Coronary endothelial dysfunction after cardiomyocyte-specific mineralocorticoid receptor overexpression

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MINERALOCORTICOID RECEPTOR (MR) antagonists are potent treatment of heart failure (19, 20), and this illustrates the deleterious effects of aldosterone on cardiovascular system structure and function. Among the possible targets of aldosterone, the vascular effects of MR activation may play a central role (24, 25). This so-called aldosterone-induced vasculopathy (25) may be related in part to the aldosterone-induced oxidative stress (21, 24). For example, aldosterone has been recently shown to impair vascular reactivity, by decreasing glucose-6-phosphate dehydrogenase (G6PD), leading to increased oxidant stress, endothelial dysfunction, and decreased nitric oxide (NO) levels (11).

The vascular oxidative stress induced by aldosterone and the resulting inflammatory response (5, 21, 22, 25, 27) probably play a triggering role in the adverse cardiac effects of MR activation, including increased fibrosis (10).

The adverse roles of aldosterone on the vasculature, and especially on endothelial cells (11, 14, 15, 24), are also reflected by the observation that MR antagonists improve endothelial function in heart failure, both in experimental models (3, 23) and in patients (1, 7). However, whether coronary protection observed with MR antagonists is a direct effect or an indirect consequence of the changes occurring in the cardiomyocytes is unclear. Indeed, the link between aldosterone-mediated effects on the cardiomyocyte on one hand and the vasculature, especially the coronary circulation, on the other hand is unknown.

We recently demonstrated that mice with cardiomyocyte-specific overexpression of aldosterone synthase (9) display impaired coronary endothelium-dependent relaxations (2). Since this occurs in the absence of major cardiac functional or structural phenotypic changes, this suggests that cardiac aldosterone may directly alter coronary function. However, the exact target of aldosterone in this setting remains unclear. Indeed, the coronary impact of aldosterone may reflect direct endothelial MR stimulation, but the coronary dysfunction might also be an indirect consequence of the phenotypic changes induced by MR activation in cardiomyocytes, secondarily impacting the coronary vasculature. However, the possible link between aldosterone-mediated effects on the cardiomyocyte and the coronary arteries has not yet been studied. To directly characterize the coronary consequences of cardiomyocyte MR activation, we took advantage of a transgenic model with conditional, cardiomyocyte-specific human MR (hMR) overexpression, which we developed (16), and demonstrated that these mice displayed marked oxidative stress-mediated coronary endothelial dysfunction. Thus, with this unique approach, we suggest a new paracrine mechanism, by which cardiomyocytes trigger NOX-dependent, reactive oxygen species-mediated coronary endothelial dysfunction.

MATERIAL AND METHODS

Animals and experimental protocols. All animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals, published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996). The protocol was approved by a regional Animal Care and Ethics Committee. The generation of transgenic mice has been described previously (16). Briefly, the previously characterized tetO-hMR mouse strain was crossed with the α-MHCtTA transactivator mouse strain (kindly provided by G.I. Fishman) to obtain MHCtTA/tetO-hMR double transgenic (TG) mice with conditional, cardiomyocyte-specific hMR expression. Doxycycline (Dox) (1 g/kg in the chow) was given to the pregnant mothers and progeny until 2 wk of age to prevent embryonic and postnatal lethality previously reported in this model. Dox administration was
then stopped to allow hMR expression, as previously described (16), and experiments were performed in 3-mo-old mice. Subgroups of control and transgenic mice were treated for 1 mo (starting at 2 mo of age), either with the active metabolite of spironolactone, canrenone (40 mg.kg⁻¹.day⁻¹ in water), the antioxidants vitamin E (1% in chow) and vitamin C (0.05% in water), or the NADPH oxidase (NOX) inhibitor apocynin (50 mg.kg⁻¹.day⁻¹ in chow).

**Blood pressure, plasma urine collection, and echocardiographic analysis.** The blood was collected by aorta puncture in anesthetized mice, and plasma was isolated by centrifugation for determination of plasma aldosterone levels. Urine samples (24 h) were collected in individual metabolic cages (Phymep Marty Technology, Paris, France) for 8 days. Plasma and urine aldosterone concentration was determined by radioimmunooassay (Diagnostics Products, Los Angeles, CA). Systolic blood pressure (BP) and heart rate (HR) were measured by the tail-cuff method. Echocardiography was performed on lightly anesthetized mice (isoflurane, Abbot, in oxygen) as previously described (18).

**In vitro vascular studies.** Coronary vascular studies were performed as described before (2, 8). Mice were anesthetized by intraperitoneal 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, 190–220 μm) was carefully dissected and mounted in a small vessel myograph for isometric tension recording (JP Trading Aarhus, Denmark). For this purpose, the artery was threaded onto two 25-μm tungsten wires. After an equilibration period, the vessels were contracted with 10⁻⁵ M serotonin before applying increasing concentrations of acetylcholine (10⁻⁸ to 3 x 10⁻⁵ M). Endothelium-dependent, NO-independent relaxations to acetylcholine were assessed in the presence of the NO synthase inhibitor N⁵-nitro-l-arginine (l-NNa; 10⁻⁴ M) after 30 min preincubation. In some experiments, the responses to acetylcholine were assessed again after incubation with tetrahydrobiopterin (BH₂; 10⁻³ M)(17). Endothelium-independent relaxations induced by the NO donor sodium nitroprusside (SNP; 10⁻⁹ to 10⁻⁷ M) were also assessed in serotonin-precontracted arteries.

In some experiments, segments of mesenteric arteries (1 to 2 mm length; diameter, 200–300 μm) were isolated and mounted as described for coronary vessels. In these segments, relaxing responses to acetylcholine were assessed after precontraction by phenylephrine. Cardiac production of reactive oxygen species.** Reactive oxygen species (ROS) production was evaluated by electron paramagnetic resonance (EPR) spectroscopy. Hearts were incubated at 37°C for 60 min in Krebs-HEPES buffer containing 5 μM diethyliothiocarbamate, 25 μM deferoxamine, and the spin probe 1-hydroxy-3-methoxy-carbonyl-2,2,5,5-tetramethyl pyrrolidine hydrochloride (CMH; 500 μM; Noxygen, Elzach, Germany). Spectra of the oxidized product of CMH (SNP; 10⁻⁹ to 10⁻⁷ M) were recorded in 100 μg aliquots of ventricular homogenates was assayed in modified HEPES buffer containing (in mM) 140 NaCl, 5 KCl, 5.5 glucose and 25 HEPES and 1% glucose (pH 7.2) in a 96-well microplate luminescence reader (BioRad) at 37°C. Measurements were made in duplicate. The NADPH oxidase (NOX) inhibitor apocynin (300 μmol/L; Sigma-Aldrich) was used to confirm that the assay was determining ROS production from NOX.

**Statistical analyses.** Results were expressed as means ± SE. For in vitro experiments of coronary function, n represents the number of animals from which the arteries were taken. Concentration-response curves were compared by ANOVA for repeated measures. EPR spectroscopy data were analyzed by ANOVA followed when significant by a Student’s t-test with Bonferroni correction. Hemodynamic, PCR, and Western blot data were compared by t-test. P < 0.05 was considered as statistically significant.

**RESULTS**

**Hemodynamic and cardiac parameters, and aldosterone concentrations.** The effect of cardiac hMR overexpression on heart rate, blood pressure, and cardiac hypertrophy as well as left ventricular (LV) remodeling and LV function are shown in Table 1. When compared with wild-type (WT; control) mice, cardiac hMR overexpression was not associated with signi-
Cardiomyocyte hMR overexpression also altered a small, NO-responsive responses (maximal relaxations: base, 69 ± 5% vs. hMR, 64 ± 9%). The impaired relaxation observed in hMR/MHC mice is not due to increased aldosterone, norepinephrine, or angiotensin II. Table 1 shows the measured parameters between any of the measured parameters.

Cardiac hMR overexpression induced modest and nonsignificant increases in cardiac weight (normalized to tibia length) as well as LV end-diastolic and end-systolic volumes (measured by echocardiography) and did not affect LV ejection fraction (assessed by echocardiography). When compared with WT, TG mice also did not display any changes in plasma or urinary aldosterone.

**Coronary function.** When compared with WT mice, coronary arteries isolated from TG mice with conditional, cardiomyocyte-specific hMR overexpression (hMR/MHC) and precontracted with serotonin displayed a severe impairment in relaxing responses induced by acetylcholine (Fig. 1, top left). These different relaxing responses were observed in the context of similar levels of serotonin precontraction (WT: 0.64 ± 0.12, n = 7; hMR/MHC: 0.51 ± 0.09 mN/mm, n = 8). Incubation of coronary arteries with the NOS inhibitor L-NNA (10−4 M) abolished the relaxing response in hMR/MHC mice and markedly reduced it in control mice, suggesting that the impaired relaxation observed in hMR/MHC mice is largely due to a decreased NO-mediated relaxation (Fig. 1, bottom left). However, a small alteration in the coronary responses persisted in the presence of L-NNA, suggesting that cardiomyocyte hMR overexpression also altered a small, NO-independent component of relaxation (Fig. 1, bottom left). Responses to acetylcholine were not increased by incubation of the hMR arteries with BH4, which in fact tended to reduce the responses (maximal relaxations: base, 69 ± 7%; n = 6; BH4, 59 ± 8%; n = 6). This lack of improvement does not support the hypothesis that the altered relaxations are due eNOS uncoupling.

In contrast with the changes observed in the coronary arteries, we found that cardiac hMR overexpression did not affect the responses to acetylcholine in mesenteric arteries (maximal responses: WT, 95 ± 4%; hMR, 92 ± 5%, n = 5).

Long-term (1-mo) treatment with the MR antagonist canrenoate also affected the coronary responses to acetylcholine in control mice, but markedly and significantly increased them in hMR/MHC mice. As a result, canrenoate abolished the impaired relaxing response observed in TG mice (Fig. 1, top right). Canrenoate treatment also abolished the differences in relaxations observed between control and TG mice in the presence of L-NNA (Fig. 1, bottom right). Together this suggests that the MR antagonist restored NO-dependent relaxations and also possibly prevented the alteration of the small NO-independent component of relaxation.

The impaired coronary relaxing responses induced by cardiomyocyte hMR overexpression were also prevented by a 1-mo treatment with the antioxidants vitamin C/vitamin E. In fact, coronary arteries from vitamin C/vitamin E-treated hMR/MHC mice tended to show a modest, nonsignificant increase in relaxation compared with vitamin C/vitamin E-treated control mice (Fig. 2, top left). Vitamin C/vitamin E treatment also appeared to be associated with an increased NO-independent relaxation to acetylcholine both in control and TG mice (Fig. 2, bottom left). This NO-independent relaxation was not impaired in treated hMR/MHC mice.

Long-term in vivo treatment with the NADPH oxidase (NOX) inhibitor apocynin also prevented the impaired relaxation of hMR mice, both in the absence (Fig. 2, top right) or the presence (Fig. 2, bottom right) of the NOS inhibitor.

Figure 3 represents the relaxing responses induced by the NO donor SNP. hMR overexpression did not affect the responses to SNP, suggesting an absence of alterations of the smooth muscle responsiveness to NO. The responses to SNP were also unaffected by canrenoate, vitamin E/vitamin C, or apocynin. Additionally, none of the treatments affected the levels of precontraction induced by serotonin (data not shown).

**Coronary eNOS content and eNOS 1177-ser phosphorylation.** Figure 4A shows levels of eNOS protein and eNOS 1177-Ser phosphorylation (P-eNOS) assessed by Western blot in isolated coronary arteries. When compared with WT mice, coronary arteries isolated from hMR/MHC mice did not show any changes in eNOS content and displayed a modest nonsignificant increase in P-eNOS and P-eNOS-to-eNOS ratio.

**Cardiac oxidative stress.** Figure 4B shows cardiac production of ROS evaluated by EPR spectroscopy. When compared with WT, hMR/MHC mice displayed a significant increase in cardiac ROS production. This increased ROS production was abolished by canrenoate, vitamin E/vitamin C, and apocynin.

Figure 5A shows that hMR overexpression induced a significant increase in NOX activity in hMR mice, compared with WT. This increased activity was associated with significant increases in the expression of the NOX subunit gp91phox in whole hearts (Fig. 5C). These changes in gp91phox occurred in the absence of detectable modifications of p47phox and p67phox expression (Fig. 5B). In addition, we observed no changes in the expression of the antioxidant enzymes G6PD, SOD, and catalase (Fig. 5, top right). We also observed no change in the expression of epithelial sodium channel (ENaC), which was expressed at low levels in the heart of WT or hMR mice (relative to ubiquitin C: WT, 0.99 ± 0.15; hMR, 0.81 ± 0.08, n = 5, P = 0.13).

Immunohistological results (Fig. 6) shows that cardiac gp91phox appear exclusively localized within the endothelial cells, both at the level or coronary arteries and capillaries. Gp91 was undetectable in cardiomyocytes. This localization was not affected in hMR/MHC mice. Moreover, with this technique we were unable to detect marked changes in gp91 expression within the endothelial cells in hMR/MHC mice vs. controls.

**Table 1. Physiological parameters measured in wild-type mice and human mineralocorticoid receptor/myosin heavy chain mice**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Wild-type</th>
<th>Human Mineralocorticoid Receptor/Myosin Heavy Chain Mice</th>
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<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>100 ± 2</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>550 ± 17</td>
<td>519 ± 14</td>
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<tr>
<td>Body weight, g</td>
<td>32 ± 1</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>Plasma aldosterone, pg/ml</td>
<td>103 ± 10</td>
<td>105 ± 11</td>
</tr>
<tr>
<td>Urinary aldosterone, pg/ml</td>
<td>256 ± 27</td>
<td>254 ± 29</td>
</tr>
<tr>
<td>Heart weight/tibia length, mg/mm</td>
<td>7.9 ± 0.3</td>
<td>9.2 ± 0.7</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>Left ventricular end-diastolic volume</td>
<td>86.4 ± 7.2</td>
<td>95.5 ± 8.3</td>
</tr>
<tr>
<td>Left ventricular end-systolic volume</td>
<td>16.9 ± 3.1</td>
<td>25.2 ± 5.6</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>80 ± 3</td>
<td>75 ± 4</td>
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Values are means ± SE of 7 animals per group (except for urinary aldosterone, n = 4). No statistically significant differences were observed between any of the measured parameters.
DISCUSSION

The main results of the present study performed in mice are that: 1) a selective overexpression of hMR restricted to cardiomyocytes induced a potent coronary endothelial dysfunction, which mostly involved impaired NO availability, and could be prevented by MR blockade; this endothelial dysfunction occurred in the absence of detectable cardiac dysfunction and remodeling; and 2) coronary endothelial dysfunction associated with cardiomyocyte hMR overexpression was totally prevented by a 1-mo treatment with the antioxidants vitamin E/vitamin C and by the NOX inhibitor apocynin; this coronary dysfunction was associated with an increased cardiac ROS production, together with increased NOX expression and activity.

Although a deleterious role of MR activation on the vasculature, and especially the coronary circulation, has been suggested by a number of studies using either MR antagonists (11, 13, 21, 22, 24) or different TG models (2, 11), the exact targets and mechanisms of this impairment remain elusive, especially because of the lack of cellular selectivity of the approaches used to activate or inhibit the aldosterone/MR pathway. Another complicating factor is the fact that aldosterone, even when produced locally within the cardiomyocyte [e.g., after cardiomyocyte-specific overexpression of aldosterone synthase (2, 9)], may influence the coronary vasculature either directly, by diffusing toward vascular cells, or indirectly by inducing phenotypic changes within the cardiomyocyte that secondarily influence vascular function. To the best of our knowledge, our study is the first to discriminate between these two mechanisms. Especially the use of a unique model with MR overexpression restricted to the cardiomyocytes reveals a second mechanism implying indirect coronary vascular alterations that are secondary to cardiac-induced phenotypic changes. This most likely plays a major role in the coronary effects of aldosterone. Moreover, the fact that these marked coronary alterations occur in the absence of detectable changes in systemic and cardiac hemodynamics (Table 1) rules out the hypothesis that the observed coronary changes are due to

![Fig. 1. Relaxing responses induced by increasing concentrations of ACh in the absence (A and B) or the presence (C and D) of the nitric oxide synthase NOS inhibitor N^G^-nitro-L-arginine (L-NNA; 10^-4 M) in serotonin-precontracted coronary arteries isolated from wild-type (WT) mice (C) and human mineralocorticoid receptor/myosin heavy chain (hMR/MHC) mice (D) either untreated (A–C) or treated for 1 mo with canrenoate (40 mg·kg^-1·day^-1; B–D). Values are means ± SE. *P < 0.05 vs. control.](http://ajpheart.physiology.org/)

**A** Untreated

**B** Canrenoate

**C** + L-NNA

**D**
indirect effects secondary to hemodynamic modifications or changes in cardiac remodeling/function, but directly reflect local changes due to MR activation in cardiomyocytes.

In our previous study, using cardiomyocyte-specific overexpression of the aldosterone synthase, we concentrated on the changes in NO-independent coronary relaxations, especially those mediated by the endothelium-derived hyperpolarizing factors (EDHF)/smooth muscle potassium channels pathways (2). In the present study, we chose to concentrate on the changes in NO-mediated coronary relaxations and on the link with oxidative stress, since this pathway represents a favorite target for cardiovascular risk factors and cardiovascular diseases. Separate investigations of these two pathways for endothelium-dependent coronary relaxation are indeed possible in mouse models, taking advantage of the differences that exist between different strains of mice. Indeed, in our previous study, we used FVB mice in which we observed a strong NO-independent component of coronary relaxation, whereas the present study was performed in mice with a predominant C57/BL6 background, characterized by a dominant NO-mediated relaxation.

Apart from the abovementioned differences in mouse strain, it is also possible that differences may exist between the coronary consequences of cardiomyocyte aldosterone synthase versus mineralocorticoid receptor overexpression. Possible differences include the cellular targets (e.g., through diffusion of aldosterone to the different cardiac cell types in the aldosterone synthase pathway) or differences in the ligand (e.g., possible aldosterone-independent receptor activation in the present MR model). To reconcile the two models and test these hypotheses it would be interesting to study changes in NO-independent mediated responses after MR overexpression, which would require developing MR overexpression in mice with FVB background; however, this is beyond the scope of the present study.

One possible mechanism of reduced NO-mediated relaxations involves changes in eNOS expression, leading to decreased eNOS protein content in the endothelial cells. We found that hMR overexpression did not affect eNOS content in the coronary artery segments, ruling out the hypothesis that changes in eNOS may play a role in the observed dysfunction. In this context, another possibility would involve impaired transduction pathways involving eNOS activation (28). Among

Fig. 2. Relaxing responses induced by increasing concentrations of ACh in the absence (A and B) or the presence (C and D) of the NOS inhibitor l-NNA (10^-4 M) in serotonin-precontracted coronary arteries isolated from WT mice (>) and hMR/MHC mice (o) treated for 1 mo with vitamin E (1% in chow)/vitamin C (0.05% in water) (A–C) or with apocynin (50 mg·kg^-1·day^-1; B–D). Values are means ± SE.
these pathways, phosphorylation of eNOS on its serine 1177 residue is known to play a central role in eNOS activation (6). In this context, the fact that we found that hMR overexpression was not associated with any changes in eNOS serine 1177 phosphorylation does not support the hypothesis that changes in eNOS activity are involved in the observed functional changes. To the best of our knowledge, analysis of eNOS phosphorylation had never been performed before in mouse coronary segments. Such an approach if highly physiologically relevant since the protein analysis is performed at the same site as the functional measurements, however, is highly limited in terms of the number of different proteins that can be assessed (1 per sample). Moreover, to the best of our knowledge, no current technique allows actual measurements of NO production or content in this kind of vascular preparations. Thus, based on the current technologies available for analysis of small arteries, we cannot completely rule out the hypothesis that mechanisms other than impaired eNOS phosphorylation, leading to decreased eNOS activity, may be operative, although our current data would rather point toward an increased degradation of NO by ROS. In addition, the fact that the impairment of the coronary relaxing responses was not affected by incubation with BH₄ does not support a potential role for eNOS uncoupling in the altered coronary responses.

Although many different mechanisms may contribute to the endothelial dysfunction in diseases, oxidative stress is known to play a central role. Our results obtained using EPR spectroscopy demonstrate an increased cardiac production of ROS in hMR/MHC mice, compared with controls. These results are in agreement with those obtained after chronic in vivo infusion of aldosterone (11). However, to the best of our knowledge this study is the first to demonstrate the existence of a direct, local cardiac MR-induced oxidative stress. Furthermore, the fact that chronic treatment with the antioxidants vitamin C/vitamin E restored NO-mediated relaxation suggests that this local oxidative stress is directly responsible for coronary endothelial dysfunction in transgenic hMR mice. Moreover, the fact that this endothelial dysfunction (as well as the prevention by scavengers) can be detected ex vivo in isolated coronary arteries points toward long-term deleterious effects of ROS on the coronary endothelium, rather than a direct, acute inactivation of NO by the oxygen species. In agreement with this, we
found that acute incubation of the isolated arteries with the scavengers had no effect on the coronary relaxing responses of hMR mice (data not shown).

One of the major sources of ROS in the cardiovascular system is represented by the NOX family of enzymes. In the present study, we found that hMR overexpression induced an increased cardiac NOX activity. Moreover, chronic treatment with the NOX inhibitor apocynin both reduced cardiac ROS production and prevented the impaired response to acetylcholine. This increased NOX activity was not accompanied by detectable changes in the expression of the antioxidant enzymes SOD and catalase, or G6PD. Taken together, this suggests that the impaired NO-mediated coronary relaxation in transgenic mice is the consequence of NOX-mediated cardiac ROS production in this model.

The fact that cardiac hMR overexpression did not lead to changes in G6PD expression may be surprising, since recent data suggested that decreased G6PD activity plays a central role in oxidative stress-induced NO impairment in mice chronically treated with aldosterone (11). The reason for these differences are unclear; however, it may reflect differences in the levels of oxidative stress induced by chronic infusion of aldosterone versus localized increase in MR activation, or it may be related to specificities of the vascular bed studied (i.e., coronary artery in the present study vs. peripheral resistance arteries in the work of Leopold et al.) (11). Moreover, since aldosterone decreased G6PD in cultured endothelial cells (11), this suggests that these cells may be the main site of aldosterone-induced decrease in G6PD, an effect that would thus not be found in our model of MR expression restricted to cardiomyocytes.

In our experiments, the increased NOX activity was associated with an augmented expression of its major catalytic subunit gp91phox, without detectable changes in p47 and p67phox. Thus one likely possibility is that the coronary dysfunction observed in our experiments is due to the increased gp91phox expression leading to increased NOX-mediated production of superoxide responsible for impaired NO availability. This gp91phox appeared, however, localized to endothelial cells, which thus would appear to be the main source of superoxide in this model, although one cannot exclude that other sources may be also activated in other cell types, and especially in cardiomyocytes.

Our experiments suggest that phenotypic modifications localized to cardiomyocytes may secondly affect coronary endothelial function, thus supporting the view that important communications exist between these two cell types. Indeed, several evidences suggest that cardiac myocytes release substances that modulate endothelial function. These communications may have a strong physiological relevance, for example to adapt coronary perfusion to increased metabolic demands (4), but may also be important in pathological conditions, for example by contributing to trigger endothelial dysfunction (26). Importantly, cardiac myocytes have been shown to trigger the release of endothelin from endothelial cells, especially in response to α-adrenergic stimulation (12, 29). Since endothelin may per se induce endothelial dysfunction, it is possible that
this peptide, as well as angiotensin II, may contribute to the alterations of coronary relaxations that we observed. However, at present, the exact actors of these communication between cardiomyocytes and endothelial cells are still largely unknown.

Another limitation of the present study is that the evaluation of coronary dysfunction and oxidative stress after hMR overexpression, as well as the effect of the pharmacological treatments, were performed at only one time point. Thus, based on the available data, one cannot precisely assess the time course of development of impaired coronary function and oxidative stress. The complexity of the genetic model (double TG), however, precludes large scale studies such as those necessary for the evaluation of the time course of coronary injury or its reversal.

Conclusion

We demonstrate that an increase in MR expression restricted to cardiomyocytes is sufficient to induce a severe coronary...
endothelial dysfunction. We propose a paracrine mechanism by which cardiomyocytes trigger coronary endothelial dysfunction, most likely via a NOX-mediated production of ROS. Our results also suggest that the so-called aldosterone vasculopathy in coronary vessels is, at least partly, the consequence of the aldosterone-induced changes that occur within the cardiomyocytes.

REFERENCES


