Calcium-Activated Potassium Channels and NO Regulate Human Peripheral Conduit Artery Mechanics

Jeremy Bellien, Robinson Joannides, Michele Iacob, Philippe Arnaud, Christian Thuillez

Abstract—The role of NO in the regulation of the mechanical properties of conduit arteries is controversial in humans, and the involvement of an endothelium-derived hyperpolarizing factor (EDHF), acting through calcium-activated potassium (K_{Ca}) channels, has never been investigated at this level in vivo. We assessed in healthy volunteers, after oral administration of aspirin (500 mg), the effect of local infusion of N^{G}-monomethyl-L-arginine (L-NMMA; 8 μmol/min for 8 minutes), an NO synthase inhibitor, tetraethylammonium chloride (TEA; 9 μmol/min for 8 minutes), a K_{Ca} channels inhibitor, and the combination of both on radial artery internal diameter, wall thickness (echo tracking), blood flow (Doppler), and pressure. The incremental elastic modulus and compliance were fitted as functions of midwall stress. L-NMMA decreased modulus and increased compliance at high levels of midwall stress (all P<0.05) without affecting radial diameter. TEA reduced radial diameter from 2.68±0.07 to 2.50±0.08 10^{-3} m, increased the modulus, and decreased the compliance at all levels of stress (all P<0.05). Combination of both inhibitors synergistically enhanced the increase in modulus, the decrease in diameter (from 2.71±0.10 to 2.42±0.09 10^{-3} m), and compliance compared with TEA alone (all P<0.05). These results confirm that inhibition of NO synthesis is associated with a paradoxical isometric smooth muscle relaxation of the radial artery. They demonstrate the involvement of K_{Ca} channels in the regulation of the mechanical properties of peripheral conduit arteries, supporting a role for EDHF at this level in vivo. Moreover, the synergistic effect of L-NMMA and TEA shows that K_{Ca} channels compensate for the loss of NO synthesis to maintain peripheral conduit artery diameter and mechanics. (Hypertension. 2005;46:210-216.)

Key Words: arteries ■ elasticity ■ compliance ■ nitric oxide ■ potassium channels ■ endothelium-derived factors

Vascular endothelium regulates smooth muscle tone by the release of vasorelaxant and vasoconstricting factors.1,2 Smooth muscle cell relaxation induces a decrease in wall stiffness through a reduction in isometric tone. The presence of a basal release of NO resulting in a permanent NO-dependent vasodilatory influence has been largely demonstrated at the arteriolar level.1–3 However, at the level of conduit arteries, although the contribution of NO to agonists and flow-mediated endothelium-dependent vasodilatation has been demonstrated, local administration of NO synthesize inhibitors such as N^{G}-monomethyl-L-arginine (L-NMMA) do not constantly induce a decrease in diameter or an increase in the measured indicators of arterial stiffness, thus questioning the role of a basal release of NO in the regulation of conduit artery geometry and mechanics.2–10 In addition, although NO synthase inhibition was associated to an increased sensitivity to exogenous NO as expected from the suppression of an endogenous NO release,3,11 we previously observed a surprising decrease in arterial stiffness without change in arterial pressure and diameter after L-NMMA, suggesting the development of compensatory vasorelaxant mechanisms.7 In this way, prostacyclin (PGI_{2}) derived from endothelial cyclooxygenase appears to play no role in this regulation in physiological condition as after acute NO synthase inhibition.2,4 Whether an increase in vascular calcium-activated potassium (K_{Ca}) channel activity after NO synthesis inhibition could contribute to the maintenance of basal conduit artery diameter and mechanics has never been investigated in vivo in humans. Indeed, endothelium-derived hyperpolarizing factor (EDHF) is described as the non-NO and non-PGI_{2} factor leading to smooth muscle cell hyperpolarization and relaxation by the opening of vascular K_{Ca} channels.12,13 In humans, the recent demonstration of the contribution of K_{Ca} channels in the regulation of forearm arteriolar resistance strongly suggests a role for EDHF in vivo.14,15 Moreover, the involvement of K_{Ca} channels and EDHF in the control of conduit artery mechanics and diameter is consistent with previous animal and ex vivo studies.16–19 Thus, the present study was designed to assess in vivo, at the level of the radial artery, the effect of the acute vascular K_{Ca} channel blockade in the regulation of basal conduit artery diameter and mechanical properties before and after inhibition of NO synthesis.

Methods

Subjects
Nine healthy male volunteers (mean±SEM 23±1 years) were examined on 3 separate days, with a 3- to 4-week washout period
TABLE 1. Radial Artery Parameters Obtained at Operational Pressure Before and After Infusion of L-NMMA and TEA and Their Combination

<table>
<thead>
<tr>
<th>Arterial Parameters</th>
<th>Time</th>
<th>L-NMMA</th>
<th>TEA</th>
<th>L-NMMA + TEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal diameter (10^{-3} m)</td>
<td>Base</td>
<td>2.699±0.099</td>
<td>2.678±0.071</td>
<td>2.707±0.101</td>
</tr>
<tr>
<td>Wall thickness (10^{-3} m)</td>
<td>Change (%)</td>
<td>−0.5±0.9</td>
<td>−6.8±0.7†</td>
<td>−10.8±0.5‡‡</td>
</tr>
<tr>
<td>Radius-to-wall thickness ratio</td>
<td>Base</td>
<td>3.798±0.038</td>
<td>3.988±0.123</td>
<td>3.975±0.121</td>
</tr>
<tr>
<td>Cross-sectional area (10^{-4} m²)</td>
<td>Change (%)</td>
<td>−1.3±1.0</td>
<td>0.8±1.3</td>
<td>0.6±0.4</td>
</tr>
<tr>
<td>Midwall stress (kPa)</td>
<td>Change (%)</td>
<td>3.8±2.0</td>
<td>−10.9±3.3†</td>
<td>−18.0±1.9‡‡</td>
</tr>
<tr>
<td>Elastic modulus (10^3 kPa)</td>
<td>Change (%)</td>
<td>1.15±0.25</td>
<td>1.22±0.24</td>
<td>1.06±0.22</td>
</tr>
<tr>
<td>Compliance (10^{-5} m²/kPa)</td>
<td>Change (%)</td>
<td>5.04±0.19</td>
<td>5.16±0.81</td>
<td>5.12±0.80</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *P<0.05 vs corresponding control value; †P<0.05 vs L-NMMA; ‡P<0.05 vs TEA.

between each. The forearm volume was measured by using the water displacement method to adjust the doses of the inhibitors to be infused. All the procedures followed were in accordance with our institutional guidelines. The protocol was approved by the Consultative Committee for the Protection of Persons Engaged in Biomedical Research of Haute-Normandie, and all participants gave informed written consent.

Instrumentation
Systemic blood pressure and heart rate were measured on the dominant arm by mean of a brachial cuff oscillometric device (Dinamap). Radial internal diameter, wall thickness, blood flow, and arterial pressure were continuously measured in the nondominant arm using a high-precision echo-tracking device (NIUS 02) coupled to a Doppler system (Doptek) and a finger photoplethysmograph (Finapres) as described previously. From arterial blood samples, total blood viscosity was measured using a cone-plate viscometer (Ex100 constant temperature bath). From the individual values of radial artery internal diameter (d), blood flow (Q), and total blood viscosity (μ), the mean arterial wall shear stress (τ) was calculated as τ=(4μQ)/(πd^2) and τ=r2/2).

Mechanics of the Radial Artery
From the measured variables arterial pressure (p), internal diameter (d), and wall thickness (h), the cross-sectional (S)–pressure curve was fitted as S=ε(πd^2+tan^-1((p−β)/γ)), S=md^3/4, where α, β, and γ are the 3 optimal fit parameters of the model. The cross-sectional compliance (C) was expressed as C=(ε(πd^2)/(1+(p−β)/γ)) and the incremental elastic modulus (Ei) as Ei=3P(d+2h)/(h(d+h))p/αd. The midwall stress (σw) was calculated as σw=2πr1·τ1/3(r1−r2)^2, where re and ri are the external and internal radii, respectively, and r the radius at midwall (r=(r1+ri)/2). Finally, from the individual values, the diameter–midwall stress, the modulus–midwall stress, and the compliance–midwall stress curves were constructed to assess the effect of the inhibitors at identical levels of wall-loading conditions.

Study Protocol
Subjects were supine in a quiet, air-conditioned room (22°C to 24°C). A 27-gauge needle was inserted under local anesthesia (1% lidocaine) into the brachial artery of the nondominant arm, and saline was infused (1 mL/min). After instrumentation, oral aspirin (UPSA 500 mg; laboratoire UPSA) was given to block vascular cyclooxygenase activity. After 30 minutes of resting, arterial parameters were recorded at baseline for 5 minutes. Then, sodium nitroprusside (SNP; 20 nmol/L per minute) was infused for 3 minutes to assess the NO-mediated endothelium-independent dilatation. Thirty minutes after completion of SNP infusion and return to basal values of radial artery blood flow and diameter, for 8 minutes, subjects received, in random order, either the NO synthase inhibitor L-NMMA (8 μmol/L per minute; Clinalfa) or the vascular Kc channel inhibitor tetrathyammonium chloride (TEA; 9 μmol/L per minute; Clinalfa), or their combination. At the end of the inhibitor infusion, the same protocol of SNP administration was repeated. From this continuous recording, mean values were calculated from 15 consecutive cardiac cycles during the last minute of each infusion period. At each time, all parameters were calculated at operational pressure (mean arterial pressure). In absence of change in systemic blood pressure during the different experimental procedures, only digital arterial pressure used for calculations is shown.

Statistical Analysis
Results are expressed as mean±SEM. The effects of the inhibitors on the mean values were compared using ANOVA with subjects, periods, and inhibitors as factors, followed by a modified Student t test when applicable. This analysis was repeated with the mean wall shear stress or the variation of the radial artery flow as covariate. The relationships obtained after the inhibitors were compared with those obtained at baseline using an ANCOVA with midwall stress as covariate and subjects and periods as factors. A value of P<0.05 was considered statistically significant.

Results
Mean Hemodynamic and Mechanical Parameters
At baseline before infusion of L-NMMA and TEA, and the combination of L-NMMA and TEA, there was no significant difference between the mean values of the geometric and mechanical parameters of the radial artery (Table 1) and between the mean values of arterial pressure and heart rate (Table 2).

None of the inhibitors affected arterial pressure or heart rate (Table 2). In addition, cross-sectional area was not modified by L-NMMA or TEA, or their combination (Table 1).
After the combination of l-NMMA and TEA, internal diameter decreased, and wall thickness increased (both \(P<0.05\)). The radius-to-wall thickness ratio decreased (\(P<0.05\)), explaining, in absence of change in arterial pressure, the decrease in radial artery midwall stress (\(P<0.05\)). Radial artery flow decreased from 10.5\(\pm\)2.4 to 7.7\(\pm\)0.8 \(10^{-3}\) L/min (\(P<0.05\)), but as a result of the concomitant decrease in radial artery diameter and flow, the mean wall shear stress was not significantly modified by the combination (from 4.0\(\pm\)0.6 to 4.0\(\pm\)0.7 \(10^{-1}\) Pa). After NO synthesis inhibition combined to \(\text{K}_\text{Ca}\) blockade, the pulse diameter-to-pulse pressure ratio decreased by \(-34\pm5\%\), from 8.5\(\pm\)1.1 \(10^{-2}\) m/Pa (\(P<0.05\)). The incremental elastic modulus of the arterial wall increased, and the radial artery compliance decreased (both \(P<0.05\)). The effect of the combination of l-NMMA and TEA on all these parameters was more pronounced than those of TEA alone (all \(P<0.05\)).

The effects of l-NMMA and TEA and their combination on the geometric and mechanical parameters of the radial artery remained significant even after mean wall shear stress or changes in radial artery flow were included as covariates into analysis (all \(P<0.05\)).

### Internal Diameter, Elastic Modulus, and Arterial Compliance–Midwall Stress Curves

Figure 1 shows the effect of l-NMMA on the internal diameter, elastic modulus, and arterial compliance–midwall stress curves. Before and after l-NMMA, the radial artery diameter and the elastic modulus of the arterial wall increased, and the radial artery compliance decreased with the midwall stress (both \(P<0.001\)). After l-NMMA, there was no significant change in the diameter–midwall stress curve. The modulus–midwall stress curve was shifted downward (\(P<0.001\)), reflecting a decrease in arterial wall stiffness. The compliance–midwall stress curve was shifted upward (\(P<0.001\)). These effects were more marked at high levels of midwall stress. The decrease in arterial wall stiffness and the increase in compliance, which occurred in the absence of any change in arterial pressure or geometry, suggest that inhibition of NO synthesis was associated with an isometric smooth muscle relaxation.

Figure 2 shows the effects of TEA and of the combination of l-NMMA and TEA on the internal diameter, elastic modulus, and arterial compliance–midwall stress curves. The radial artery diameter and the elastic modulus of the arterial wall increased, and the radial artery compliance decreased with the midwall stress in all cases (all \(P<0.001\)).

![Radial artery diameter (left), incremental elastic modulus (middle), and compliance–midwall (right) stress curves obtained before (○) and after (●) infusion of l-NMMA. After l-NMMA, in absence of significant shift of the diameter–stress curve (NS), there was a downward shift of the incremental modulus–stress curve at high values of stress (\(P<0.001\)) that indicates the decrease in wall stiffness and an upward shift of the compliance–stress curve (\(P<0.001\)) that reflects at the level of the arterial chamber the decrease in wall stiffness obtained after NO synthase inhibition. \(P<0.001\) for stress effect.](http://hyper.ahajournals.org/)

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**TABLE 2. Arterial Hemodynamic Parameters Measured Before and After Infusion of l-NMMA and TEA and Their Combination**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Inhibitors</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>l-NMMA</td>
<td>112±3</td>
<td>112±2</td>
</tr>
<tr>
<td></td>
<td>TEA</td>
<td>112±5</td>
<td>114±6</td>
</tr>
<tr>
<td></td>
<td>l-NMMA + TEA</td>
<td>116±7</td>
<td>118±8</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>l-NMMA</td>
<td>62±2</td>
<td>64±2</td>
</tr>
<tr>
<td></td>
<td>TEA</td>
<td>61±3</td>
<td>61±3</td>
</tr>
<tr>
<td></td>
<td>l-NMMA + TEA</td>
<td>62±4</td>
<td>61±3</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>l-NMMA</td>
<td>79±1</td>
<td>83±2</td>
</tr>
<tr>
<td></td>
<td>TEA</td>
<td>79±3</td>
<td>80±4</td>
</tr>
<tr>
<td></td>
<td>l-NMMA + TEA</td>
<td>80±5</td>
<td>80±4</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>l-NMMA</td>
<td>50±4</td>
<td>48±3</td>
</tr>
<tr>
<td></td>
<td>TEA</td>
<td>51±4</td>
<td>52±5</td>
</tr>
<tr>
<td></td>
<td>l-NMMA + TEA</td>
<td>54±5</td>
<td>57±5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>l-NMMA</td>
<td>64±3</td>
<td>63±3</td>
</tr>
<tr>
<td></td>
<td>TEA</td>
<td>59±2</td>
<td>62±2</td>
</tr>
<tr>
<td></td>
<td>l-NMMA + TEA</td>
<td>60±2</td>
<td>64±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

After l-NMMA, internal diameter, wall thickness, radius-to-wall thickness ratio, and midwall stress were not modified (all NS). Radial artery flow decreased from 11.7±2.6 to 9.2±1.8 \(10^{-3}\) L/min (\(P<0.05\)), and the mean wall shear stress decreased from 4.3±0.6 to 3.5±0.5 \(10^{-1}\) Pa (\(P<0.05\)). After inhibition of NO synthesis, the pulse diameter to pulse pressure ratio increased nonsignificantly by 9\%\%, from 8.0\±1.1 \(10^{-2}\) m/Pa. The incremental elastic modulus of the arterial wall decreased (\(P<0.05\)), and the radial artery compliance decreased, however, not significantly.

After TEA, internal diameter decreased (\(P<0.05\)), and wall thickness increased, however, not significantly. The radius-to-wall thickness ratio decreased (\(P<0.05\)), explaining, in absence of change in arterial pressure, the decrease in radial artery midwall stress (\(P<0.05\)). Radial artery flow decreased from 10.9±2.3 to 8.5±1.8 \(10^{-3}\) L/min (\(P<0.05\)), but as a result of the concomitant decrease in radial artery diameter and flow, the mean wall shear stress was not significantly modified by TEA (from 4.6±0.8 to 4.4±0.8 \(10^{-1}\) Pa). After the blockade of \(\text{K}_\text{Ca}\) channels, the pulse diameter-to-pulse pressure ratio decreased by \(-18\pm5\%\), from 8.9±1.7 \(10^{-2}\) m/Pa (\(P<0.05\)). The incremental elastic modulus of the arterial wall was not modified (NS), but the radial artery compliance decreased (\(P<0.05\)).
After TEA, there was a downward shift in the diameter–midwall stress curve and an upward shift in the modulus–midwall stress curve (both \( P<0.001 \)). Thus, \( KCa \) channel blockade was associated with a smooth muscle contraction that explains the decrease in arterial diameter and the increase in arterial wall stiffness at each level of stress. As a result, the compliance–midwall stress curve was shifted downward at each level of stress (\( P<0.001 \)).

After the combination of \( \L-NMMA \) and TEA, the internal diameter–, elastic modulus–, and arterial compliance–midwall stress curves were shifted in the same way as after TEA alone (all \( P<0.001 \)). However, the shift of these curves was more pronounced after the combination of \( \L-NMMA \) and TEA than after TEA alone (all \( P<0.01 \)). Thus, when combined with \( KCa \) channel blockade, the NO synthesis inhibition was associated to a larger smooth muscle contraction than after TEA alone.

**Radial Artery Endothelium-Independent Dilatation**

Figure 3 shows the effects of SNP on the internal diameter–, elastic modulus–, and arterial compliance–midwall stress curves in control conditions. After SNP, there was an upward shift of the diameter–midwall stress curve and a downward shift in the modulus–midwall stress curve (both \( P<0.001 \)). As a result, the compliance–midwall stress curve was shifted upward at each level of stress (\( P<0.001 \)).

SNP induced an increase in radial artery diameter before (2.724±0.072 to 3.293±0.109 \( \times10^{-3} \) m; \( P<0.05 \)) and after \( \L-NMMA \) (from 2.691±0.095 to 3.360±0.128 \( \times10^{-3} \) m; \( P<0.05 \)), before (2.694±0.084 to 3.274±0.117 \( \times10^{-3} \) m; \( P<0.05 \)) and after TEA (2.502±0.078 to 3.143±0.116 \( \times10^{-3} \) m; \( P<0.05 \)), and before (2.694±0.084 to 3.274±0.117 \( \times10^{-3} \) m; \( P<0.05 \)) and after their combination (2.415±0.093 to 3.207±0.134 \( \times10^{-3} \) m; \( P<0.05 \)). The increase in radial artery diameter was enhanced by \( \L-NMMA \) alone and in combination with TEA (both \( P<0.05 \)), whereas TEA alone did not significantly modify this response.

**Discussion**

Our results obtained from humans demonstrate that \( KCa \) channels are involved in regulation of the mechanical properties of peripheral conduit arteries, supporting a role for EDHF at this level in vivo. In addition, the synergistic effect of \( \L-NMMA \) and TEA on radial artery constriction and arterial wall stiffening in absence of such effects after administration of \( \L-NMMA \) alone shows that \( KCa \) channels compensate for the loss of NO synthesis to maintain peripheral conduit artery diameter and mechanics.

As a result, the compliance–midwall stress curve was shifted upward at each level of stress (\( P<0.001 \)).

**Figure 2.** Radial artery diameter (left)–, incremental elastic modulus (middle)–, and compliance–midwall (right) stress curves obtained before (C) and after (●) infusion of TEA (A) and before (●) and after (○) infusion of the combination of \( \L-NMMA \) and TEA (B). TEA induced a downward shift of the diameter–stress curve (\( P<0.001 \)) and an upward shift of the incremental modulus–stress curve (\( P<0.001 \)), indicating that the vasoconstriction of the radial artery observed after TEA was associated with a simultaneous increase in wall stiffness at each level of midwall stress. Thus, the downward shift of the compliance–stress curve (\( P<0.001 \)) after SNP is explained by the increase in diameter and the decrease in wall stiffness.

**Figure 3.** Radial artery diameter (left)–, incremental elastic modulus (middle)–, and compliance–midwall (right) stress curves obtained before (C) and after (●) infusion of SNP in control conditions. SNP induced an upward shift of the diameter–stress curve (\( P<0.001 \)) and a downward shift of the incremental modulus–stress curve (\( P<0.001 \)), indicating that the vasodilatation observed after administration of exogenous NO is associated to a decrease in wall stiffness. Thus, the upward shift of the compliance–stress curve (\( P<0.001 \)) for stress effect.
The present study was performed in healthy subjects at the level of the radial artery to assess in vivo the role of NO and vascular KCa channels and their potential interaction in the regulation of basal conduit artery diameter and mechanics. All experiments were performed after administration of aspirin to inhibit vascular cyclooxygenase and to exclude a role for PGI2 in our results. The inhibition of endothelial NO synthesis was obtained with l-NMMA, infused at a dose of 8 μmol/min, known to abolish the radial artery dilatation to high gradual doses of acetylcholine without affecting hemodynamics. In addition, we used the nonspecific inhibitor of vascular KCa channels, TEA, as a pharmacological tool for the exploration of EDHF activity. Indeed, although the biological nature of EDHF remains to be discussed, its endothelium-dependent hyperpolarizing mechanism appears mainly related to the opening of vascular KCa channels leading to smooth muscle cell relaxation. Thus, TEA was infused at a dose of 9 μmol/min to obtain, for a basal radial artery flow of 10 mL/min, a local concentration of 1 mmol/L higher than those shown to selectively block a single KCa channel without affecting the function of other potassium channels. As expected, l-NMMA reduced radial artery flow, confirming the role of NO in the regulation of the basal arteriolar tone in humans. In addition, as more recently reported by use of plethysmography in healthy subjects, TEA reduced radial artery flow in our study, also demonstrating a role of KCa channels in the control of basal arteriolar tone.

Concerning the conduit arteries, the local administration of l-NMMA did not significantly modify blood pressure nor the radial diameter but decreased the arterial wall stiffness, thus demonstrating, in accordance with our previous report, although less marked, paradoxical isometric smooth muscle cell relaxation after NO synthase inhibition. An absence of decrease in the diameter or alteration in the mechanical properties of conduit arteries was reported in vivo despite local administration of doses of l-NMMA up to 60 μmol/min in absence of significant change in blood pressure. Conversely, other studies demonstrated a significant effect of local NO synthesis inhibition on arterial diameter and mechanics. These results could be explained by the heterogeneity of the vascular tree and by the increase in blood pressure after systemic administration of l-NMMA. In addition, the invasive methodological approaches used in some studies could have provided more sensitivity, but they also could have potentiated the vascular effect of NO synthesis inhibition by majoring the local decrease in flow or by interfering with KCa channel activity. In this context, l-NMMA induced in our subjects an enhanced dilatation to SNP compared with baseline conditions. This hypersensitivity of the smooth muscle cells to a nitrovasodilator after NO synthase inhibition has been observed previously in vitro and in vivo and reflects the suppression of an endogenous NO release in the arterial wall. Thus, this hypersensitivity and the absence of decrease in resting diameter despite the concomitant decrease in flow after l-NMMA once again suggest more the presence of compensatory mechanisms occurring after inhibition of NO synthesis to maintain this diameter than the absence of NO basal release. Thus, according to the magnitude or the ability to develop such mechanisms, the effect of l-NMMA on diameter and mechanics could vary, explaining also the apparent divergences observed. Indeed, although the impact of arterial pressure on this mechanism needs to be evaluated, the higher blood pressure level observed in the present study, although within the normal range, could have decreased the magnitude of the effect noted after l-NMMA compared with our previous experiment.

In this context, TEA induced a significant decrease in radial artery diameter and compliance obtained at operational pressure and at each level of stress, demonstrating for the first time in vivo that vascular KCa channels are involved in the regulation of basal peripheral conduit artery mechanics in humans. At operational pressure, the elastic modulus was not modified. This was the consequence of the simultaneous decrease in midwall stress attributable to the lower radius-to-wall thickness ratio after vasoconstriction. When evaluated at stable wall-loading conditions by use of the elastic modulus–midwall stress curve, TEA was associated to an increase in modulus at each level of stress, thus confirming the wall stiffness increase and the withdrawing of a relaxant influence after KCa channel blockade. The effect of TEA on radial artery geometry and stiffness cannot be related to a flow-dependent mechanism because radial artery mean wall shear stress (ie, the physiological flow stimulus) was not significantly affected by TEA. In addition, as described previously in human resistance arteries, TEA did not modify radial artery dilatation to SNP, arguing against a decrease in smooth muscle cell ability to relax after KCa channel blockade. Previous animal and ex vivo experiments have shown that vascular KCa channels are involved in the endothelium-dependent dilatation of conduit arteries. However, their role in the regulation of basal conduit artery diameter and tone has been less investigated. Nevertheless, it was demonstrated that KCa channels contribute to the control of the resting membrane potential of human gastroepiploic arteries. In addition, Popp et al showed that the activation of muscular KCa channels was mainly dependent of the basal release of an EDHF in porcine coronary arteries and participates in the regulation of arterial compliance. Thus, our results obtained at the level of the radial artery suggest that the activation of vascular KCa channels involved in the regulation of resting diameter and mechanics results from the basal release of an EDHF in vivo.

Finally, we observed that the combined administration of l-NMMA and TEA induced a greater decrease in radial artery diameter and compliance than TEA alone. In addition, this combination induced a significant increase in the operational elastic modulus despite the larger decrease in midwall stress than after TEA alone, thus supporting the dramatic increase in wall stiffness at each level of stress reflected by the upward shift of the modulus–midwall stress curve. As already discussed for TEA alone, this effect could not be related to a flow-dependent mechanism or to a decrease in vascular smooth muscle cell reactivity. In this context, KCa channel blockade unmasks the vasoconstrictor effect of l-NMMA on the radial artery, thus giving evidence of the role of NO in the regulation of resting diameter and mechanics at the level of a peripheral conduit artery in humans. Moreover, this syner-
gistic effect of the combined administration of l-NMMA and TEA demonstrates that vascular KCa channels compensate for the loss of endothelial NO synthesis to maintain the basal radial diameter and mechanics, explaining why l-NMMA, when administered alone, was ineffective to induce radial artery constriction and, in contrast, decreased the isometric wall artery muscular tone. These results are consistent with previous studies showing that an increase in NO availability decreases EDHF-mediated conduit artery dilation in animals and that at the opposite, chronically impaired NO-dependent dilatation present in pathology is associated to an upregulation of EDHF, acting as a back-up mechanism to preserve endothelium-dependent dilatation of resistance and conduit arteries.

Perspectives

Our in vivo study gives evidence for the first time that an alternative pathway acting through the stimulation of KCa channels is activated at baseline and upregulated during NO deficiency at the level of human peripheral conduit arteries to maintain resting diameter and mechanical properties in physiological state. These results strongly support the hypothesis of a basal release of an EDHF at this level. Whether this mechanism is still effective in aging humans and in pathophysiological conditions needs further investigation. This could be of importance in the regulation of cardiovascular coupling and arterial conductance at rest and during exercise, and therefore its alteration could contribute to the pathophysiology of many cardiovascular diseases. Furthermore, the presence of such mechanisms at the level of epicardial coronary arteries or proximal conduit arteries more frequently concerned by atherosclerosis could participate in the prevention of atherosclerosis in addition to NO.

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References


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