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The contribution of prostaglandins versus prostacyclin in ventricular remodeling during heart failure

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Abstract

Although the role of Cox-2 in the heart's response to physiologic stress remains controversial (i.e. expression in myocytes versus other resident myocardial cells) the ever expanding role of prostanoids in multiple models of heart failure cannot be denied. Due to the fact that prostanoids are metabolized rather quickly (half life of seconds to minutes) it is believed these signaling mediators act in a paracrine fashion at the site of production. Evidence to date is quite convincing that these bioactive lipid derivatives are involved in physiologic homeostatic regulation as well as beneficial and maladaptive ventricular remodeling in heart failure. Thus, this review will assess the direct contribution of each PG on remodeling in the left ventricle (e.g. hypertrophy, functional effects, and fibrosis).

Keywords

Cardiac; Eicosanoid; Prostaglandin receptor; Myocardium; Hypertrophy; Fibrosis; Remodeling

Introduction

The name eicosanoid encompasses a large family of arachidonic acid-derived 20-carbon biologically active fatty acid metabolites (Jenkins et al., 2009). A subgroup of that catchall classification is the prostanoid category which is composed of prostaglandins (PGE, PGF, PGD), prostacyclins (PGI) and thromboxanes (TXA). These subclasses differ by their characteristic carbon ring structures. The term prostaglandin (PG) was originally coined in 1935 by von Euler (1981) and independently by Goldblatt (1935) from their work with the prostate gland. Since that time PGs have been studied in the body and found to not only have a role in homeostasis but also pathophysiologic responses particularly associated with inflammation. Due to the fact that PGs are metabolized rather quickly (half life of seconds to minutes) it is believed these signaling mediators act in their immediate environment at the site of production Yuhki et al. (2011) Generation of prostanoids is governed by the formation of the key precursor prostaglandin H₂. This rate limiting step is dependent upon either prostaglandin endoperoxide H synthases-1 or -2 more commonly referred to as cyclo-

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oxygenase-1 and cyclooxygenase-2 (Cox-1 and Cox-2). Further conversion of prostaglandin H₂ to the various (PGE, PGF, PGD and PGI) prostanoids is dependent upon tissue specific isomerases also termed terminal prostaglandin synthases.

Although Cox-1 has been noted as the constitutively expressed cyclooxygenase enzyme, Cox-2 has emerged as playing a significant role in cardiac and vascular homeostasis. Interestingly, due to its endoperoxidase activity Cox-2 is activated by hydrogen peroxide at significantly lower levels than Cox-1. Thus, Cox-2 could be especially important in cells that are involved in oxidative stress induced inflammation such as in the setting of heart failure (AOCS Lipid Library, 2011). Although the role of Cox-2 in the heart's response to physiologic stress remains controversial (i.e. expression in myocytes versus other resident myocardial cells) the ever expanding role of prostanoids in multiple models of heart failure cannot be denied (Fig. 1). The involvement of PGs in the setting of pulmonary hypertension has been excluded from this review due to the preponderance of work in this area with clinical trials and therapeutics already in place. Thus, this limited review will assess the direct contribution of each PG on left-ventricle (LV) remodeling (e.g. hypertrophy, functional affects, and fibrosis).

Prostaglandin E₂

Prostaglandin E (active metabolite; PGE₂) is possibly the most extensively studied PG in the cardiovascular system conceivably due to the multiple receptor subtypes (EP₁₋₄). Specifically, EP₂ and EP₄ (both linked to G_s signaling) and EP₃ (linked to G_i pathway) have demonstrated direct effects in cardiac remodeling in response to pathophysiologic stress. In 2002, Mendez and LaPointe reported the anti-hypertrophic effects of Cox-2 inhibition in neonatal ventricular myocytes were mediated through the inhibition of PGE₂ formation (Mendez and Lapointe, 2002). A follow up mechanistic study by the same group demonstrated that the PGE₂ induced hypertrophic effect on myocytes was an EP₄ dependent phenomenon which utilized the p42/44 MAPK pathway (Mendez and Lapointe, 2005). A more recent study by Frias et al. (2007) has also implicated the ERK 1/2/Stat 3 pathway as having a role in PGE₂ induced hypertrophy.

Pioneering work by Hohlfeld et al. (1997) revealed the anti-ischemic properties of the EP₃ receptor in pig hearts. A subsequent study by the same group showed that the reduction in infarct size and preservation of cardiac function and rhythmicity were potentially due to interaction with the β -adrenergic pathway (Hohlfeld et al., 2000). Work by Martin et al. (2005) as well as Meyer-Kirchrath et al. (2009) using a cardiac specific EP₃ overexpressing transgenic mouse model demonstrated cardioprotective effects but also revealed a calcineurin mediated hypertrophic result as well. These findings suggest that the anti-ischemic properties of EP₃ activation may be at the expense of a pro-hypertrophic signals.

The direct effects of PGE₂ on left ventricular contractility have been investigated but remain unresolved. In cardiac myocytes exposed to post ischemic effluent, both EP₂ and EP₄ antagonists blocked the deleterious effects on calcium movement (Birkenmeier et al., 2008). LaPointe et al. (2004) had previously concluded that the Cox-2 inhibition mediated improvement of ventricular function post myocardial infarction was due to decreased PGE₂ formation. Contrastingly, Xiao et al. (2004) reported a cardioprotective role for PGE₂ following ischemia/reperfusion injury. Moreover, post myocardial infarction ventricular function was markedly impaired in a murine model of cardiac specific deletion of the EP₄ receptor but this response was also associated with decreased hypertrophy (Qian et al., 2008). A longitudinal study with the same cardiac specific EP₄ knockout model revealed that these aged mice develop decreased cardiac function assessed by ejection fraction and a phenotype of dilated cardiomyopathy (Harding et al., 2010).

Several studies have investigated a role for PGE₂ mediated ECM remodeling. Characterization of the cardiac specific EP4 knockout model by Harding et al. (2010) demonstrated no cardiac phenotype in young animals under basal conditions but increased fibrosis and decreased cardiac function (reduced ejection fraction) associated with aging. However, the induction of a pathologic stress revealed an alternate outcome. This same transgenic model showed a decrease in interstitial collagen following myocardial infarction compared to wild type littermates but this was associated with a worsening of cardiac function (Qian et al., 2008). Further, the use of an EP4 agonist following ischemia/reperfusion injury significantly attenuated the typical increase in myocardial collagen (Hishikari et al., 2009). Recently, the importance of PGE₂ to overall myocardial function and structure has emerged in the course of the deletion of its terminal synthase. Through the use of transgenic mice, Degousee et al. (2008) demonstrated exacerbated remodeling (i.e. eccentric hypertrophy and chamber dilatation) as well as worsening of both systolic and diastolic functions in microsomal prostaglandin E₂ synthase-1 knockout mice (mPGES-1 KO) post myocardial infarction. That study was followed by Harding et al. (2011) confirming the importance of PGE₂ to cardiac function. In an ANGII induced model of pressure overload, mPGES-1 KO mice had markedly reduced ejection fraction, enlarged left ventricular chamber and increased apoptosis compared to control mice. Interestingly, in a separate study by Harding and LaPointe, PGE₂ stimulated proliferation of neonatal rat cardiac fibroblasts via the EP1 or EP3 receptors (Harding and Lapointe, 2011). However, the two previous studies using the in vivo model reported no significant differences in myocardial collagen content or collagen type in wild type or mPGES-1 KO mice post MI or Ang II infusion. In a series of studies by Jia Z et al. mPGES-1 was shown to protect against both Ang II-induced hypertension and DOCA-salt hypertension via inhibition of oxidative stress, suggesting a possible mechanism for the deleterious effects of its gene knockout on cardiac function (Jia et al., 2008; Jia et al., 2010).

Prostaglandin F

Prostaglandin F (active metabolite; PGF₂) is generated predominantly by Cox-2 in the cardiovascular system. The PGF receptor FP acts via the Gq subunit to raise intracellular calcium. A study by Jovanovic et al. (2006) which examined the mRNA expression profile of prostaglandin receptors in the right ventricle reported that the FP receptor was expressed higher than any other prostaglandin receptor [FP>EP1=TP>EP4>EP3>DP=IP]. Moreover, PGF₂ is abundantly produced under stress conditions in the heart (Gupte and Okada, 2001; Takayama et al., 2005b).

Earlier work by Adams et al. (1996) and Adams et al. (1998) demonstrated that PGF₂ was capable of stimulating hypertrophic growth in neonatal cardiomyocytes. Shortly thereafter this was confirmed by two separate groups; Kunapuli et al. (1998) as well as Lai et al. (1996). However, the latter study also found the same phenomenon in adult cardiac myocytes. Additionally, the use of fluprostenol, an analogue of PGF₂ caused dose dependent hypertrophy in vivo which was evident as an increase in ventricular weight to body weight ratio. A later mechanistic study by Ponick et al. (2000a) revealed that PGF₂ induced inositol phosphate formation and subsequent trophic (e.g. protein synthesis) effects via FP receptor dependent activation in left ventricular strips from rat hearts. FP receptor activation has also been linked to MEK/Erk2 signaling pathway (Kunapuli et al., 1998). An exquisite study by Kehat et al. nicely documented the regulatory role of G protein receptor activation of MEK1-ERK1/2 in programming cardiac hypertrophy toward a perceived beneficial concentric (increased myocyte width) as opposed to dilative eccentric hypertrophy (increased myocyte length) (Kehat et al., 2011).

Originally, a few groups documented PGF₂ mediated increase in intracellular calcium and subsequent myocyte shortening suggesting a positive inotropic effect (Yew et al., 1998; Otani et al., 1988; Ponick et al., 2000b). In contrast to those early reports, Jovanovic et al. (2006) found PGF₂ acting through the FP receptor mediated a negative inotropic effect in isolated right ventricular muscle. The authors concluded this may have been due to PLC activation upstream of inositol phosphate formation or activation of PKC leading to decreased contractility. It should be noted that the differences in contractile effects may in part be explained by the use of atrial tissue, isolated cardiac myocytes and ventricular tissue.

Most recently stable metabolites of PGF₂ have been investigated as potential biomarkers for the severity of heart failure in humans. Specifically, multiple investigators have demonstrated that the stable PGF metabolite isoprostane 8-epi-prostaglandin F₂ could be used to differentiate congestive heart failure NYHA class (I–IV) patients (Polidori et al., 2004; Wolfram et al., 2005; Radovanovic et al., 2008). Moreover, F₂ isoprostane was negatively correlated with ejection fraction (Polidori et al., 2004; Wolfram et al., 2005). The use of these molecules as indicators of oxidative stress via lipid peroxidation of arachidonic acid does not address their potential contributory role to the worsening of heart failure. Taking into consideration the receptor expression profile of prostaglandins in the heart and the direct role for PGF₂ on myocyte remodeling, future studies should not neglect to examine the causal effect of these lead inflammatory mediators.

Prostaglandin D

Prostaglandin D (active metabolite; PGD₂) could regrettably be best denoted for the relatively miniscule information on this particular PG in the cardiovascular system. There are two cognate receptors for PGD₂ (DP1 and DP2) and they are expressed in the heart (Herlong and Scott, 2006). The DP1 receptor is linked to G_s and associated with increases in cAMP. DP2 is linked to the Gi subunit which acts to decrease cAMP (Herlong and Scott, 2006). These receptor subtypes may act to counter balance PGD signaling as DP1 inhibits cytokines and chemotaxis whereas DP2 promotes chemotaxis of numerous immune cells. Currently, it remains uncertain if expression levels of these receptors are responsive to myocardial infarction or pressure overload. Increase in PGD₂ from basal levels in oxidative challenged hearts is highest compared to all other PGs (Gupte and Okada, 2001). Mast cells which are involved in the primary response to stress in the heart are considered the initial source of PGD₂ however levels remain persistently high in the stressed myocardium suggesting alternate resident sources as the cause of continued formation (Pettipher, 2008). There are two terminal isomerases for the conversion of PGH₂ to PGD₂: 1) Hematopoietic (H-type) PGD synthase, originally discovered in mast cells, is expressed in cardiac myocytes and fibroblasts, and 2) Lipocalin (L-type; also known as Beta Trace) PGD synthase has been extensively studied in the central nervous system but its only other place of expression is in the heart.

Tokudome et al. (2009) investigated the beneficial effects of dexamethasone during cardiac ischemia/reperfusion injury. Glucocorticoid receptor activation was able to reduce infarct size; however, this effect was greatly diminished in L-type PGD synthase deficient mice. Han et al. (2009) showed increased expression of L-PGD in chronic hypoxic myocardium. However, the authors concluded this was not directly related to the hypoxia but rather due to the cardiac remodeling response to pressure overload. Moreover, studies in humans with angina documented increased levels of L-type PGD synthase in coronary effluent due to spill over from the myocardium (Eguchi et al., 1997; Urade et al., 1999; Manzano-Fernandez et al., 2011). The authors suggested L-type PGD synthase may be a useful biomarker of cardiac pathology. Recent findings from our own laboratory (data not shown) using an abdominal aortic constriction model in rats revealed H-type PGD synthase

myocardial protein levels were elevated after 14 and 28 days pressure overload, whereas L-type PGD synthase expression was unchanged. These findings are consistent with an earlier study by Schuligoi et al. (2005) which examined the mRNA expression profile of H- type and L-type PGD synthases in hearts from LPS treated mice.

An extensive study by Ponicke et al. (2000a) included PGD2 in their comparison of trophic effects between various prostanoids. Their findings demonstrated PGD2 was capable of inducing inositol phosphate formation and incorporation of phenylalanine (a marker of myocyte growth) in neonatal and adult cardiomyocytes which rivaled PGE2 and was closely behind PGF2. The authors unfortunately did not report PGD2's effects on contractility in ventricular strips. However, Birkenmeier et al. (2008) performed a similar comparison study of PGs involved in cell shortening and calcium handling. Their results demonstrated DP receptor expression in the heart but that this was not activated by ischemic coronary effluent and appeared to play no role in cardiac function. A recent study by Hao et al. (2008) demonstrated the anti-fibrotic effects of the PGD2 metabolite 15-deoxy- 12,14-PGJ2 (15-d-PGJ2). The levels of the PGJ series of prostaglandins (namely 15-d-PGJ2) are high in the stressed myocardium yet the only source for this specific subclass of PGs is PGD2 as this is a dehydration process and does not require the enzymatic activity of any particular synthase.

15-d-PGJ2 is best known as the natural ligand for PPAR, however it is capable of binding the DP2 receptor with greater affinity than PPAR (Herlong and Scott, 2006). Initial studies show Rosiglitazone or 15-d PGJ2 stimulation of PPAR led to decreased infarct size, decreased TNF- and TGF- expressions, decreased collagen, and decreased AngII induced fibrosis (Ogata et al., 2004; Sivarajah et al., 2005; Wayman et al., 2002; Chen et al., 2004; Diep et al., 2004; Iglarz et al., 2003). Disappointingly, similar to long term use with selective Cox-2 inhibition recent clinical cardiovascular complications (ACCORD trial) have come to light with the use of the PPAR agonist, Avandia® (Lincoff et al., 2007; Pop-Busui et al., 2010; Nissen and Wolski, 2010). Two independent groups demonstrated 15-d-PGJ2, the endogenous activator of PPAR, induced fibroproliferation, cytokine production and collagen deposition (fibrosis) in the kidney, lung, and testis (Levi-Schaffer and Piliponsky, 2003; Frungieri et al., 2002; Frungieri et al., 2005). Interestingly these studies identified a cell-cell signaling pathway between mast cells (as a source of tryptase) and activation of protease activated receptor-2 (PAR-2) on fibroblasts. PAR-2 activation, which is associated with beneficial effects in infarcted hearts is capable of regulating Cox-2 expression and thus ultimately giving rise to 15-d-PGJ2. 15-d-PGJ2 in these other organ systems feeds back in an autocrine fashion on PPAR in the fibroblasts to promote fibrotic remodeling. One plausible explanation for these findings may be divergence for synthetic versus endogenous activators of PPAR as has been suggested previously by several independent investigators (Nikitakis et al., 2002; Kaplan et al., 2007; Zingarelli et al., 2007). Another point of discrepancy for the differing effects of 15-d-PGJ2 mediated PPAR activation may lie in the cell type being stimulated (e.g. myocyte versus fibroblast). Taking into consideration that there are three times as many fibroblasts as myocytes in the heart, (Souders et al., 2009) this pathway needs to be further explored.

Prostacyclin (PGI2)

Prostaglandin I (active metabolite; PGI2) is generated by both Cox-1 and Cox-2. The PGI receptor IP has a wide tissue distribution throughout the cardiovascular system and acts via the G_s subunit to raise intracellular cAMP concentrations. Most often PGI2 has opposing effects against TXA2. It was the loss of this counter balance role that gave rise to diminished renal blood flow and prothrombotic events in Vioxx™ patients as TXA2 was left uninhibited during chronic selective Cox-2 inhibition (Abbate et al., 2004). However,

numerous studies have demonstrated a clear role for PGI₂ in the pathologic response of the heart.

PGI₂ is predominantly anti-hypertrophic in the whole animal setting. In 2001, Xiao et al. (2001) utilized the IP^{-/-} mouse to show that the ischemia/reperfusion induced increase in PGI₂ exerted a protective effect on cardiomyocytes. Use of a Langendorff ex vivo heart preparation demonstrated that this effect was independent of PGI₂ effects on platelets and neutrophils. This was followed by a study by Hara et al. (2005a) which found increased cardiac and myocyte hypertrophy secondary to a transverse aortic constriction pressure overload model in the same IP^{-/-} model compared to wild type animals. Whereas, IP activation with cicaprost, a PGI analogue, failed to induce cardiomyocyte hypertrophy, the apparent concomitant decrease in atrial natriuretic peptide may account for some of the anti-hypertrophic effects in these hearts. In the same year, Francois et al. (2005) demonstrated significant LV hypertrophy via a salt induced hypertensive diet in the IP^{-/-} mouse which was preventable with vasodilator (hydralazine) treatment. Next Rossoni et al. (2006) found that compared to Cox inhibition or nitric oxide-donors the potent PGI releaser defibrotide was markedly better at reducing infarct size and multiple indicators of myocyte injury following myocardial ischemia/reperfusion.

The effects of PGI₂ on left ventricular contractility have been modestly studied. Using pressure-volume loops in a pig model, Kisch-Wedel et al. demonstrated that infusion of the PGI₂ analogues epoprostenol or iloprost was able to increase myocardial contractility as assessed by the slope of end systolic pressure volume relationship (a load independent measure of left ventricular contractility) also known as the end-systolic elastance (Kisch-Wedel et al., 2003). This effect was evident without changes in heart rate or arterial blood pressure. In a follow up study, the same group compared the effect of the identical PGI₂ analogues to sodium nitroprusside on isovolumic relaxation as assessed by the maximum velocity of left ventricular pressure drop. Sodium nitroprusside worsened this parameter whereas it remained stable during infusion of the PGI₂ analogues, suggesting that PGI₂ is able to preserve active relaxation during diastole presumably via its purported intracellular signaling intermediate, cAMP (Kisch-Wedel et al., 2005). In the same year, Kemming et al. (2005) reported the effects of aerosolized epoprostenol or iloprost on myocardial contractility. Using pressure volume conductance catheter the authors found an increase in myocardial contractility evident by an increase in end systolic elastance.

The ultimate pathologic indicator of adverse remodeling is altered content and constituency of the extracellular matrix (ECM). Excessive collagen, also known as fibrosis, in the myocardial interstitial space severely impacts the overall cellular activity, function of the ventricle and ultimately the prognosis of heart failure. Multiple in vitro and in vivo studies have detailed a role for PGI₂ acting on cardiac fibroblasts to mediate ECM remodeling. Yu et al. (1997) investigated the effects of ANG II on cardiac fibroblasts from Wistar Kyoto and Spontaneously Hypertensive rats. Stimulation with angiotensin II (ANG II) caused an increase in PGF₂ and PGI₂ release from cardiac fibroblasts. Although strain differences existed between the required stimulating concentrations, the stable PGI₂ analogue, beraprost sodium, was able to limit cell growth, fibroproliferation, and collagen expression (Yu et al., 1997). In the whole animal, several investigators reported that compared to wild type litter mates the IP^{-/-} mouse develops severe cardiac fibrosis (perivascular and interstitial locales) as a result of myocardial infarction, aortic banding and salt sensitive hypertension (Kaneshige et al., 2007; Hara et al., 2005b; Xiao et al., 2001; Francois et al., 2004). Potential signaling mechanisms for these effects have been investigated. Stratton et al. (2002) found in dermal and NIH 3 T3 cells that the prostacyclin analogue Iloprost was able to prevent TGF- β induced collagen deposition via PKA-dependent inhibition of the Ras/MEK/ERK pathway and that Smad was not a target of this suppression. Most recently, Chan et al.

(2010) demonstrated that cicaprost activation of the IP receptor in mouse cardiac fibroblasts was able to prevent TGF- β induced upregulation of collagen I and other ECM related genes and that this was not Smad dependent. Taken together these findings strongly indicate a prostacyclin/IP mediated inhibitory effect on cardiac fibrosis.

Thromboxane

Thromboxane (active metabolite; TXA₂), derived mainly from circulating platelets, is predominantly generated via Cox-1 activity. TXA₂ plays a significant role in vasomotor tone, vascular remodeling as well as atherosclerosis (Kobayashi et al., 2004; Yuhki et al., 2010). Specifically, TXA₂ acts on TP receptors to increase intracellular Ca⁺⁺ via the Gq subunit in vascular smooth muscle cells. A tachycardic response to TXA₂ in the setting of inflammation has been reported by Takayama et al. who showed that TP^{-/-} mice demonstrate a reduced increase in heart rate after lipopolysaccharide administration (Takayama et al., 2005a). These findings were corroborated in a separate study using the TP agonist I-BOP which increased the beating rate of isolated atrium in mice (Jia et al., 2010; Yamada et al., 2003). In addition, Wacker et al. reported TXA₂-induced arrhythmias in the rabbit heart, an effect that was independent of alterations in either coronary blood flow or activation of the autonomic nervous system (Wacker et al., 2006).

Conclusion

Cardiac remodeling is an inflammatory event. PGs are produced in the heart in response to stress and by their nature are meant to act locally. The current body of work on these front line inflammatory mediators is sorely lacking. Individual synthases and receptors are present in the heart as well. Evidence to date is quite convincing that these bioactive lipid derivatives are involved in physiologic homeostatic regulation as well as beneficial and maladaptive ventricular remodeling in multiple models of heart failure. PGs bind receptors which are members of the GPCR superfamily with diverse subunits. However, there is evidence presented herein demonstrating convergence on multiple intracellular signaling pathways linked to adverse or cardioprotective pathways. Additionally, there is also the potential for cross reactivity between individual PGs and alternate prostaglandin receptors. Table 1 summarizes potential key experiments that could be performed to drive the field forward and aid in our understanding of these individual PGs.

Evidence for the benefit of Cox-2 inhibition in myocardial infarction or pressure overload induced remodeling is clear. The only mechanism for these effects is the reduction of prostacyclin and PGs. Obviously long-term treatment with selective Cox-2 inhibitors is contraindicated. While the use of PG metabolites as biomarkers has potential diagnostic value this information does not reveal causative or responsive phenomenon. The multiple points of regulation in the biological pathways for each individual PG (e.g. synthases and receptors) offer tremendous pharmacologic potential by developing therapeutic strategies aimed at maximizing the beneficial properties and inhibiting maladaptive PG effects and needs to be further investigated.

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Fig. 1.

Synthesis and signaling mechanisms of prostanoids. Arachidonic acid is metabolized by Cox-1 or Cox-2 to the universal precursor PGH₂ for subsequent formation of prostaglandins (PGE₂, PGF₂, PGD₂), prostacyclins (PGI₂) and thromboxanes (TXA₂) via their individual terminal synthases. Each prostanoid subclass has individual G protein coupled receptors which elicit various direct contributions on remodeling in the left ventricle (e.g. hypertrophy, functional effects, and fibrosis).

Table 1

Prospective studies to further understanding of the specific contribution of prostaglandins and prostacyclin to LV remodeling.

Future studies	
Prostaglandin E ₂	Investigate the interaction(s) between the EP signaling pathways. (i.e. how do both EP3 and EP4 contribute to cardiac hypertrophy when one reduces cAMP and the other increases cAMP).
Prostaglandin F ₂	Study the mechanistic link between FP receptor activation and trophic stimulation in myocytes needs to be further explored.
Prostaglandin D ₂	Differentiating between direct actions of PGD ₂ binding to DP1 and DP2 on resident myocardial cells would significantly add to the current knowledge gap concerning this receptor system.
Prostacyclin (PG I ₂)	Potential connection between anti-hypertrophic action of PGI ₂ and ANP expression should be further explored. Alternatively, investigating the interaction between PGI ₂ and TGF- β signaling could generate a novel anti-fibrotic therapeutic approach.