wall stiffness. Whether this adaptation of arterial mechanics to blood flow variation is similarly attributed or not to the action of NO and EDHF has never been assessed. Therefore, the aim of the present study was, thus, to assess the effects of the local inhibition of NO synthase, $K_{Ca}$ channels, and cytochrome epoxygenases on the mechanical properties of the radial artery, used as a model of peripheral conduit artery, during a sustained and stable increase in blood flow induced by heating.

Methods

Subjects

The study was performed in 11 nonsmoking healthy male volunteers (age: 24±2 years) explored on separate days with a 2- to 3-week washout period between each experiment. The forearm volume was measured by using the water displacement method to adjust the doses of the inhibitors to be infused. The study was approved by the local ethical committee (Committee for the Protection of Persons of Haute-Normandie), and all of the participants gave written informed consent. This study adheres to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

Instrumentation

Measurements were performed in the morning while subjects were in a supine position, in a quiet air-conditioned room, maintained at a constant temperature (22°C to 24°C). A 27-gauge needle was inserted, under local anesthesia (1% lidocaine), into the brachial artery of the nondominant arm to permit infusion of saline (0.9%) and pharmacological agents at a constant rate (1 mL/min). Systemic blood pressures were measured on the dominant arm by means of a brachial cuff oscillometric device (Dinapam). Radial internal diameter ($d$), wall thickness ($h$), blood flow ($Q$), and digital arterial pressure were continuously obtained using a high-precision echo-tracking device coupled to a Doppler system (NIUS 02, Asulab) and a finger photoptlethysmograph (Finapres System, Ohmeda), as described previously.

The hand skin temperature was modified by use of a water-filled thermocontrolled device (Polystat 1, Biosbell Scientific) and heating to gradually increase the water temperature from 34°C to 44°C, as published previously. This procedure allows us to induce a sustained and stable increase in blood flow without affecting systemic hemodynamics. Total blood viscosity ($\eta$) was measured using a cone-plate viscometer (Ex100 CTB, Brookfield) at a shear rate of 241 s$^{-1}$ at 37°C, allowing the calculation of the mean arterial wall shear stress ($\tau$), the flow-dependent stimulus, assuming a Poiseuillean model, that is, $\tau=4/3 \mu Q/(\pi r^4)$, ($r=\sqrt{d^2/2}$). Oral aspirin (500 mg) was administered to all of the subjects to block the production of vasomotor prostanooids. To assess the roles of NO and EDHF in the regulation of arterial mechanics, each subject participated in 4 experimental procedures and, thus, received saline, used as the control, the NO-synthase inhibitor N$^\mathcal{G}$-monomethyl-L-arginine (l-NMMA, Clinalfa), or l-NMMA combined with either the nonspecific inhibitor of vascular $K_{Ca}$ channels, tetraethylammonium chloride (TEA, Clinalfa), or the potent inhibitor of cytochrome epoxygenases, fluconazole (Pfizer Holding France). All of the drugs were continuously infused during heating. We gradually increased the doses of l-NMMA (from 8 to 20 µmol/min per liter) and fluconazole (from 0.4 to 1.6 µmol/min per liter) to compensate for the diluting effect of the increase in flow during heating, whereas to avoid any change in systemic hemodynamics, we kept the dose of TEA constant (9 µmol/min per liter). Each inhibitor was infused at doses producing only a local inhibitory effect without affecting blood pressure or heart rate, and, therefore, their impact on arterial mechanics was not related to changes in systemic hemodynamics.

Arterial Mechanics

From the values of arterial pressure ($p$), internal diameter ($d$), and wall thickness ($h$) measured during 10 consecutive heartbeats, the cross-section ($S$) pressure curve was fitted as $S = \alpha p^2 + 2\arctan[(p - \beta y)/S]$, $S = \pi d^4/4$, where $\alpha$, $\beta$, and $\gamma$ are the optimal fit parameters of the model. The cross-sectional compliance ($C$) was expressed as $C = (\alpha/(\alpha + 1) - (p - \beta y)/S)$ to evaluate the arterial chamber deformability and the incremental elastic modulus (Ei) as $Ei = 38((d/d + 2h^3)/(h + d))/p\sigma d$, to evaluate the arterial wall stiffness. The midwall stress ($\sigma$) was calculated to evaluate the arterial wall-loading conditions as $\sigma = 2(\pi r_1 + \pi r_2)/(r_1^2+r_2^2)$, where $r_1$ and $r_2$ are the external and internal radii, respectively, and $r$ is the radius at midwall: $r = (r_1 + r_2)/2$. Then, from the individual values, the diameter-, compliance-, and modulus-midwall stress curves were constructed at 34°C and 44°C to assess the effect of the inhibitors at identical levels of wall-loading conditions (ie, midwall stress), thus suppressing the confounding effects of changes in arterial geometry or pressure. In the absence of change in systemic blood pressure during the different experimental procedures, only digital arterial pressure used for calculations is shown.

Animal Experiments

To detail the mechanism of action of the pharmacological inhibitors of the EDHF pathway used in the human investigations, we performed in vitro coronary vascular studies in male wild-type Friend virus B mice used at 3 to 4 months, as described elsewhere. The vascular model was chosen on the basis of previous experiments demonstrating that it is characterized by prominent NO-independent, EDHF-mediated relaxations. The study was approved by a local institutional review committee and conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Mice were anesthetized by IP injection of a mixture of ketamine (150 mg/kg) and xylazine (6 mg/kg). The heart was removed and immediately placed in cold, oxygenated Krebs buffer. A small segment (<1 mm) of the main left coronary artery (diameter: 190 to 220 µm) was carefully dissected and mounted in a small-vessel myograph for isometric tension recording (JP Trading). For this purpose, the artery was threaded onto two 25-µm tungsten wires. Normalization procedure was performed after an equilibration period, as described previously. To assess endothelium-dependent, NO-independent relaxations, the vessels were pretreated with the NO-synthase inhibitor N$^\mathcal{G}$-nitro-l-arginine (10$^{-5}$ mol/L for 30 minutes), after which increasing concentrations of acetylcholine (10$^{-9}$ to 3 · 10$^{-5}$ mol/L) were applied on arteries precontracted with serotonin (10$^{-5}$ mol/L). These N$^\mathcal{G}$-nitro-l-arginine–resistant, acetylcholine-induced relaxations were assessed in the absence or in the presence of diclofenac (10$^{-5}$ mol/L), TEA (10$^{-5}$ mol/L), or fluconazole (5·10$^{-5}$ mol/L) and the association of TEA with fluconazole. Furthermore, the coronary relaxation responses to the large-conductance, calcium-activated potassium (BK$_{Ca}$) channels opener NS1619 (10$^{-6}$ to 3·10$^{-4}$ mol/L) were assessed in the absence or in the presence ofiberotoxin (specific inhibitor of BK$_{Ca}$ channels: 10$^{-7}$ mol/L), TEA (10$^{-5}$ mol/L), or fluconazole (5·10$^{-10}$ mol/L).
mol/L). In the same way, the coronary relaxing responses to the small-conductance and intermediate-conductance channels opener NS309 (10^-6 to 3.10^-8 mol/L) were assessed in the absence or in the presence of the combination of the inhibitors of small-conductance KCa channels apamin (10^-7 mol/L) and of intermediate-conductance KCa and BKCa channels charybdotoxin (10^-7 mol/L) and iberiotoxin (10^-7 mol/L), as well as in the presence of TEA (10^-4 mol/L) or fluconazole (5.10^-5 mol/L). All of the inhibitors were applied for 30 minutes before assessing the relaxant responses. The concentrations of TEA and fluconazole used in these experiments were chosen to be close to the calculated local concentrations obtained in the radial artery during the human investigations. A total of 60 animals were used for these experiments.

**Statistical Analysis**

All of the results are expressed as mean±SEM. The shifts of the diameter-, modulus-, and compliance-midwall stress curves between 34°C and 44°C were analyzed using an ANCOVA with temperature and subject as factors and midwall stress as the covariate. The effects of the inhibitors on these shifts were analyzed on the calculated differences between 34°C and 44°C at each level of midwall stress for each subject using an ANOVA with midwall stress as a factor followed by a modified Student t test when applicable. For the in vitro experiments of coronary function, “n” represents the number of arteries used, and concentration-response curves were compared by ANOVA for repeated measures followed by a modified Student t test when applicable. A value of P≤0.05 was considered statistically significant.

**Results**

**Human Investigations**

There were no modifications in arterial blood pressure or heart rate during the different experimental sequences performed in the healthy volunteers (Table). Heating induced in all of the cases an increase in mean wall shear stress (Figure 1). The increase in wall shear stress was not affected by L-NMMA alone or combined with fluconazole but was reduced by L-NMMA combined with TEA.

Regarding the relationships, the increase in midwall stress was associated in all of the cases with an increase in radial artery diameter (Figure 2) and elastic modulus (Figure 3) and a decrease in compliance (Figure 4). Heating induced an upward shift of the diameter-midwall stress curves in all of the cases. However, compared with saline (mean difference between 34°C and 44°C: 0.498±0.078 mm), this shift was reduced by L-NMMA (0.345±0.036 mm) and, to a larger extent, by L-NMMA combined with TEA (0.223±0.032 mm) or with fluconazole (0.164±0.045 mm; all P<0.05). During saline infusion, heating induced a downward shift of the modulus-midwall stress curve demonstrating vascular smooth muscle relaxation and subsequent decrease in wall stiffness. As a result of the increase in diameter and the decrease in modulus with midwall stress, there was an upward shift of the compliance-midwall stress curve. Compared with saline (−0.52±0.06 10^5 kilopascals [kPa]), the downward shift of the modulus-midwall stress curve was reduced by L-NMMA (−0.35±0.04 10^5 kPa) and abolished by both L-NMMA combined with TEA (−0.06±0.03 10^5 kPa) and L-NMMA combined with fluconazole (−0.08±0.01 10^5 kPa; all P<0.05). Similarly, compared with saline (7.3±0.5 m²·kPa^−1·10^−8), the upward shift of the compliance-midwall stress curve was reduced by L-NMMA (5.8±1.0 m²·kPa^−1·10^−8) and abolished both by L-NMMA combined with TEA (1.2±0.1 m²·kPa^−1·10^−8) and L-NMMA combined with fluconazole (1.1±0.2 m²·kPa^−1·10^−8; all P<0.05).

**Animal Experiments**

The coronary relaxations to acetylcholine assessed in the presence of the NO-synthase inhibitor Δ^6-nitro-L-arginine at 10^-4 mol/L were not affected by the cyclooxygenase inhibitor diclofenac. For example, the coronary relaxation was 59±8% before and 53±8% after diclofenac (n=10; P value not significant) at 10^-6 mol/L of acetylcholine. In contrast, the coronary relaxations to acetylcholine were similarly reduced by TEA, fluconazole, and their combination (Figure 5). As expected, iberiotoxin reduced the coronary relaxations to the BKCa channels opener NS1619, whereas apamin+charybdotoxin but not iberiotoxin reduced the relaxations to the small-conductance KCa and intermediate-conductance KCa channels opener NS309. In this context, fluconazole did not affect the relaxations to NS309 or NS1619, whereas TEA altered the relaxation to NS1619 but not to NS309.

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**Table. Values of Mean Arterial Pressure and Heart Rate Measured at 34°C and 44°C in the Presence of Saline, L-NMMA Alone, and Combined With TEA or With Fluconazole**

<table>
<thead>
<tr>
<th>Substance Infused</th>
<th>34°C</th>
<th>44°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>87±1</td>
<td>83±2</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>84±1</td>
<td>85±1</td>
</tr>
<tr>
<td>L-NMMA+TEA</td>
<td>82±1</td>
<td>84±1</td>
</tr>
<tr>
<td>L-NMMA+fluconazole</td>
<td>86±2</td>
<td>89±2</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>72±3</td>
<td>71±5</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>68±2</td>
<td>73±4</td>
</tr>
<tr>
<td>L-NMMA+TEA</td>
<td>71±4</td>
<td>71±2</td>
</tr>
<tr>
<td>L-NMMA+fluconazole</td>
<td>72±2</td>
<td>69±4</td>
</tr>
</tbody>
</table>

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**Figure 1. Variations in mean wall shear stress during heating in the presence of saline, L-NMMA alone, and combined with TEA or with fluconazole. *P<0.05 vs other conditions.**
Figure 2. Radial artery diameter-midwall stress curves obtained at 34°C (●) and 44°C (■) in the presence of saline (A), L-NMMA alone (B), and L-NMMA combined with TEA (C) or with fluconazole (D).

†P<0.05 vs 34°C; †P<0.05 vs saline; ‡P<0.05 vs L-NMMA.

Figure 3. Radial artery elastic modulus-midwall stress curves obtained at 34°C (●) and 44°C (■) in the presence of saline (A), L-NMMA alone (B), and L-NMMA combined with TEA (C) or with fluconazole (D).

*P<0.05 vs 34°C; †P<0.05 vs saline; ‡P<0.05 vs L-NMMA.
The major finding of this study is that the local inhibition of both NO and EDHF pathways in vivo in humans fully prevents the decrease in smooth muscle tone and wall stiffness of the radial artery during hand skin heating, thus demonstrating the major role of these endothelium-derived factors in the adaptation of peripheral conduit artery mechanics to changes in blood flow.

Discussion

The major finding of this study is that the local inhibition of both NO and EDHF pathways in vivo in humans fully prevents the decrease in smooth muscle tone and wall stiffness of the radial artery during hand skin heating, thus demonstrating the major role of these endothelium-derived factors in the adaptation of peripheral conduit artery mechanics to changes in blood flow.
To assess the role of EDHF in peripheral conduit artery mechanics, we infused locally, in addition to the NO-synthase inhibitor L-NMMA, different inhibitors of the EDHF pathway.16 TEA was, thus, used to block the hyperpolarizing mechanism of EDHF mediated by the opening of vascular KCa channels, and fluconazole was used to inhibit cytochrome epoxygenases, which produce epoxyeicosatrienoic acids (EETs) identified as EDHF in conduit arteries.14,21,22 However, to detail the mechanism of the inhibitory effects of TEA and fluconazole on the EDHF pathway, we performed some experiments in Friend virus B mice, because previous data obtained in our laboratory indicate that this strain of mice exhibits an important contribution of EDHF to endothelium-dependent responses in the left coronary artery.19 We first observed that the coronary relaxations to acetylcholine studied in the presence of an NO-synthase inhibitor were similarly reduced by TEA, fluconazole, or their combination, which is quite similar to the inhibitory effect obtained on radial artery flow-mediated dilatation.16 Of importance to note, these results contrast with recent data indicating that this strain of mice did not exhibit significant contribution of EETs to the relaxing response to acetylcholine when assessed in mesenteric arteries.23 As expected, iberiotoxin significantly reduced the relaxations to the opener of large-conductance KCa channel NS1619, although a substantial remaining relaxation persisted probably because of a nonspecific effect of NS1619 on other ion channels.24 In addition, we observed that NS309 induced potent coronary relaxing responses that were largely reduced by the combination of apamin and charybdotoxin but not by iberiotoxin, confirming that this agent is a potent opener of small-conductance KCa and intermediate-conductance KCa channels, as shown recently in human coronary arteries.25 Of importance, fluconazole did not alter the relaxations to NS1619 or NS309, demonstrating that its effect at the concentration used on endothelium-dependent responses is not related to a direct interaction with vascular KCa channels, as reported previously with other antifungal agents.14 Furthermore, TEA reduced the relaxation to NS1619 to a similar extent as iberiotoxin but did not affect the relaxation to NS309, strongly suggesting that, at a concentration of <1 mmol/L, TEA predominantly affects the BKCa channels located on the smooth muscle cells, which are largely, but not exclusively, involved in the hyperpolarizing effect of EETs.21

Concerning the human investigations, arterial mechanical parameters were calculated at each stable level of flow during hand skin heating and fitted as a function of midwall stress, to provide comparable wall-loading conditions between different shear stress levels. Thus, it was possible to consider the effects of the different inhibitors infused on arterial mechanics, considering their proper action on the increase in flow and diameter. Indeed, the increase in flow can alter arterial mechanics through 2 opposite effects. The associated increase in arterial diameter with blood flow enhances midwall stress and increases wall stiffness by the recruitment of the peripheral stiffer elements through the vascular wall.6 Inversely, the increase in blood flow may promote the release of vasorelaxing factors, which decrease isometric tone and wall stiffness.6 In this respect, we observed during saline infusion that heating induced an upward shift of the compliance midwall stress curve and a downward shift of the modulus-midwall stress curve demonstrating a compensatory decrease in vascular smooth muscle tone and wall stiffness when blood flow increases. Thus, these results confirm the presence of a flow-mediated regulation of peripheral conduit artery mechanics in our subjects, which is probably explained by the flow-dependent release of vasorelaxing factors by the endothelium.4,6

In this context, as expected from the role of NO in the regulation of sustained flow-mediated dilatation,14 the infusion of L-NMMA was associated with a lesser upward shift of the diameter-midwall stress curve despite a similar increase in the flow-dependent stimulus, that is, mean wall shear stress. However, despite this lesser increase in diameter and, thus, lesser recruitment function, the downward shift of the modulus-midwall stress curve was reduced when compared with saline infusion. Moreover, as a result of the lesser increase in diameter and lesser decrease in wall stiffness, the increase in arterial compliance during heating was reduced compared with control conditions. Thus, these data demonstrate the role of NO in the control of arterial mechanics during blood flow variations in accordance with previous studies performed in peripheral conduit arteries but under basal flow conditions.11,12 Regarding the EDHF pathway, we observed that the combinations of L-NMMA with tetraethylammonium or with fluconazole reduced to a larger extent but did not abolish the upward shift of the diameter-midwall stress curve compared with L-NMMA alone despite a significant reduction in the increase in mean wall shear stress for L-NMMA combined with TEA.16 In contrast, both combinations fully prevented the decrease in elastic modulus and the increase in compliance at all levels of midwall stress. These effects demonstrate for the first time the major role of a cytochrome-related EDHF in the adaptation of peripheral conduit artery mechanical properties to the increase in flow in humans. In accordance with these data, it was shown in porcine coronary arteries that the increase in pulsatile stretch elicits the release of an EDHF, which may contribute to the control of coronary blood flow and adjustment of an adequate vascular compliance.26 Furthermore, although the mechanisms involved are not known, the persistence of a residual flow-mediated dilatation while the adaptation of arterial mechanics is suppressed during combined blockade of NO and EDHF pathways is probably of critical importance, still allowing the blood flow to increase while limiting the rise in mean wall shear stress.

On the basis of the present experimental and clinical data and previous ex vivo studies,22 we can hypothesize that the increase in shear stress in peripheral conduit arteries elicits the release, in addition to NO, of an EDHF belonging to the group of EETs, which may diffuse from the endothelium to act on the smooth muscle cells and activate BKCa channels. The resulting smooth muscle hyperpolarization promotes the decrease in isometric tone and wall stiffness, allowing the adaptation of arterial compliance and, thus, the maintenance of the buffering function of the arterial system during the increase in blood flow.
In conclusion, these results show that, in human peripheral conduit arteries, the adaptation of smooth muscle tone and arterial stiffness during blood flow variations is regulated by the vascular endothelium through the release of both NO and cytochrome-related EDHF, demonstrating its major role in the regulation of arterial conductance and ventricular vascular coupling.

Perspectives
Additional experiments are needed to identify the EDHF involved as ≥1 EET and to investigate the evolution of this endothelial pathway in ageing and diseases. In addition, the abnormalities of this pathway in more proximal elastic arteries and in the mismatch between proximal and distal conduit arteries in the branching circulation should be investigated because, on a clinical point of view, by increasing the arterial stiffness and the transmission of backward pressure waves from the more peripheral reflection sites, these abnormalities may contribute to the development of systolic hypertension and related heart failure.1,2

In this context, increasing the availability of these cytochrome metabolites might be a promising therapeutic approach in humans diseases to reduce cardiovascular morbidity and mortality.14 Specific pharmacological drugs are under development, such as the inhibitors of soluble epoxide hydrolase, which increase the availability of EETs by preventing their hydrolysis, and recent animal experiments show that these agents have antihypertensive and cardioprotective actions but may also display beneficial effects on endothelial function.27,28

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Disclosures
None.

References
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