Loss of Epidermal Growth Factor Receptor in Vascular Smooth Muscle Cells and Cardiomyocytes Causes Arterial Hypotension and Cardiac Hypertrophy

Barbara Schreier, Sindy Rabe, Bettina Schneider, Maria Bretschneider, Sebastian Rupp, Stefanie Ruhs, Joachim Neumann, Uwe Rueckenschloss, Maria Sibilia, Michael Gotthardt, Claudia Grossmann, Michael Gekle

Abstract—The epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, contributes to parainflammatory dysregulation, possibly causing cardiovascular dysfunction and remodeling. The physiological role of cardiovascular EGFR is not completely understood. To investigate the physiological importance of EGFR in vascular smooth muscle cells and cardiomyocytes, we generated a mouse model with targeted deletion of the EGFR using the SM22 (smooth muscle-specific protein 22) promoter. While the reproduction of knockout animals was not impaired, life span was significantly reduced. Systolic blood pressure was not different between the 2 genotypes—neither in tail cuff nor in intravascular measurements—whereas total peripheral vascular resistance, diastolic blood pressure, and mean blood pressure were reduced. Loss of vascular smooth muscle cell-EGFR results in a dilated vascular phenotype with minor signs of fibrosis and inflammation. Echocardiography, necropsy, and histology revealed a dramatic eccentric cardiac hypertrophy in knockout mice (2.5-fold increase in heart weight), with increased stroke volume and cardiac output as well as left ventricular wall thickness and lumen. Cardiac hypertrophy is accompanied by an increase in cardiomyocyte volume, a strong tendency to cardiac fibrosis and inflammation, as well as enhanced NADPH-oxidase 4 and hypertrophy marker expression. Thus, in cardiomyocytes, EGFR prevents excessive hypertrophic growth through its impact on reactive oxygen species balance, whereas in vascular smooth muscle cells EGFR contributes to the appropriate vascular wall architecture and vessel reactivity, thereby supporting a physiological vascular tone. (Hypertension. 2013;61:333-340.) ○ Online Data Supplement

Key Words: blood pressure • growth substances • hypertrophy • receptors • smooth muscle

The epidermal growth factor receptor (EGFR) family consists of 4 related tyrosine kinase receptors, EGFR (ErbB1), ErbB2, ErbB3, and ErbB4.1,2 On ligand binding, the receptors form homodimers and activate various signaling pathways.3 With the ability of EGFR to form functional dimers with all 4 family members, activated ErbB receptors control various signaling modules and their downstream targets, including mitogen-activated protein kinases, phosphoinositide-3 kinase, phospholipase C-γ, and cellular Src-kinase, thereby regulating cell proliferation, survival, differentiation, migration, and matrix homeostasis.4

In addition to activation by its classical ligands, EGFR is also subject to activation by cross-talk with nonreceptor tyrosine kinase pathways, a mechanism called transactivation.5,6 Both mechanisms may induce pathophysiological effects that include cell proliferation and parainflammatory dysregulation of tissue homeostasis, leading, for example, to vascular dysfunction and remodeling.6 In this regard, EGFR transactivation is supposed to be responsible for endothelin 1, angiotensin II (Ang II), or phenylephrine-mediated extracellular signal–regulated kinase1/2 phosphorylation7 and their pathophysiological effects on vascular smooth muscle cell (VSMC) proliferation, migration, and matrix homeostasis.7

To elucidate the pivotal roles of the EGFR family members in development and tumorigenesis, gain- and loss-of-function mutants have been generated.8 Their analysis revealed differential contribution of ErbB2, ErbB3, and ErbB4 to cardiac development.9-12 In contrast, until now only limited in-depth analysis of EGFR cardiovascular relevance has been obtained. Mice lacking the EGFR die at day 11.5 of gestation or survive until postnatal day 20, depending on the genetic background.13 Surviving mutant mice show abnormalities in bone, heart, and epithelia of skin, hair follicles, and eyes.14-15 The predominant heart phenotype in these mice, and in the wa-2 mice (mice with a global reduced...
EGFR kinase activity), is a defect in valve formation.\textsuperscript{17,20,21} As the function of the EGFR is impaired in all cell types in these models, it is difficult to draw specific conclusions regarding EGFR in different cardiovascular cell types.

The aim of the present study was to characterize the role of VSMC and myocardial EGFR (ErbB1) on cardiovascular function and tissue homeostasis. We hypothesized that EGFR contributes to the maintenance of physiological function and tissue homeostasis. To exclude interference with non-cardiovascular EGFR, we generated mice with a deletion of EGFR in VSMC and a strong reduction in cardiomyocytes (EGFR\textsuperscript{ΔVSMC&CM}) and compared them with littermate control mice (EGFR\textsuperscript{flox/flox}). Here, we present the phenotype of these mice showing a reduced peripheral resistance, arterial hypertension, and cardiac hypertrophy.

**Methods**

See the online-only Data Supplement for details on methods.

**Results**

**Expression of ErbB Receptors in Aortas and Hearts of EGFR\textsuperscript{ΔVSMC&CM} Mice**

We generated a mouse model with a specific deletion of the EGFR in VSMC and a strong reduction in cardiomyocytes (EGFR\textsuperscript{ΔVSMC&CM}, knockout [KO]) crossing EGFR\textsuperscript{flox/flox} mice (con) with SM22-Cre mice (SM22-Cre +/−; Figure S1A in the online-only Data Supplement).\textsuperscript{22–26}

As demonstrated earlier,\textsuperscript{22} EGFR expression was almost abolished in the aortas (Figure 1A), indicating a deletion of EGFR in VSMC. This result was confirmed by primary culture of VSMC demonstrating a reduction to 10±5% compared with controls.\textsuperscript{22} In lung, liver, and kidney, EGFR expression was unchanged (Table S2). In the heart, where the SM22 promoter is active during embryogenesis,\textsuperscript{25,26} expression of EGFR was reduced by one third (Figure 1A). To ensure that reduced cardiac EGFR expression resulted from cardiomyocytes, we analyzed isolated cardiomyocytes and observed a significant decrease in EGFR expression (Figure 1A) and protein level (41±13% of con; n=11; Figure 1C).\textsuperscript{22}

Because EGF can also exert its intracellular effects by binding to a heterodimer consisting of the receptors ErbB2 and ErbB3, we analyzed mRNA expression for these receptors in hearts, aortas, and isolated cardiomyocytes. Only the expression of ErbB3 mRNA was reduced in aortas of KO animals (Table S2). Taken together, the data show a specific deletion of the EGFR in VSMC and a significant reduction in cardiomyocytes.

**Population Parameters**

EGFR\textsuperscript{ΔVSMC&CM} animals show a significantly reduced life span with an increased number of deaths starting from...
Blood Pressure and Heart Rate

Activation of the EGFR may not only affect proliferation of VSMC but also VSMC function. Therefore, we investigated blood pressure. There was no difference in systolic blood pressure (SBP) and heart rate in conscious animals determined by the tail cuff method as indicated by preliminary measurements. As tail cuff does not allow reliable assessment of diastolic blood pressure (DBP), we performed measurements in anesthetized animals using a Millar catheter. During ketamine/xylazine anesthesia, we detected a reduced DBP in KO animals, as well as mean arterial blood pressure. Systolic pressure was not different. Blood pressure amplitude was increased in KO animals (Figure 2B).

Echocardiography

Echocardiography revealed a significant increase in left ventricular wall thickness and lumen dimensions in EGFR<sup>KO</sup> mice (Table S3). Nevertheless, ejection fraction or fractional shortening was similar in both genotypes. Besides the increase in end-diastolic and end-systolic volume, stroke volume in KO animals was higher than in control animals (Figure 2C), resulting in an increased cardiac output. Assuming a comparable right ventricular pressure, total peripheral resistance can be calculated by Ohm’s law and is reduced in KO animals (con, 27.5±0.15 mm Hg · min · mL<sup>-1</sup>; KO, 16.8±0.13 mm Hg · min · mL<sup>-1</sup>).

Calculated systolic left ventricular wall stress (law of Laplace) was not different compared with control animals (con, 74.5±3.5 mm Hg; KO, 75.6±12.4 mm Hg; n=6–14 animals/genotype)

Estimated from pulse-wave Doppler recordings, the peak velocity and mean velocity of blood in the descending aorta were higher in KO animals compared with controls, whereas the velocity time integral was unaffected (Figure 3).

Histology of Hearts, Lungs, and Aorta

In sections, left ventricular wall thickness and left ventricular diameter were increased, confirming the echocardiography data of left ventricular hypertrophy and dilatation (Figure 1D and Table S3). Cardiomyocyte diameter was increased in KO animals compared with controls (Figures 1G and 2A), albeit to a smaller degree compared with cardiac hypertrophy. Therefore, we analyzed length and area from isolated cardiomyocytes revealing a comparable relative increase in cardiomyocyte volume and heart weight/tibia length (Table S3). The increases in cardiomyocyte area and diameter result in an increase in cardiomyocyte volume—assuming a cylindrical shape of the cardiomyocyte—of ≈2.2±0.4-fold, thus explaining the increased heart weight.

No significant difference in interstitial fibrosis between controls and KO animals was observed in heart and lung sections (Figure 1F and Table S3). Preliminary data on the histology of aortas and intramyocardial vessels indicated a difference in aortic wall/lumen area ratio. In the complete series presented here, the aortic diameter determined by echocardiography (aortic sinus, n=4–11/group; Figure 3) and histology (abdominal aorta, n=10/group; Figure 4) was not different between the genotypes. Media thickness was slightly reduced in EGFR<sup>KO</sup> animals (Figure 4A and 4B), resulting in a significant 30% decrease in the wall-to-lumen ratio of aortas from EGFR<sup>KO</sup> animals. Consequently, aortic wall stress (law of Laplace) was increased slightly (≈1.18 of con).

Wall-to-lumen ratio of intramyocardial arteries from KO animals was also reduced compared with controls, but in

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Table. Aortic and Cardiac mRNA Expression of Different Hypertrophy, Fibrosis, Inflammation, Ca<sup>2+</sup> Handling, and Nutrient Supply–Related Markers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Aortas</th>
<th>Hearts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=11)</td>
<td>Knockout (n=11)</td>
</tr>
<tr>
<td>Col1a1/18S</td>
<td>1.0±0.3</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>Col3a1/18S</td>
<td>1.0±0.2</td>
<td>2.7±0.8*</td>
</tr>
<tr>
<td>FN-1/18S</td>
<td>1.0±0.2</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>PAI-1/18S</td>
<td>1.0±0.2</td>
<td>2.0±0.9</td>
</tr>
<tr>
<td>TNF-α/18S</td>
<td>1.0±0.4</td>
<td>8.0±4.4</td>
</tr>
<tr>
<td>MCP-1/18S</td>
<td>1.0±0.3</td>
<td>6.3±2.9*</td>
</tr>
<tr>
<td>SPP-1/18S</td>
<td>1.0±0.2</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Col 1a1/18S</td>
<td>1.0±0.2</td>
<td>2.8±1.0</td>
</tr>
<tr>
<td>Col3a1/18S</td>
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</tr>
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</tr>
<tr>
<td>Col1a1/18S</td>
<td>1.0±0.2</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>Col3a1/18S</td>
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<td>1.2±0.1</td>
</tr>
<tr>
<td>FN-1/18S</td>
<td>1.0±0.2</td>
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<td>HIF1α/18S</td>
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</tr>
<tr>
<td>GLUT1/18S</td>
<td>1.0±0.1</td>
<td>1.1±0.1</td>
</tr>
</tbody>
</table>

TNF indicates tumor necrosis factor.
*P<0.05 vs control.
contrast to the aortas the luminal diameter was increased (Figure 4C). Calculated wall stress of intramyocardial arteries is significantly increased in KO animals (con, 105.3±7.0 mm Hg; KO, 172.4±20.0 mm Hg; n=9–10; P≤0.05).

### mRNA Expression

In hearts of KO animals, mRNA expression of hypertrophy markers (atrial natriuretic peptide, B-type natriuretic peptide, β-myosin heavy chain/α-myosin heavy chain) was increased

#### Figure 2. Blood pressure and heart function of control and epidermal growth factor receptor (EGFR)ΔVSMCAM animals. A, Heart weight/tibia length was increased in knockout animals, as well as cardiomyocyte diameter, determined in hematoxylin and eosin–stained semithin sections of the left ventricle. B, Systolic blood pressure was the same between both genotypes in intravascular blood pressure measurements performed with a Millar catheter. Diastolic blood pressure, as well as mean blood pressure, was significantly reduced in knockout animals, whereas the amplitude of blood pressure was increased. C, Echocardiography studies showed that left ventricular systolic function was not impaired in knockout animals. Stroke volume, as well as end-diastolic and end-systolic left ventricular volume, was increased in knockout animals. n=6 to 14/group, *P≤0.05 vs control.

#### Figure 3. Estimation of intravitral aortic dimension and blood flow velocity parameters by echocardiography. Aortic sinus diameter was measured during heart ventricle diastole in B-mode. There was no significant difference between the 2 genotypes. Velocity parameters were obtained from ≥5 heart cycles in the descending aortas. Although the velocity time interval was not different between the 2 genotypes, peak velocity and mean velocity of blood flow were significantly increased in EGFRΔVSMCAM animals. n=4 to 11/group, *P≤0.05 vs control.
Here, we were able to show that EGFR mRNA and protein are reduced to \( \approx 40\% \) of the initial amount. As fibroblasts are the major cardiac cell type in number, a complete reduction of the EGFR cannot be expected in whole hearts. The same is true also for isolated cardiomyocytes, allowing only an enrichment of cardiomyocytes in the presence of residual fibroblasts. Thus, the model presented is suitable to gain further insight into the importance of VSMC and cardiomyocyte EGFR in vivo.

Mice with a global deletion of EGFR die in utero or within the first 20 days postpartum.\(^\text{13}\) In EGFR\(^{-/-}\)VSMC\&CM mice, embryonic lethality was not increased, leading to the conclusions that (1) reduction of cardiac EGFR does not impair embryonic heart development or function to a life-threatening extent and (2) EGFR deletion in VSMC does not impair placental function. It has been suggested that EGFR is involved in the preservation of cardiac function and tissue homeostasis.\(^\text{28,29}\) Our data support this hypothesis. The partial loss of cardiomyocyte (ROS) production. This increased ROS production was not inhibited by \( \text{L-NAME} \) but was nearly completely abolished by diphenyleneiodonium (DPI) (Figure 7). As neither NOX4 nor NOX2 mRNA expression was different in aortas of KO animals compared with WT (\( n=4-6 \) animals/group; NOX2 con, 1.0±0.2; KO, 0.6±0.2; NOX-4 con, 1.0±0.3; KO, 0.9±0.1), we did not perform lucigenin assays on isolated aortas.

**Discussion**

To further elucidate the role of EGFR in VSMC and cardiomyocytes, we investigated the phenotype of mice with a deletion of EGFR in VSMC and a strong reduction in cardiomyocytes. The SM22 promoter is frequently used for VSMC-specific deletions.\(^\text{23}\) Yet, it has been shown that transient embryonic activation of SM22 in cardiomyocytes\(^\text{26}\) leads to a partial KO of \( >50\% \) of the protein of interest.\(^\text{27}\)

**Figure 4.** Morphology of aortas and intramyocardial arteries ex vivo and estimation of wall stress, respectively. Media thickness, lumen radius, wall-to-lumen ratio, and the corresponding wall stress were obtained and calculated from semithin sections of aorta (A) or myocardium (C) stained with hematoxylin and eosin, respectively. In the aortas, the wall-to-lumen ratio was reduced significantly. Media thickness was increased, although this difference did not reach statistical significance (\( P=0.078 \) vs the respective control). The wall stress, calculated according to the law of Laplace, was the same in both genotypes. In intramyocardial arteries, the wall-to-lumen ratio was decreased and media thickness was increased in knockout animals. This increases the wall stress in these animals. Exemplary Sirius red–stained semithin sections from con and KO animals are shown in section B (\( \times 40 \) magnification; scale bar, 100 \( \mu \)m). \( n=8 \) to 11/group, \( *P<0.05 \) vs control.

**Figure 5.** Functional responses of aortic rings to KCl, serotonin, and epidermal growth factor (EGF). Contractility of aortic rings on stimulation with KCl, serotonin (5-HT), or EGF, respectively, was detected using a Mulvany wire myograph. Although force development on 5-HT (10 \( \mu \)M) stimulation was the same in both genotypes, a significant lesser force was developed by stimulation with KCl. No response could be obtained on incubation with EGF in aortic rings from knockout animals. \( n=5 \) to 10 per group, \( *P<0.05 \) vs control.
EGFR led to an eccentric hypertrophy without detectable cardiac lesions in the absence of arterial hypertension, although parameters for fibrosis were not increased. Thus, mice seem to experience a physiological heart hypertrophy. There are no signs for systolic dysfunction, as fractional shortening, stroke volume, and cardiac output were not reduced, which corresponds to physiological heart hypertrophy, and the increase in cardiomyocyte volume accounts for the relative increase in heart weight. Possibly, the increase in heart size favors fatal arrhythmias, thereby increasing lethality. Future studies have to address these questions.

In wa-2 mice on a C57BL/6 background, left ventricles are dilated while septal and chamber walls were thickened, presumably caused by aortic valve cusp thickening and aortic valve stenosis, similar as for hEGFR\textsuperscript{KO/KO} and EGFR\textsuperscript{−/−} animals. This results from accumulation of mesenchymal cells as a result of reduced endothelial/endocardial EGFR expression. Heart valves originate from endocardial/endothelial cells undergoing mesenchymal transition and generating the mesenchymal cells responsible for cushion formation of heart valves. To our knowledge, there is no indication for SM22 promoter activation in vivo during embryonic valve formation. Furthermore, our results do not indicate a functional relevant stenosis of the aortic valve nor developmental aortic or cardiac malformation. Another possible explanation for the increase in heart weight would be that reduced EGFR expression leads to reduced ErbB2 activation, with subsequently reduced ErbB2/ErbB4 dimer formation, and thereby to heart hypertrophy. But as ErbB2 and ErbB4 expression in the heart are unaltered, this explanation seems unlikely.

We suggest that hypertrophy results from a mild tonic dysbalance of cardiac ROS homeostasis, known to activate prohypertrophic cascades. In support of this hypothesis, we detected enhanced NOX4 mRNA expression in the heart of KO mice, as well as a nonsignificant increase in protein level (preliminary data). Measurements of cardiac NOX activity by the lucigenin method showed increased ROS formation in cardiac tissue of KO animals. The signal was completely abrogated by DPI but not by l-NAME, supporting the conclusion of an enhanced NOX activity. Furthermore, increased NOX4 expression under conditions of reduced Angiotensin II

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Change in mean arterial blood pressure induced by angiotensin II. \textbf{A}, In wild-type and knockout animals, angiotensin II induces an increase in mean arterial blood pressure to the same maximal height. \textbf{B}, But the blood pressure in knockout animals decreases and increases significantly faster than in wild-type animals, resulting in a reduced width 50 (n= 6–11 per group; \text{*}P≤0.05 vs control).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Change of lucigenin chemiluminescence in cardiomyocytes. \textbf{A}, Lucigenin chemiluminescence accumulates in isolated cardiomyocytes of knockout animals faster than in cardiomyocytes of control animals, indicating an enhanced ROS production in knockout cells. \textbf{B}, This increased ROS production results in an increased lucigenin chemiluminescence in cardiomyocytes of knockout animals after 15 minutes. \textbf{C}, L-NAME does not reduce the ROS production in cardiomyocyte lysates of wild-type and knockout animals. \textbf{D}, DPI abrogates the difference in ROS production between the 2 genotypes (n=3–5 per group; \text{*}P≤0.05 vs control).}
\end{figure}
EGFR activity has been reported before.\textsuperscript{36,37} Possibly, the ROS dysbalance is not strong enough to elicit major fibrotic alterations.

In VSMC, the EGFR can be transactivated by vasoactive substances mediating physiological or pathophysiological responses.\textsuperscript{7} In our KO model, SBP was not affected neither in conscious\textsuperscript{12} nor in anesthetized animals, whereas DBP and MAP were reduced because of reduced peripheral vascular resistance. This does not seem to lead to reduced tissue perfusion, at least in the heart, as neither hypoxia inducible factor-\textgreek{1}\textgreek{0} nor glucose transporter-1 expression was herein increased. The low blood pressure levels during Millar catheter measurements are most probably because of ketamine/xylazine anesthesia, which has been reported to reduce SBP down to 46±5 mm Hg.\textsuperscript{38} Therefore, the invasively measured blood pressure is lower compared with conscious animals independent of the genotypes. Because there is no difference in SBP between the genotypes neither in tail cuff\textsuperscript{12} nor in Millar catheter measurements, the reduced DBP results from the loss of EGFR.

As expected from its function as a growth factor for VSMC and the reduced proliferation of VSMC\textsuperscript{EGFR−/−},\textsuperscript{22} media thickness was decreased in aortas of KO mice. The luminal diameter of intramyocardial vessels was increased, indicative of a reduced vascular tone when EGFR is missing. This finding corresponds with results from isolated, primary VSMC where the number of cells responding to vasoactive hormones was reduced by deletion of the EGFR.\textsuperscript{22} On infusion of Ang II, the MAP increased to the physiological development of vessel structure, pre-
mits to the physiological development of vessel structure, pre-

time, until the blood pressure fell below the half maximal value thereafter (ΔP/2) was significantly short in KO animals, resulting in a reduced plateau phase of blood pressure increase. Taken together, these data support our hypothesis that EGFR is also involved in blood pressure regulation of Ang II. In vivo these effects would lead to a less sustained blood pressure increase in Ang II generation and therefore a reduced range of physiological blood pressure regulation. However, under pathophysiological conditions of arterial hypertension, blood pressure increases would be smaller, protecting the arterial wall from remodeling. Taken together, these changes in VSMC function, combined with the observed structural changes, explain the reduced peripheral vascular resistance resulting in the lower DBP and MAP of KO animals, whereas the increase in stroke volume prevents a reduction in SBP.

In aortas of KO animals, markers of fibrosis and inflammation were elevated. We were able to show that in cultured VSMC from KO animals Col3a1 expression was enhanced and cells from control animals responded to EGF with reduced Col3a1 expression.\textsuperscript{22} Thus, our data show that EGFR contributes to the physiological development of vessel structure, prevents parainflamatory alterations of tissue homeostasis, and is important for a proper vascular function.

In contrast to our results, Griol-Charhbili et al\textsuperscript{19} did not observe significant alterations in the structure and basic function in vessels from \textit{wa-2} mice that carry a global and spontaneous mutation of the EGFR,\textsuperscript{21} leading to a reduction in the kinase activity but a longer plasma membrane half-life. Probably, the remaining EGFR activity was sufficient to prevent major remodeling. Furthermore, these mice\textsuperscript{39} were kept on a mixed background (C57BL/6xC3H), and at least some EGFR effects seem to depend on the genetic background,\textsuperscript{17} making it difficult to compare the 2 studies.

\textbf{Perspective}

Taken together, the data presented show that in cardiomyocytes EGFR prevents excessive hypertrophic growth through its impact on ROS balance, whereas in VSMC, EGFR contributes to the appropriate vascular wall architecture and vessel reactivity, thereby supporting a physiological vascular tone. Thus, although EGFR serves as a heterologous transducer of adverse cardiovascular stimuli, it is also required for physiological cardiovascular tissue homeostasis. EGFR is a target for cancer therapy, with specific therapeutics approved.\textsuperscript{40} Unfortunately, cardiac toxicity is a known side effect of tyrosine kinase inhibitor treatment.\textsuperscript{40} Therefore, it is necessary to analyze the long-term consequences of suppressed EGFR activity in VSMC and cardiomyocytes in vivo in more detail.

\textbf{Acknowledgments}

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\textbf{Disclosures}

None.

\textbf{References}


Novelty and Significance

**What Is New?**

- Physiological role of epidermal growth factor receptor in the cardiovascular system.
- Genetic model for the cardiovascular epidermal growth factor receptor in adult animals.

**What Is Relevant?**

- Hearts of knockouts show an increase in heart weight, stroke volume, cardiac output, and hypertrophy markers, but not for markers of fibrosis or inflammation.


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