ESC European Society of Cardiology

Cardiovascular Research (2017) **113**, 1533–1535
doi:10.1093/cvr/cvx192

EDITORIAL

Physiological and pathological gestational cardiac hypertrophy: what can we learn from rodents?

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Online publish-ahead-of-print 26 September 2017

This editorial refers to 'Fgf21 is required for cardiac remodeling in pregnancy' by I. Redondo-Angulo *et al.*, pp. 1574–1584.

Hypertensive disorders in pregnancy are common (10% of pregnancies) and are associated with severe complications for both the mother (pre-eclampsia, renal and cardiac dysfunction, and cerebrovascular bleeding) and the child (prematurity and growth restriction).[1] Both poor placentation and maternal cardiovascular maladaptation to the pregnancy have been shown to have a role in the development of these cardiovascular complications in pregnancy. A normal pregnancy is accompanied by a great biological reorganization that involves the heart and circulation mainly due to physiological and hormonal changes. Gestational cardiac hypertrophy is a physiological adaptation that compensates the increased cardiac output and volume load. In addition, electrical cardiac remodelling results in palpitations and syncope early symptoms of pregnancy and visible in the electrocardiogram.

Similar to the inability of the maternal pancreas to deal with the metabolic load of the pregnancy in patients with gestational diabetes mellitus, it appears that certain women cannot make the cardiovascular changes that are required to deal with the additional needs of a pregnancy. The underlying mechanisms are still largely unknown. Unfortunately, the dynamic nature of pregnancy and the variability among pregnant women are the main issues that hamper a clear data interpretation in human studies.

With obvious limitations, the use of mouse models to understand regulation of cardiac remodelling during gestation is based on a certain degree of similarity in implantation, placentation, and parturition. Moreover, the use of transgenic mice allows researchers to unveil critical key players of this benign and reversible cardiac remodelling. Indeed, understanding of the molecular mechanisms related to the physiological hypertrophy in contrast with those in pathological hypertrophy could reveal critical information for the treatment of cardiac disease.

Dysregulation in autophagy, microRNAs, metabolism, and histone modification in cardiomyocytes promotes cardiac hypertrophy.[2] Modifiers of cardiac hypertrophy include also exogenous and endogenous factors, such as hormones, cytokines, and growth factors. The gene encoding Fgf21 was first identified in mouse embryo in 2000.[3] FGF21 belongs to the fibroblast growth factor (FGF) family and shares similar endocrine properties of FGF15, FGF19, and FGF23 and often referred together as FGF15/19. Those circulating FGFs lack a heparin-binding domain, and FGF21 requires the interaction with β-klotho co-receptor to act via FGF receptors. FGF21 is involved in several physiological and pathological processes including regulation of glucose and lipid metabolism as well as reduction of atherosclerotic plaque formation in the great vessels. It has also been shown to exert cardioprotective effects in myocardial infarction, cardiac ischaemia–reperfusion injury, cardiac hypertrophy, and diabetic cardiomyopathy.[4] Moreover, FGF21 assists the energy supply to the heart through fatty acid β-oxidation, although FGF21 knockout mice were found to have normal development[5] and do not develop insulin resistance or other pathological conditions.[6] In mice, the high levels of FGF21 present at the onset of lactation imply its involvement in the required adaptations to face the energy demand of late pregnancy.[7]

In this issue of *Cardiovascular Research*, Redondo-Angulo *et al.*[8] report a lack of hypertrophic response in pregnant Fgf21-null mice, extending their previous study regarding the role of Fgf21 in the regulation of antioxidant pathways in cardiomyocytes.[9,10] The authors show that in animal models of pregnant mice and rats and in pregnant women in their 3rd trimester, there is a significant increase in plasma Fgf21/FGF21 levels. Fgf21 expression is enhanced in the liver and in the heart in a peroxisome proliferator-activated receptor-α (PPARα)-dependent manner, activating the intracellular Fgf21 signalling. In addition, using Fgf21-null mice, the authors demonstrate that Fgf21 is causally involved in the physiological pregnancy-induced cardiac remodelling and myocardial fatty acid oxidation (FAO). They noted that Fgf21-null mice are incapable of inducing FAO during pregnancy and maintain a glucose metabolism typically present in pathological cardiac hypertrophy. A significant increase in the expression levels of Col3 and TGFβ, the master regulator of fibrosis, was observed in the hearts of Fgf21-null pregnant mice. However, a significant reduction in the protein levels of cytochrome *c* oxidase II and IV subunits indicated that the lack of Fgf21 during pregnancy negatively affected the mitochondrial oxidative activity. Moreover, PPARα pathway appears to play a crucial role in the control of FGF21 expression during pregnancy. Therefore, the novel findings in the report by Redondo-Angulo *et al.* have highlighted Fgf21 as a major mediator of physiological cardiac hypertrophy during pregnancy, and due to its cardioprotective characteristics, it could be potentially used for therapeutic applications.

The opinions expressed in this article are not necessarily those of the Editors of *Cardiovascular Research* or of the European Society of Cardiology.

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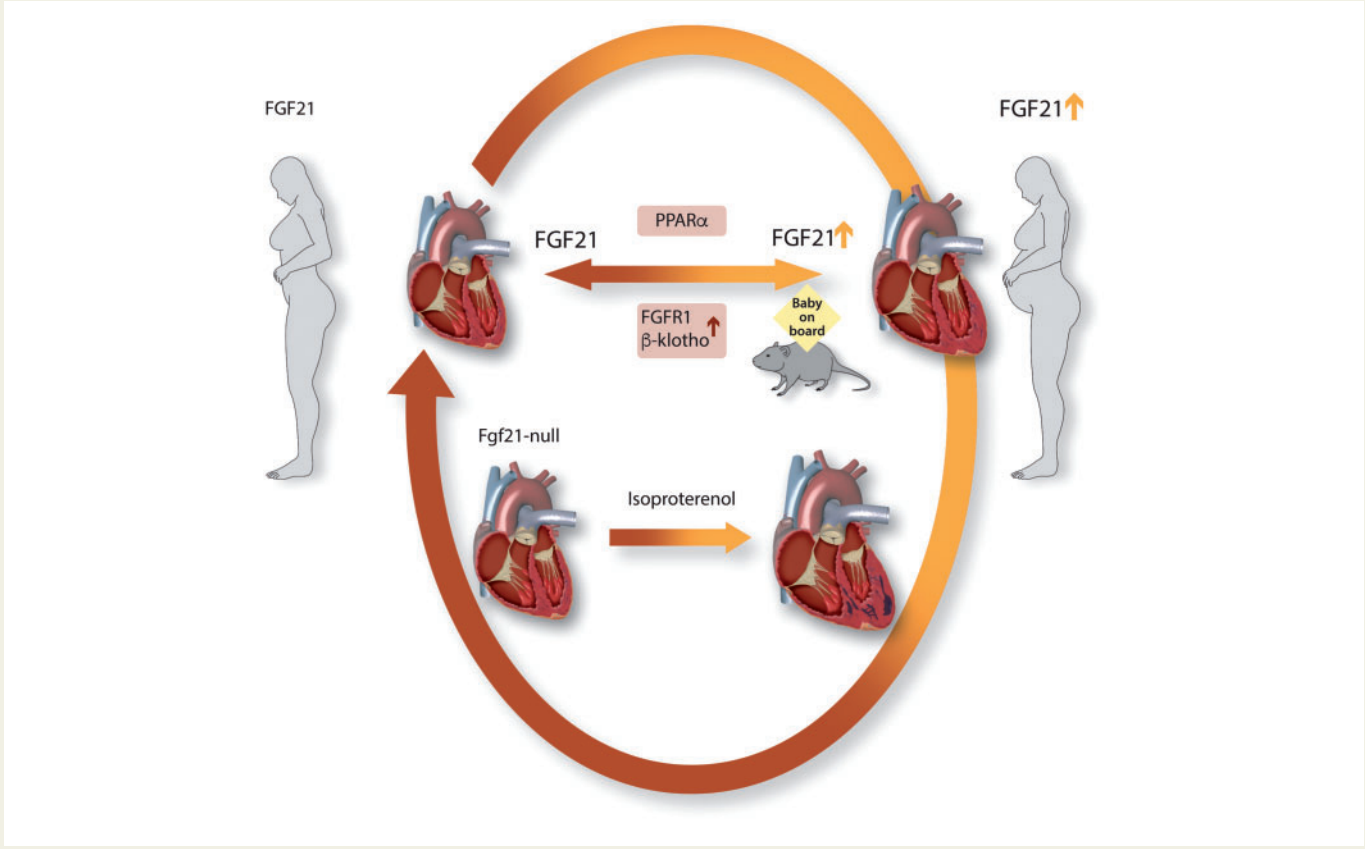

Figure 1 Does Fgf21 play a distinct role in pathological vs. physiological cardiac hypertrophy? During pregnancy there is an increase of circulating Fgf21 in murine and rat models of pregnancy and in pregnant women. This overexpression is mediated by PPARα that in turn induces the up-regulation of the Fgf21 receptor-1 (FGFR1) and the co-receptor β-klotho in late murine pregnancy. Fgf21-null mice do not develop cardiac hypertrophy during pregnancy; however, upon isoproterenol treatment, cardiac hypertrophy was significantly enhanced in transgenic mice compared with the controls.

Is the gestational cardiac hypertrophy specifically driven by Fgf21 and has distinct characteristics from other causes of hypertrophy? To address this issue, the authors performed complementary experiments in which they induced cardiac hypertrophy in Fgf21-null mice by isoproterenol exposure with osmotic minipumps. Echocardiographic measurements showed that isoproterenol-induced cardiac hypertrophy was significantly enhanced in Fgf21-null mice compared with wild-type mice (*Figure 1*). Thus, the results obtained from these experiments generated some apparent contradictions. In literature, there are examples where the lack or the overexpression of specific genes can convert in similar phenotype. For instance, the lack of gamma sarcoglycan protein determines in murine model muscle degenerations similar to those observed in patients with mutation in gamma sarcoglycan gene and affected by limb-girdle muscular dystrophy type 2C. However, the overexpression of gamma sarcoglycan gene in a murine model was responsible in even a more severe muscle phenotype.[11] It is clear that Fgf21 acts as an endocrine/autocrine factor eventually required for the cardiac remodelling response to gestation. The question placed here could be related to the Fgf21 dose effect that could move from physiological to pathological hypertrophy status. According to the authors, FGF21 could play a protective role against pathogenic cardiac hypertrophy, and it acts positively to promote adaptive physiological hypertrophy during pregnancy. Effectively, they cannot rule out the influence of side variables associated with experimental model of genetic invalidation and the conclusion should be considered with caution.

In a recent article, FGF21 was associated with diastolic dysfunction and circulating FGF21 (log-rank $P < 0.0001$) levels showed good predictive power to the 1-year adverse cardiac events.[12] Other studies have shown that in pathological conditions, including obesity or diabetes, the circulating FGF21 is further increased, despite the known beneficial effects of this protein as a metabolic regulator.[13–15] What could be the reasons for the higher circulating levels of FGF21 in women suffering from gestational diabetes and pre-eclampsia near delivery compared to women experiencing normal gestation? This phenomenon could be associated with resistance to FGF21 in such pathological conditions.[13–15] Nevertheless, if a resistance to FGF21 might explain high FGF21 circulating levels and enhanced cardiac hypertrophy in pathological gestations, it is still an open question.

Besides FGF21, sex hormones progesterone and oestrogen have been investigated for their role in pregnancy-related cardiac hypertrophy. In early pregnancy, the increased level of progesterone leads to cardiomyocyte hypertrophy via the activation of calcineurin.[16] Conversely, the increased levels of oestrogen in late pregnancy inhibit calcineurin, thereby regressing the hypertrophy and initiating post-partum cardiac remodelling to pregestational heart dimensions. Calcineurin activates extracellular signal-regulated kinases (Erk1/2), Akt, and the transcription

factor NFAT. Mice with cardiac-specific constitutive activation of Akt have increased myocardial mass with normal systolic function, whereas mice with targeted disruption of the Akt1 gene do not undergo exercise-induced cardiac hypertrophy.[16] As the downstream targets of Akt are significantly increased in mid-pregnancy, it is suggested that pregnancy-induced physiological cardiac hypertrophy is also mediated by Akt and its downstream molecules. Interestingly, Saito *et al.*[17] provide evidence that, in p32-deficient myocytes, Akt1-mTOR pathway was compromised in association with increased levels of cardiac Fgf21. This is extremely appealing, because Fgf21 expression is directly controlled by PI3-kinase/Akt signalling[18] and could occur in response to defective energy metabolism.

It was recently reported that endothelial protein tyrosine phosphatase-1B (PTP1B) deletion protects against chronic afterload-induced heart failure via Akt and ERK1/2 pathways.[19] Thus, it could be of interest to evaluate the role of PTP1B in gestational cardiac hypertrophy and the potential interaction with Fgf21. Similarly, Elabela/Toddler/Apela (ELA) has been found to activate the apelin receptor, known as APJ receptor, and the downstream targets Akt and ERK1/2.[20] Importantly, only ELA-APJ interaction determined the down-regulation of the transcription factor FoxM1, that in turn determined the reduction of angiotensin 1-converting enzyme. It is likely that the cardioprotective signalling activated by ELA-APJ could overlap with Apelin-APJ axis; however, ELA antagonized angiotensin II-induced cardiac hypertrophy at least in mice. How PTP1B, Apelin, ELA, and FGF21 are co-operating to orchestrate the fine-tuning of cardiac hypertrophy is still unknown. Novel studies in this direction would shed light on the mechanisms of cardiac hypertrophy during pregnancy and eventually provide therapeutic strategies for peripartum cardiomyopathy.

In conclusion, the involvement of FGF21 in cardiac hypertrophy is established, and it can be contemplated as biological marker that should be carefully considered during pregnancy. In a recent study, relaxin-2 serum levels were found reduced in patients affected by peripartum cardiomyopathy; however, high pregnancy-related variance makes relaxin-2 unsuitable as a biomarker.[21] Thus, some caution should be taken considering circulating FGF21 as a potential biomarker and a screening in a large cohort of patients is warranted. Both FGF21 insufficiency and resistance can be associated with cardiac maladaptation to pregnancy, which increases the risk of important gestational complications including pre-eclampsia. Understanding the pathogenesis is the first step in the development of treatment strategies, and murine models are effective systems to reveal mechanistic insights into physiological and pathological cardiac remodelling. Thus, the interesting data by Redondo-Angulo *et al.*,[8] in this issue of *Cardiovascular Research*, solicit focused follow-up studies to better grasp the role of FGF21 in gestational cardiac hypertrophy.

Conflict of interest: none declared.

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