Prostaglandins and Other Lipid Mediators xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

journal homepage: www.elsevier.com/locate/prostaglandins

Review

# Prostanoids in the pathophysiology of human coronary artery

Gulsev Ozen[a], Xavier Norel[a,b,*]

[a] INSERM U1148, CHU X. Bichat, 46 rue H. Huchard, 75018 Paris, France
[b] Paris Nord University, Sorbonne Paris Cité, UMR-S1148, 75018 Paris, France

ARTICLE INFO

*Keywords:*
Human coronary artery
Prostanoid
Coronary artery disease
COX inhibitors
Vascular tone
Vascular remodelling

ABSTRACT

Coronary artery disease is one of the leading causes of death in wordwide. There is growing evidence that prostanoids are involved in the physiology and pathophysiology of the human coronary artery by controlling vascular tone, remodelling of the vascular wall or angiogenesis. In this review, the production of prostanoids and the expression of prostanoid receptors in human coronary artery in health or disease are described. In addition, the interactions between sex hormones and prostanoids, their participations in the development of coronary artery diseases have been addressed. Globally, most of the studies performed in human coronary artery preparations have shown that prostacyclin ($PGI_2$) has beneficial effects by inducing vasodilatation and promoting angiogenesis while reverse effects are confirmed by thromboxane $A_2$ ($TxA_2$). More studies are needed to determine the roles of the other prostanoids ($PGE_2$, $PGD_2$ and $PGF_{2\alpha}$) in vascular functions of the human coronary artery. Finally, in addition to the *in vitro* data about the human coronary artery, myocardial infarction induced by cyclooxygenase-2 (COX-2) inhibitor and the protective effects of aspirin after coronary artery bypass surgery suggest that prostanoids are key mediators in coronary homeostasis.

## 1. Introduction

Coronary arteries play a critical role in the supply of blood flow to the myocardium. When the plaque builds up inside the coronary artery, blood flow is partially or totally blocked. This change is named by atherosclerosis and it is the main common reason for coronary artery disease (CAD). This disease has severe implications by decreasing the supply of oxygen and nutrients to the myocardium and may result in myocardial infarction [1]. Several endogenous factors are implicated in the development or progression of CAD, among them prostanoids could be important key elements because of their substantial involvements in the physiology and pathophysiology of the coronary artery.

Prostanoid synthesis is initiated by arachidonic acid release from phospholipids by the action of phospholipase A2 ($PLA_2$) enzymes in the cell membrane. Then arachidonic acid is converted to prostaglandin $(PG)H_2$ via cyclooxygenases (COX-1 and COX-2) enzymes. $PGE_2$, prostacyclin ($PGI_2$), $PGD_2$, $PGF_{2\alpha}$ and thromboxane A2 ($TxA_2$) are formed from $PGH_2$ via prostanoid synthase enzymes. The prostanoids are involved in vascular homeostasis by regulating vascular wall remodelling and muscular tone [2,3]. Basically, the vascular wall produces mainly the vasodilator and antiplatelet prostanoid $PGI_2$, while blood components such as platelets release the vasoconstrictor and proaggregant prostanoid $TxA_2$. However, increasing evidences demonstrate synthesis and roles for $PGE_2$ in the cardiovascular system [3,4]. Interactions between the vascular wall and blood cells could be maintained by the balance between detrimental and beneficial prostanoids in physiological conditions [5]. However, this balance in prostanoid release is impaired in pathophysiological conditions such as CAD. For this reason, the prostanoids could have important impacts on the prevention or treatment of CAD. In fact, emerging evidence on the impact of the prostanoids in coronary artery physiology is strongly suggested by numerous clinical studies concerning both the beneficial effects of aspirin administration in the post-operative period of coronary artery bypass grafting (CABG) surgery [6] and the cardiovascular side effects (such as myocardial infarction) induced by COX-2 inhibitors or NSAIDs (non-steroidal anti-inflammatory drugs) [7]. In this review, we focused on the role of prostanoids in the regulation of human coronary artery homeostasis (vascular tone and wall remodelling) and their involvements in the development of CAD are addressed.

## 2. *In vitro* prostanoid synthesis and receptors in human coronary artery cells

### 2.1. In healthy condition

In normal conditions without inflammatory stimuli, only COX-1 is detectable by western blot and/or RT-PCR analysis in cultured human coronary artery endothelial cells (HCAEC) [8,9] or smooth muscle cells

* Corresponding author at: INSERM U1148, LVTS, Laboratory on Eicosanoids & Vascular Pharmacology, CHU X. Bichat, 46 rue Huchard, 75018, Paris, France.
*E-mail address:* xavier.norel@inserm.fr (X. Norel).

http://dx.doi.org/10.1016/j.prostaglandins.2017.03.003
Received 6 January 2017; Received in revised form 16 February 2017; Accepted 23 March 2017

(HCASMC) [10,11]. Respective synthase enzymes for $PGI_2$, $TxA_2$ or $PGE_2$ have been detected in HCAEC [9]. In addition, in isolated fresh human coronary artery, the production of all major prostanoids ($PGI_2$, $TxA_2$, $PGD_2$, $PGF_{2\alpha}$, $PGE_2$, $PGE_1$) has been confirmed by radioimmunoassay [12]. Immunohistochemistry studies on human coronary artery serial sections (obtained after autopsy) with anti-$TxA_2$ synthase and anti-$PGI_2$ synthase antibodies have exhibited positive staining in several types of cells including in endothelial cells, smooth muscle cells and macrophages [12]. However, measurements of $TxA_2$ stable metabolite released by human coronary segments, with and without an intact endothelium, have suggested the absence of $TxA_2$ synthesis by the endothelium [13]. Interestingly and paradoxically, one non-inflammatory stimulus (oleanolic acid) was able to induce COX-2 expression via mitogen activated protein kinase (MAPK) signalling pathways in HCASMC. Oleanolic acid which is a triterpenoid derived from olive oil may contribute to the cardio-protective effects of Mediterranean diet by increasing $PGI_2$ concentration after COX-2 induction [14].

The effects of prostanoids are dependent on specific prostanoid receptors named DP1-2, EP1–4, FP, IP and TP which are preferentially activated by $PGD_2$, $PGE_2$, $PGF_{2\alpha}$, $PGI_2$ and $TxA_2$, respectively [2]. One study has shown that HCASMC express EP3, EP3-I, IP and TP mRNA [15]. Expressions of the IP and TP receptor proteins were also detected in HCASMC [16,17]. On the other hand, HCAEC expressed mRNA for the IP, TP, all four EP receptors (EP1-4) and expressed the proteins for the EP1, EP2 and EP3 receptors [15]. It was suggested that the protein for EP4 receptor could not be synthesized, even though the mRNA of EP4 was detected in HCAEC [18].

### 2.2. In inflammatory condition

Under inflammatory conditions, the production of prostanoids could be modified in cultures of human coronary cells as in many other cells. This effect is associated with the induction of COX-2 expression in human coronary cell cultures subjected to inflammatory stimuli such as interleukin-1beta (IL-1β), lipopolysaccharide (LPS), tumor necrosis factor alpha (TNFα) in HCASMC [10] or HCAEC [9,19]. In most of the cases, these inductions of COX-2 are associated with a specific increase in the production of $PGE_2$ or $PGI_2$. Similarly, in HCAEC, another inflammatory mediator, histamine, has been shown to stimulate the expression of COX-2 (mRNA and protein), microsomal prostaglandin E synthase-1 (mPGES-1) and $PGI_2$ synthase (PGIS) mRNA transcription. Consequently, in this study histamine augmented the production of $PGI_2$ and $PGE_2$ via H1 receptor activation without affecting $TxA_2$ release [20].

Much evidence has shown that inflammation promotes atherogenesis and the associated thrombotic events. Incubation with inflammatory cytokines such as IL-1β results in higher IL-6 and tissue factor (procoagulant protein) productions in HCAEC as compared to human umbilical vein endothelial cells (HUVEC) or dermal microvascular endothelial cells. The greater susceptibility of HCAEC to inflammatory cytokines might provide a greater risk of inflammation and/or coagulation in coronary vessels [21]. Inhibition of $PLA_2$ in HCAEC could block the production of several inflammatory metabolites involved in the pathophysiology of atherosclerosis such as $PGE_2$ [22]. Similarly, the anti-inflammatory role of ghrelin has been shown, this “hunger hormone” is known to assist in tissue revascularization and to attenuate endothelial cell damage in diabetes or atherosclerosis [23]. Pre-treatment of HCAEC with ghrelin attenuated the increased COX-2 mRNA expression induced by acute inflammation [15]. As well as in inflammatory conditions, HCAEC under hypoxia are able to induce neutrophil chemotaxis. Such mechanism is mostly dependent of the increased production of $PGF_{2\alpha}$ [24].

C-reactive protein (CRP), a prototypic marker of inflammation, is involved in the development of CAD. Jiao et al. have shown that CRP significantly increased COX-1 and COX-2 levels in a time- and concentration-dependent manner in HCAEC [8]. In contrast, other group has indicated that CRP decreased $PGI_2$ synthesis in HCAEC, an effect possibly due to the inactivation of PGIS by nitration via inducible nitric oxide synthase (iNOS) induction [25]. Another study performed in porcine coronary artery suggested that CRP induced endothelial dysfunction by impairing $PGI_2$ production and involved in the development of CAD [26].

## 3. Physiological effects of prostanoids in the human coronary artery

### 3.1. Regulation of vascular tone by prostanoids in vitro

Prostanoids are implicated in the regulation of human vascular tone by activating their specific receptors. When these receptors are localized on the smooth muscle, classically the activation of IP, EP2, EP4 or DP receptors by prostanoids induces vasodilatation, while the activation of TP, EP1, EP3, or FP receptors is responsible for vasoconstriction [2]. Control of vascular tone by prostanoids in human coronary artery could be differently regulated depending on the stimulus (agonist, hypoxia, bacterial peptide) or the patient characteristics/pathology. In patients with diabetes mellitus, *in vitro* coronary arteriolar dilatation induced by bradykinin was more potent when compared to preparations derived from patients without this pathology. This greater relaxation was dependent on prostanoids since it was significantly decreased by the non-selective COX inhibitor (indomethacin) or the selective COX-2 inhibitor (NS-398) while in non-diabetic group it was not modified. This effect was accompanied with increased expression of COX-2 in coronary arterioles of diabetic patients [27] and probably involved the greater production of $PGI_2$ as frequently reported when the COX-2 enzyme was induced in isolated human vessels [28,29].

Contradictory results have been described with hypoxia whereby it induces either vasoconstriction or vasodilatation of human coronary arteries depending on their initial muscular tone and/or the *in vitro* model used [30,31]. However, the involvement of prostanoids in hypoxia has been linked to a contractile role. The vasoconstriction of isolated monkey or human coronary artery induced by hypoxia was associated with vasoconstrictor prostanoids released from subendothelial tissues [31]. In accordance with this effect of endogenous prostanoids, indomethacin enhanced dilatation of human coronary arterioles under hypoxia [30].

N-formyl oligopeptides produced by tissue bacterial infection are responsible for macrophage or neutrophil activations. One synthetic mimetic of these peptides, the chemotactic peptide N-formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP), is responsible for biphasic response of the vascular tone in isolated human coronary artery [12,32]. The contraction and relaxation induced by FMLP were mainly due to the generation of $TxA_2$ and $PGI_2$, respectively. They were endothelium-independent and completely abolished in the presence of the COX inhibitors aspirin or indomethacin [12,32].

Pharmacological studies on the effects of prostanoid mimetics (U46619, carbocyclic $TxA_2$; $PGI_2$ and iloprost) have suggested that the prostanoid receptors involved in vascular responses are the TP and the IP receptor respectively [13,33–36]. However, other prostanoids could be involved since stimulation of human coronary artery preparations with FMLP resulted in a marked production of $PGF_{2\alpha}$, a smaller production of $PGD_2$ and a slight increase of $TxB_2$. All these prostanoids constricted coronary artery *in vitro*, but the stable $TxA_2$ mimetic U46619 was 100 times more potent than $PGE_2$, $PGF_{2\alpha}$ or $PGD_2$ [12,32,37]. These results also suggest that EP3, EP1 and/or FP receptors could be expressed and control the human coronary muscular tone. It is not excluded that $PGE_2$ could also act on EP2/EP4 receptor subtypes since one report has shown that $PGE_2$ stimulated large-conductance calcium-activated-$K^+$ channel ($BK_{Ca}$) activity in HCASMC via enhanced production of cyclic adenosine monophosphate (cAMP). This potassium channel activation leads to membrane repolarisation

[38]. However, the dominant effect of $PGE_2$ is the vasoconstriction in human coronary artery [12].

In addition to the direct *in vitro* effect of prostanoids on vascular tone, they could have synergistic effect with other vasoactive substances. For example, several studies have shown that endogenous $TxA_2$ could enhance vascular contractile responses to both 5-HT (5-hydroxytryptamine) and also 5-$HT_1$ like receptor agonist sumatriptan in the human isolated coronary artery [13,36,39]. This synergistic action of 5-HT and $TxA_2$ could easily occur and have implications in CAD, since both platelet-derived and locally produced $TxA_2$ by vascular wall could increase contraction responses induced by 5-HT [13].

### 3.2. Regulation of vascular tone by prostanoids in vivo

The effects of prostanoids on coronary hemodynamic parameters were studied either after intracoronary or systemic [oral or intravenous (iv)] administration of prostanoids or prostanoid synthase inhibitors. Administration of $PGI_2$ (iv infusion) in patients with CAD has resulted in a decrease of coronary vascular resistance [40–42]. A similar effect was obtained in patients with CAD after TxAS inhibitor (intracoronary administration) or nisoldipine (calcium channel blocker, oral administration), due to a decrease of $TxA_2$ levels in coronary sinus in both cases [43,44].

In patients without CAD, administration of COX inhibitors such as ibuprofen (oral), ketoprofen (iv) or aspirin (iv) did not induce any differences in coronary hemodynamics [45,46] (Table 1). However, when cold pressure tests (sympathetic stimulation) were applied to these patients, increased coronary blood flow and decreased coronary vascular resistance were observed. In addition, an increase of $PGI_2$ and $PGE_2$ productions was detected in blood samples obtained from the coronary sinus and the aorta. Administration of ketoprofen or aspirin after cold pressure test inhibited these prostanoid releases and caused an increase in coronary vascular resistance [46].

In humans with CAD, iv or oral administration of indomethacin decreased coronary blood flow or increased coronary vascular resistance, demonstrating a vasodilator role for prostanoids [47–51] (Table 1). This is in accordance with another study where aspirin was administered intracoronary and suggesting also that endogenous prostanoids strongly contributed to metabolic dilatation in patients with atherosclerosis or coronary risk factors [51]. On the other hand, one study has demonstrated that oral administration of aspirin did not modify coronary blood flow in patients with CAD despite the fact that $TxA_2$ levels were significantly decreased. However, $PGI_2$ metabolites were not measured in this study [52].

Overall, most of *in vivo* studies have demonstrated that COX inhibitors have no effect on basal coronary vascular tone in healthy patients. However, when the prostanoids release were increased either with cold pressure test [46] or as in patients with CAD [53–55], then in this condition, COX inhibitors especially indomethacin could increase vascular resistance and blood pressure in coronary vessels (Table 1). These results suggest that in CAD patients, the *in vivo* control of coronary vascular tone by $PGI_2$ is dominant in comparison to $TxA_2$.

### 3.3. Regulation of remodelling and angiogenesis by prostanoids in vitro

Prostanoids play notable roles in the development or progression of atherosclerosis especially in the coronary artery [4]. Vascular remodelling observed in atherosclerosis involves the changes in extracellular matrix (ECM) components such as collagen, elastin or fibronectin. These ECM components could be degraded by a family of zinc-dependent matrix metalloproteinase (MMP) endopeptidases. It has been shown that activation of the TP receptor by a selective agonist was responsible for the induction of procollagen I mRNA expression and proliferation of HCASMCs. These effects were blocked by a TP receptor antagonist or COX-1 inhibitor [11,56]. Furthermore, $PGE_2$ could directly increase mRNA and protein levels of MMP-10, which is responsible for ECM proteins and proteoglycans degradations in HCAEC [57].

Angiogenesis, the formation of new blood capillaries, is of crucial importance for the pathophysiology of several diseases, including myocardial ischemia to increase collateral blood flow. The growth of new vessels is strongly regulated by angiogenic factors. Vascular endothelial growth factor (VEGF) is one of the key regulators of angiogenesis and promotes most of the critical steps in this process

**Table 1**
Effects of COX inhibitors on human coronary hemodynamics.

| COX inhibitor | Patient characteristic | Technique | Results | Ref |
|---|---|---|---|---|
| Indomethacin, iv | CAD | Without any stimulation | CVR increased<br>CBF decreased | [47] |
| Indomethacin,oral | CAD | Same effects of indomethacin were observed in rest, atrial pacing or recovery period | CVR increased | [49] |
| Indomethacin, oral | CAD | Significant effect of indomethacin was observed after atrial pacing not in rest | CVR increased slightly CBF didn't change | [50] |
| Indomethacin, iv | CAD | Without any stimulation | CVR increased<br>CBF decreased<br>Inhibition of $TxB_2$ in CS | [48] |
| Aspirin, intracoronary | Atherosclerosis or coronary risk factors | More pronounced effects of aspirin were observed after ventricular pacing | CVR increased<br>CBF decreased | [51] |
| Aspirin, oral | CAD | Same effects of aspirin were observed in rest and coronary sinus pacing | CBF didn't change<br>Inhibition $TxB_2$ in CS | [52] |
| Aspirin, naproxen or ibuprofen, oral | CAD | Same effects of these drugs were observed in rest, atrial pacing or recovery period | CVR didn't change | [49] |
| Aspirin, ketoprofen, iv | Patients without CAD | Without any stimulation | CVR and CBF didn't change | [46] |
| Aspirin, ketoprofen, iv | Patients without CAD | CPT induced sympathetic stimulation | CVR increased<br>Inhibition of $PGE_2$ and 6-keto-$PGF_{1\alpha}$ | [46] |
| Ibuprofen, oral | Healthy man | Same effects of ibuprofen were observed in rest, during exercise or recovery period | CBF and CVR didn't change, inhibition of urinary excretion of PGI-M | [45] |

CPT: cold pressure test, CAD: coronary artery disease, CBF: coronary blood flow, CS: coronary sinus, CVR: coronary vascular resistance, iv: intravenous, PG: prostaglandin, PGI-M: Prostacyclin metabolite, $TxB_2$: thromboxane $B_2$.

[58]. The effects of prostanoids in angiogenesis regarding VEGF levels have been investigated in cultured HCASMC. Addition of PGE1 or ONO 1301 ($PGI_2$ receptor agonist and $TxA_2$ synthase inhibitor) to HCASMC resulted in a significant increase in VEGF production [59,60]. This pro-angiogenic effect of $PGI_2$ in HCASMC is paradoxical since it has been reported that $PGI_2$ analogues inhibited SMC proliferation in human aortic or pulmonary smooth muscle cells [61–63].

Prostanoids could be also involved in adhesion-migration process in HCAEC, since $PGE_2$ induced the expression of activated β1-integrin mainly via EP2 receptor activation [18]. The increased expression of β1-integrin is implicated in the vascular remodelling by promoting of migration and regulating matrix synthesis. On the other hand, TP agonists like $TxA_2$-mimetic (U46619) and isoprostanes (8-iso-$PGF_{2\alpha}$, 8-iso-$PGA_2$) could inhibit migration induced by VEGF as well as tube formation of HCAEC [64]. That is in coherence with previous study on HUVEC migration induced by VEGF, where activation of TPα and TPβ isoforms resulted in the anti-angiogenic effect [65].

Taken together, IP receptor agonists could be protective for CAD by promoting angiogenesis, while activation of TP receptor results in exacerbation of this disease by inhibiting angiogenesis and promoting SMC proliferation.

## 4. Prostanoids in coronary artery disease

Alterations of prostanoid productions and their synthase enzymes in CAD or related conditions are summarised in Table 2. *In vitro* expression of COX-2 has been detected in smooth muscle and endothelial cells of atherosclerotic human coronary artery [66,67]. In addition, during myocardial ischemia, COX-2 mRNA and protein expressions have increased while COX-1 and PGIS levels remain unchanged in human coronary arterioles [68]. Similar results have been obtained by *in vivo* studies showing that the excretion or plasma levels of 2,3-dinor-6-keto-$PGF_{1\alpha}$ (a major urinary $PGI_2$ metabolite), $TxB_2$ (stable metabolite of $TxA_2$) or $PGE_2$ were significantly higher in patients with severe atherosclerosis than in healthy volunteers [53–55]. However, one $PGI_2$ stimulating factor has been reported to be decreased *in vitro* in CASMC of patients with myocardial infarction but the effect of this factor on $PGI_2$ production was not investigated in these cells [69]. The expression of prostanoid receptors could be also modified in CAD. As an example of *in vitro* study, in acute myocardial infarction an increased number of $TxA_2$/$PGF_{2\alpha}$ receptors and a reduced number of $PGI_2$ receptors have been determined [70,71].

Both *in vitro* and *in vivo* studies showed that during CABG surgery, vasomotor dysfunction of human coronary artery has been observed after cardioplegia followed by reperfusion [72–74]. A decreased contractile response induced by $TxA_2$ mimetics has been reported in human coronary arterioles after cardioplegia/reperfusion *in vitro* [16]. However, during this period, no change in the TP receptor expression has been detected while $TxA_2$ release in coronary circulation and COX-2 expression in coronary artery have increased [16,68]. Increased $PGI_2$ release after induction of COX-2 expression might be involved in the decreased contractile response induced by $TxA_2$ mimetic after cardioplegia/reperfusion; however, it needs to be evaluated.

### 4.1. *In vivo* effect of aspirin and COX-2 inhibitors, clinical aspect on coronary artery diseases

CABG surgery involves the use of blood vessels [such as internal mammary artery (IMA), radial artery (RA) or saphenous vein (SV)] taken from another part of body to bypass narrowed or blocked

**Table 2**
Prostanoids in coronary artery disease or related conditions in humans.

| Preparation | Pathology | Prostanoids/enzyme | Results | Technique | Ref |
|---|---|---|---|---|---|
| Coronary artery | Atherosclerosis | TP receptor | + | AR | [71] |
| Epicardial coronary artery | Atherosclerosis | COX-2 | + | ICC | [66] |
| Coronary artery | Atherosclerosis | COX-2 | + | IF | [67] |
| Coronary artery | Stable angina | L-PGDS | + | IHC | [136] |
| Coronary atrial appendages | CP-Rep | COX-2<br>COX-1<br>PGIS | +<br>=<br>= | RT-PCR<br>WB | [68] |
| Coronary arterioles | CP-Rep | TP receptor<br>TxAS | =<br>= | IB, IF | [16] |
| HCASMC | MI | PSF | - | IS | [69] |
| Plasma | Atherosclerosis | $TxB_2$/6-keto $PGF_{1\alpha}$<br>$TxB_2$<br>$PGF_{2\alpha}$<br>$PGE_2$ | +<br>+<br>=<br>+ | RIA | [55] |
| Plasma | CPB | $TxB_2$<br>$PGE_2$<br>$PGI_2$ | +<br>+<br>+ | EIA | [137–140] |
| Serum | PTCA | L-PGDS | - | | [141] |
| Blood | Unstable angina | $TxB_2$<br>6-keto-$PGF_{1\alpha}$<br>$PGE_2$ | +<br>=<br>= | | [142] |
| Platelets | Angina pectoris | $TxA_2$ | + | RIA | [143] |
| Urines | Atherosclerosis | 2,3-dinor-6-keto-$PGF_{1\alpha}$ | + | | [53] |
| Urines | IHD | 11- dehydro $TxB_2$<br>2,3-dinor-6-keto-$PGF_{1\alpha}$ | =<br>+ | RIA | [144] |

'+' indicates increase, '-' indicates decrease, '=' indicates no change of relative prostanoids, prostanoid receptor or enzyme. AR: Autoradiography, COX: cyclooxygenase, CPB: Cardiopulmonary bypass, CP-Rep: Cardioplegia-reperfusion, HCASMC: human coronary artery smooth muscle cell, IB: Immunoblot, ICC: Immunocytochemistry, IF: Immunofluorescence, IHC: Immunohistochemistry, IHD: Ischemic heart disease, IS: Immunostaining, EIA: Enzyme immunoassay, L-PGDS: lipocalin type prostaglandin D synthase, MI: Myocardial infarction, PG: prostaglandin, PSF: prostacyclin stimulating factor, PTCA: Percutaneous transluminal coronary angioplasty, RIA: Radioimmunoassay, $TxA_2$: thromboxane $A_2$, WB: Western Blot.

coronary artery. In patients undergoing CABG surgery, graft patency is the most important indicator of the short and long-term success of the operation. The administration of aspirin in pre-operative or post-operative period has been shown to improve vein graft patency and decrease mortality or ischemic complications without increasing the risk of bleeding [6,75–78]. The meta-analysis studies have showed that 325 mg/day aspirin optimally improved vein graft survival and mortality and did not cause an increase in complications compared to lower doses [79]. On the other hand arterial grafts (IMA or RA), which have already higher patency rate, were not significantly affected by post-operative aspirin treatment [80–82]. Beneficial effect of aspirin mostly observed in venous grafts could be related with anti-thrombotic effect of aspirin by inhibiting the release of $TxA_2$, a potent mediator of platelet aggregation [83]. Although aspirin can also inhibit the synthesis of $PGI_2$ which has anti-thrombotic effect [84–90] more pronounced inhibition of $TxA_2$-M ($TxA_2$ metabolite) versus PGI-M in humans have been detected after low-dose aspirin [87,88,90].

Platelets are the major source of $TxA_2$, while $PGI_2$ is produced by endothelial and smooth muscle cells. After low-dose aspirin treatment, since there is no nucleus in platelet, once COX enzyme has been acetylated by aspirin in an irreversible way, platelets are unable to synthesize new COX mRNA. Thus, the formation of $TxA_2$ requires the synthesis of new platelets [91]. In contrast, nucleated cells such as endothelium or smooth muscle could recover COX activity after aspirin treatment by synthesizing new enzyme and production of $PGI_2$ could increase again [92]. These studies suggested that administration of aspirin after or before CABG surgery has beneficial effect by increasing $PGI_2/TxA_2$ ratio.

It is the reverse in treatments of rheumatoid arthritis with COX-2 inhibitors (COXIB) or NSAIDs by decreasing the $PGI_2/TxA_2$ ratio and promoting cardiovascular side effects. These inhibitors were found to decrease production of $PGI_2$, as measured by its urinary metabolite 2,3-dinor-6-keto $PGF_{1\alpha}$ in humans [93,94]. Inhibition of $PGI_2$ by COX-2 inhibitors, without the concomitant inhibition of COX-1 derived $TxA_2$ would induce myocardial infarction by obstructing coronary vessels [7,95]. In addition to selective COX-2 inhibitors, other NSAIDs such as diclofenac, indomethacin had moderately elevated cardiovascular risks [7].

Overall, the prostaglandins especially $PGI_2$ and $TxA_2$ seem to be key elements in the coronary physiology as clinically demonstrated by the beneficial effect of low dose of aspirin after CABG surgery or the detrimental effects of COX-2 inhibitors. This differential effect of aspirin and COX-2 inhibitors could be associated with their reverse effects on the $PGI_2/TxA_2$ ratio.

### 4.2. Sex hormones and coronary artery disease, link with prostanoids

Epidemiological data have demonstrated that the incidence of cardiovascular disease in women prior to menopause is lower than in men. Administration of estrogen (especially 17β-estradiol) closer to menopause is associated with a reduced incidence of CAD [96]. On the other side, low serum testosterone levels have been detected in men with CAD [97]. These beneficial effects of sex hormones might be related to their effects on regulation of coronary artery vascular tone by activation of their specific receptors in interaction with the prostanoids pathway [98–100].

*In vitro* studies described that estrogen receptor (ER)β is the predominant ER in human coronary arteries and suggested that increased ERβ expression may be associated with severe atherosclerosis and could be involved in compensatory mechanism [101]. On the other hand, activation of ERα (not ERβ) in HUVEC [102] and in mice aorta SMC increased $PGI_2$ production [103]. Similarly, HCAEC or HUVEC stimulated with 17β-estradiol increased $PGI_2$ production [104,105]. In accordance with these studies, in postmenopausal women, acute 17β−estradiol administration enhanced the endothelium-dependent vasodilation induced by acethylcholine which involved $PGI_2$ [106,107]. In addition, chronic administration of 17β-estradiol resulted in enhanced COX-1 and PGIS expressions in rats [108]. Moreover, 17β-estradiol augmented the expression of $PGI_2$ receptor gene (IP) in human endothelial cells [109]. This regulation of IP expression in response to estrogen occurred through “estrogen-ERα-estrogen response element” mechanism [110] and may provide an explanation, at least in part, for protective roles of estrogen against CAD [98,99]. However, depending on species studied, 17β-estradiol could have differential effects on prostanoid release in coronary artery [111–115]. Several *in vitro* studies have shown that 17β-estradiol could be also responsible for relaxation in coronary arteries derived from different female species while this effect was independent from COX pathway [116–118].

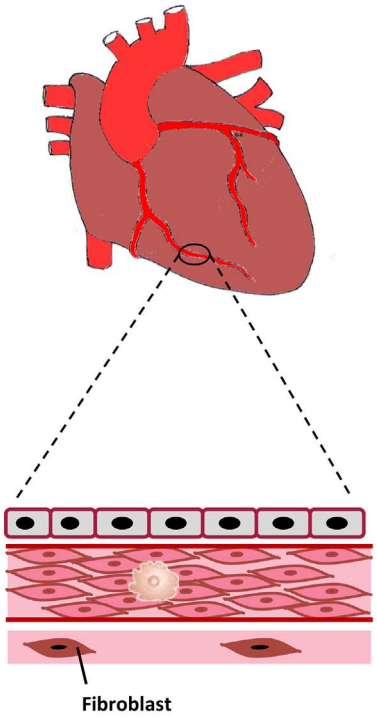
Testosterone like estrogen has *in vivo* or *in vitro* vasodilatory effects by inhibition of L-calcium channel and activation of potassium channel on several vascular beds including coronary artery derived from different species (rat, porcine, canine, sheep or rabbit) [115,119–125]. Similarly, *in vivo* studies, acute or chronic administration of male sex hormones testosterone has increased coronary artery diameter and flow [119,126]. The mechanism underlying the vasodilator effects of testosterone could be due to prostanoids since testosterone administration significantly decreased $TxA_2$ and increased $PGI_2$ levels in elderly men with coronary heart disease [100]. Supporting this idea, several studies have shown that dihydrotestosterone increased COX-2 expression *in vitro* in HCASMC and rat periovulatory granulosa cells [10,127]. In accordance with this study, testosterone increased vasodilatory response in diabetic rabbits versus control animals due to increased COX-2 derived $PGI_2$ synthesis [128]. In addition, dihydrotestosterone can upregulate $PGI_2$ receptor (IP) expression through androgen receptor dependent mechanism in human cells [129].

Taken together, vascular regulation of human coronary artery either *in vivo* or *in vitro* is strongly influenced by estrogen or testosterone. While several evidences have suggested that prostanoids especially $PGI_2$ is involved in cardioprotective effects of sex hormones, more studies performed in human coronary artery are needed to elucidate their specific contributions.

## 5. Conclusions

The mechanism underlying coronary artery diseases is dependent on the interactions between blood cells and coronary artery vascular wall. The roles of prostanoids on platelet aggregation/thrombosis and consequently their involvements in CAD are widely documented in literature. However, there is limited data concerning the effects of prostanoids on the coronary artery vascular wall and most of them were derived from animal studies. The studies performed in human coronary artery preparations focused on the effects of $PGI_2$ and $TxA_2$. They show that $PGI_2$ has beneficial effects by inducing vasodilatation and promoting angiogenesis while $TxA_2$ has reverse effects (Fig. 1). In contrast to other human vessels, there is few *in vitro* data in literature concerning roles of other prostanoids such as $PGE_2$, $PGD_2$ or $PGF_{2\alpha}$ in human coronary artery. However, recent studies have suggested that serum levels of L-PGDS (Lipocalin-type prostaglandin D synthase) could be a biomarker for severity of CAD [130–132]. In addition to L-PGDS, the studies performed in animals suggested that inhibition of EP3 receptor or mPGES-1 enzyme could represent promising therapeutic targets in the treatment of CAD [133].

While clinical studies with aspirin or COX-2 inhibitors have shown strong involvements of prostanoids in coronary artery physiology, more fundamental studies are needed to evaluate the exact effects and mechanisms of prostanoids on human coronary vasculature. Together with their effects on blood cells, interactions between perivascular adipose tissue surrounding coronary artery and vascular wall should be also evaluated since it has been shown that adipose tissue is a source of prostanoids in humans [134,135].




Membrane phospholipids

$PLA_2$

Arachidonic acid

COX-1 [8-11]

COX-2 [66]

$PGH_2$

PGIS | mPGES-1 | TxAS

| | $PGI_2$ | $PGE_2$ | $TxA_2$ |
|---|---|---|---|
| HCAEC | •PGIS and IP receptor [12] | •MMP-10 (+) [57]<br>•β-integrin (+) [18]<br>•EP1-4 receptor [15] | •VEGF (-) [64]<br>•Tube formation (-) [64]<br>•TxAS and TP receptor [12, 16, 17] |
| HCASMC | •VEGF (+) [60]<br>•Vasodilatation [12]<br>•PGIS and IP receptor [12] | •EP3 receptor [15] | •Proliferation (+) [56]<br>•Vasoconstriction [12]<br>•Procollagen-1 (+) [11]<br>•TxAS and TP receptor [12, 16, 17] |
| Macrophage | •PGIS expression [12] | | •TxAS expression [12] |
| Neutrophil | •Chemotaxis is induced by $PGF_{2\alpha}$ derived from HCAEC under hypoxia [24] | | |

**Fig. 1.** The effects of prostanoids in the physiology or pathophsiology of human coronary artery.'+' indicates an increase and '−' indicates a decrease induced by respective prostanoids. In red are indicated the data obtained in inflammatory or pathological conditions. COX: cyclooxygenase, $PLA_2$: phospholipase $A_2$, HCAEC: human coronary artery endothelial cells, HCASMC: human coronary artery smooth muscle cells, MMP: matrix metalloproteinase, PG: prostaglandin, $TxA_2$: thromboxane $A_2$, VEGF: vascular endothelial growth factor.

## References

[1] G.K. Hansson, Inflammation, atherosclerosis, and coronary artery disease, N. Engl. J. Med. 352 (16) (2005) 1685–1695.
[2] X. Norel, Prostanoid receptors in the human vascular wall, Sci. World J. 7 (2007) 1359–1374.
[3] N. Foudi, I. Gomez, C. Benyahia, D. Longrois, X. Norel, Prostaglandin E2 receptor subtypes in human blood and vascular cells, Eur. J. Pharmacol. 695 (1–3) (2012) 1–6.
[4] I. Gomez, N. Foudi, D. Longrois, X. Norel, The role of prostaglandin E2 in human vascular inflammation, Prostaglandins Leukot. Essent. Fatty Acids 89 (2–3) (2013) 55–63.
[5] B.B. Weksler, Prostanoids and NSAIDs in cardiovascular biology and disease, Curr. Atheroscler. Rep. 17 (7) (2015) 41.
[6] T.P. Gavaghan, V. Gebski, D.W. Baron, Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study, Circulation 83 (5) (1991) 1526–1533.
[7] P. McGettigan, D. Henry, Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries, PLoS Med. 10 (2) (2013) e1001388.
[8] Q. Jiao, Q. Ke, et al., Effect of inflammatory factor-induced cyclo-oxygenase expression on the development of reperfusion-related no-reflow phenomenon in acute myocardial infarction, Clin. Exp. Pharmacol. Physiol. 42 (2) (2015) 162–170.
[9] T. He, T. Lu, L.V. d'Uscio, C.F. Lam, H.C. Lee, Angiogenic function of prostacyclin biosynthesis in human endothelial progenitor cells, Circ. Res. 103 (1) (2008) 80–88.
[10] K.L. Osterlund, R.J. Handa, R.J. Gonzales, Dihydrotestosterone alters cyclooxygenase-2 levels in human coronary artery smooth muscle cells, Am. J. Physiol. Endocrinol. Metab. 298 (4) (2010) E838–E845.
[11] A. Virdis, R. Colucci, M.F. Neves, Resistance artery mechanics and composition in angiotensin II-infused mice: effects of cyclooxygenase-1 inhibition, Eur. Heart J. 33 (17) (2012) 2225–2234.
[12] M. Keitoku, M. Kohzuki, H. Katoh, FMLP actions and its binding sites in isolated human coronary arteries, J. Mol. Cell. Cardiol. 29 (3) (1997) 881–894.
[13] A. Maassen VanDenBrink, W.A. Bax, M.D. Ferrari, F.J. Zijlstra, E. Bos, P.R. Saxena, Augmented contraction of the human isolated coronary artery by sumatriptan: a possible role for endogenous thromboxane, Br. J. Pharmacol. 119 (5) (1996) 855–862.
[14] J. Martinez-Gonzalez, R. Rodriguez-Rodriguez, M. Gonzalez-Diez, Oleanolic acid induces prostacyclin release in human vascular smooth muscle cells through a cyclooxygenase-2-dependent mechanism, J. Nutr. 138 (3) (2008) 443–448.
[15] K.B. Chow, C.H. Cheng, H. Wise, Anti-inflammatory activity of ghrelin in human carotid artery cells, Inflammation 32 (6) (2009) 402–409.
[16] J. Feng, Y. Liu, L.M. Chu, Thromboxane-induced contractile response of human coronary arterioles is diminished after cardioplegic arrest, Ann. Thorac. Surg. 92 (3) (2011) 829–836.
[17] L. Zhang, M. Bastepe, H. Juppner, K.H. Ruan, Characterization of the molecular mechanisms of the coupling between intracellular loops of prostacyclin receptor with the C-terminal domain of the Galphas protein in human coronary artery smooth muscle cells, Arch. Biochem. Biophys. 454 (1) (2006) 80–88.
[18] M. Kajimoto, T. Ichiyama, Y. Ueno, M. Shiraishi, M. Hasegawa, S. Furukawa, Enhancement of activated beta1-integrin expression by prostaglandin E2 via EP receptors in isolated human coronary arterial endothelial cells: implication for the treatment of Kawasaki disease, Inflamm. Res. 58 (4) (2009) 224–228.
[19] V.V. Raveendran, X. Tan, M.E. Sweeney, Lipopolysaccharide induces H1 receptor expression and enhances histamine responsiveness in human coronary artery endothelial cells, Immunology 132 (4) (2011) 578–588.
[20] X. Tan, S. Essengue, J. Talreja, J. Reese, D.J. Stechschulte, K.N. Dileepan, Histamine directly and synergistically with lipopolysaccharide stimulates cyclooxygenase-2 expression and prostaglandin I(2) and E(2) production in human coronary artery endothelial cells, J. Immunol. 179 (11) (2007) 7899–7906.
[21] K. Lakota, K. Mrak-Poljsak, B. Rozman, S. Sodin-Semrl, Increased responsiveness of human coronary artery endothelial cells in inflammation and coagulation, Mediators. Inflamm. 2009 (2009) 146872.
[22] P. Rastogi, C.S. Beckett, J. McHowat, Prostaglandin production in human coronary artery endothelial cells is modulated differentially by selective phospholipase A(2) inhibitors, Prostaglandins. Leukot. Essent. Fatty Acids 76 (4) (2007) 205–212.
[23] B. Callaghan, J.B. Furness, Novel and conventional receptors for ghrelin, desacyl-ghrelin, and pharmacologically related compounds, Pharmacol. Rev. 66 (4) (2014) 984–1001.
[24] T. Arnould, R. Thibaut-Vercruyssen, N. Bouaziz, M. Dieu, J. Remacle, C. Michiels, PGF(2alpha), a prostanoid released by endothelial cells activated by hypoxia, is a chemoattractant candidate for neutrophil recruitment, Am. J. Pathol. 159 (1) (2001) 345–357.
[25] S.K. Venugopal, S. Devaraj, I. Jialal, C-reactive protein decreases prostacyclin release from human aortic endothelial cells, Circulation 108 (14) (2003) 1676–1678.
[26] T.W. Hein, E. Qamirani, Y. Ren, L. Kuo, C-reactive protein impairs coronary

arteriolar dilation to prostacyclin synthase activation: role of peroxynitrite, J. Mol. Cell. Cardiol. 47 (2) (2009) 196–202.
[27] T. Szerafin, N. Erdei, T. Fulop, Increased cyclooxygenase-2 expression and prostaglandin-mediated dilation in coronary arterioles of patients with diabetes mellitus, Circ. Res. 99 (5) (2006) e12–17.
[28] N. Foudi, L. Louedec, T. Cachina, C. Brink, X. Norel, Selective cyclooxygenase-2 inhibition directly increases human vascular reactivity to norepinephrine during acute inflammation, Cardiovasc. Res. 81 (2) (2009) 269–277.
[29] D. Bishop-Bailey, J.R. Pepper, E.B. Haddad, R. Newton, S.W. Larkin, J.A. Mitchell, Induction of cyclooxygenase-2 in human saphenous vein and internal mammary artery, Arterioscler. Thromb. Vasc. Biol. 17 (9) (1997) 1644–1648.
[30] H. Miura, R.E. Wachtel, F.R. Loberiza, Diabetes mellitus impairs vasodilation to hypoxia in human coronary arterioles: reduced activity of ATP-sensitive potassium channels, Circ. Res. 92 (2) (2003) 151–158.
[31] N. Toda, T. Matsumoto, K. Yoshida, Comparison of hypoxia-induced contraction in human, monkey, and dog coronary arteries, Am. J. Physiol. 262 (3) (1992) H678–683.
[32] S.M. Bode, M. Kuhn, U. Forstermann, Chemotactic peptide FMLP contracts human coronary arteries via cyclooxygenase products, Am. J. Physiol. 258 (3) (1990) H848–H853.
[33] N. Toda, Responses of human, monkey and dog coronary arteries in vitro to carbocyclic thromboxane A2 and vasodilators, Br. J. Pharmacol. 83 (2) (1984) 399–408.
[34] J.E. Merritt, A.M. Brown, S. Bund, Primate vascular responses to octimibate, a non-prostanoid agonist at the prostacyclin receptor, Br. J. Pharmacol. 102 (1) (1991) 260–266.
[35] E.H. Ohlstein, G.A. Kopia, R.L. Zeid, et al., Effects of the thromboxane receptor antagonist SK & F 88046 in the canine, monkey and human coronary vasculature, Prostaglandins 36 (1) (1988) 69–84.
[36] T.M. Cocks, B.K. Kemp, D. Pruneau, J.A. Angus, Comparison of contractile responses to 5-hydroxytryptamine and sumatriptan in human isolated coronary artery: synergy with the thromboxane A2-receptor agonist, U46619, Br. J. Pharmacol. 110 (1) (1993) 360–368.
[37] U. Forstermann, A. Mugge, S.M. Bode, J.C. Frolich, Response of human coronary arteries to aggregating platelets: importance of endothelium-derived relaxing factor and prostanoids, Circ. Res. 63 (2) (1988) 306–312.
[38] S. Zhu, G. Han, R.E. White, PGE2 action in human coronary artery smooth muscle: role of potassium channels and signaling cross-talk, J. Vasc. Res. 39 (6) (2002) 477–488.
[39] A.H. Chester, S.P. Allen, S. Tadjkarimi, M.H. Yacoub, Interaction between thromboxane A2 and 5-hydroxytryptamine receptor subtypes in human coronary arteries, Circulation 87 (3) (1993) 874–880.
[40] P. Ganz, J. Gaspar, W.S. Colucci, W.H. Barry, G.H. Mudge, R.W. Alexander, Effects of prostacyclin on coronary hemodynamics at rest and in response to cold pressor testing in patients with angina pectoris, Am. J. Cardiol. 53 (11) (1984) 1500–1504.
[41] N. Kieler-Jensen, I. Milocco, K. Kirno, E. Houltz, S.E. Ricksten, Effects of prostacyclin on myocardial hemodynamics and metabolism after coronary artery bypass grafting, J. Cardiothorac. Vasc. Anesth. 10 (6) (1996) 741–747.
[42] B.G. Firth, M.D. Winniford, W.B. Campbell, L.D. Hillis, Hemodynamic effects of intravenous prostacyclin in stable angina pectoris, Am. J. Cardiol. 52 (5) (1983) 439–443.
[43] A. Kurita, B. Takase, A. Uehata, Effects of a low, oral dose of nisoldipine on the systemic and coronary hemodynamics and the prostaglandin metabolism of ischemic heart disease patients, Jpn. Heart J. 31 (3) (1990) 287–297.
[44] S. Sueda, H. Kohno, K. Inoue, Intracoronary administration of a thromboxane A2 synthase inhibitor relieves acetylcholine-induced coronary spasm, Circ. J. 66 (9) (2002) 826–830.
[45] A. Edlund, A. Sollevi, A. Wennmalm, The role of adenosine and prostacyclin in coronary flow regulation in healthy man, Acta Physiol. Scand. 135 (1) (1989) 39–46.
[46] G.G. Neri Serneri, G.F. Gensini, R. Abbate, Physiologic role of coronary PGI2 and PGE2 in modulating coronary vascular response to sympathetic stimulation, Am. Heart. J. 119 (4) (1990) 848–854.
[47] P.L. Friedman, E.J. Brown, S. Gunther, Coronary vasoconstrictor effect of indomethacin in patients with coronary-artery disease, N. Engl. J. Med. 305 (20) (1981) 1171–1175.
[48] M.B. Forman, H. Uderman, E.K. Jackson, et al., Effects of indomethacin on systemic and coronary hemodynamics in patients with coronary artery disease, Am. Heart J. 110 (2) (1985) 311–318.
[49] A. Edlund, B. Berglund, D. van Dorne, Coronary flow regulation in patients with ischemic heart disease: release of purines and prostacyclin and the effect of inhibitors of prostaglandin formation, Circulation 71 (6) (1985) 1113–1120.
[50] I. Pacold, M.H. Hwang, C.E. Lawless, P. Diamond, P.J. Scanlon, H.S. Loeb, Effects of indomethacin on coronary hemodynamics, myocardial metabolism and anginal threshold in coronary artery disease, Am. J. Cardiol. 57 (11) (1986) 912–915.
[51] S.J. Duffy, S.F. Castle, R.W. Harper, I.T. Meredith, Contribution of vasodilator prostanoids and nitric oxide to resting flow, metabolic vasodilation, and flow-mediated dilation in human coronary circulation, Circulation 100 (19) (1999) 1951–1957.
[52] J.L. Martin, C.A. Fisher, W.J. Untereker, Effect of high dose aspirin on coronary hemodynamics during pacing-induced myocardial ischemia, J. Am. Coll. Cardiol. 5 (2) (1985) 210–215.
[53] G.A. FitzGerald, B. Smith, A.K. Pedersen, A.R. Brash, Increased prostacyclin biosynthesis in patients with severe atherosclerosis and platelet activation, N. Engl. J. Med. 310 (17) (1984) 1065–1068.
[54] O. Belton, D. Byrne, D. Kearney, A. Leahy, D.J. Fitzgerald, Cyclooxygenase-1 and −2-dependent prostacyclin formation in patients with atherosclerosis, Circulation 102 (8) (2000) 840–845.
[55] R. Jouve, P.H. Rolland, C. Delboy, C. Mercier, Thromboxane B2, 6-keto-PGF1 alpha, PGE2, PGF2 alpha, and PGA1 plasma levels in arteriosclerosis obliterans: relationship to clinical manifestations, risk factors, and arterial pathoanatomy, Am. Heart J. 107 (1) (1984) 45–52.
[56] M.H. Petri, C. Tellier, C. Michiels, I. Ellertsen, J.M. Dogne, M. Back, Effects of the dual TP receptor antagonist and thromboxane synthase inhibitor EV-077 on human endothelial and vascular smooth muscle cells, Biochem. Biophys. Res. Commun. 441 (2) (2013) 393–398.
[57] Y. Zhao, S. Zhou, C.K. Heng, Celecoxib inhibits serum amyloid a-induced matrix metalloproteinase-10 expression in human endothelial cells, J. Vasc. Res. 46 (1) (2009) 64–72.
[58] P. Carmeliet, Angiogenesis in life, disease and medicine, Nature 438 (7070) (2005) 932–936.
[59] K. Ishimaru, S. Miyagawa, S. Fukushima, Synthetic prostacyclin agonist, ONO1301, enhances endogenous myocardial repair in a hamster model of dilated cardiomyopathy: a promising regenerative therapy for the failing heart, J. Thorac. Cardiovasc. Surg. 146 (6) (2013) 1516–1525.
[60] M.R. Mehrabi, N. Serbecic, F. Tamaddon, Clinical and experimental evidence of prostaglandin E1-induced angiogenesis in the myocardium of patients with ischemic heart disease, Cardiovasc. Res. 56 (2) (2002) 214–224.
[61] E. Falcetti, S.M. Hall, P.G. Phillips, Smooth muscle proliferation and role of the prostacyclin (IP) receptor in idiopathic pulmonary arterial hypertension, Am. J. Respir. Crit. Care. Med. 182 (9) (2010) 1161–1170.
[62] Y. Asada, A. Kisanuki, K. Hatakeyama, Inhibitory effects of prostacyclin analogue, TFC-132, on aortic neointimal thickening in vivo and smooth muscle cell proliferation in vitro, Prostaglandins Leukot. Essent. Fatty. Acids 51 (4) (1994) 245–248.
[63] C. Bulin, U. Albrecht, J.G. Bode, Differential effects of vasodilatory prostaglandins on focal adhesions, cytoskeletal architecture, and migration in human aortic smooth muscle cells, Arterioscler. Thromb. Vasc. Biol. 25 (1) (2005) 84–89.
[64] R.A. Benndorf, E. Schwedhelm, A. Gnann, Isoprostanes inhibit vascular endothelial growth factor-induced endothelial cell migration, tube formation, and cardiac vessel sprouting in vitro, as well as angiogenesis in vivo via activation of the thromboxane A(2) receptor: a potential link between oxidative stress and impaired angiogenesis, Circ. Res. 103 (9) (2008) 1037–1046.
[65] A.W. Ashton, J.A. Ware, Thromboxane A2 receptor signaling inhibits vascular endothelial growth factor-induced endothelial cell differentiation and migration, Circ. Res. 95 (4) (2004) 372–379.
[66] C.S. Baker, R.J. Hall, T.J. Evans, Cyclooxygenase-2 is widely expressed in atherosclerotic lesions affecting native and transplanted human coronary arteries and colocalizes with inducible nitric oxide synthase and nitrotyrosine particularly in macrophages, Arterioscler. Thromb. Vasc. Biol. 19 (3) (1999) 646–655.
[67] B.R. Cho, M.K. Kim, D.H. Suh, Increased tissue transglutaminase expression in human atherosclerotic coronary arteries, Coron. Artery. Dis. 19 (7) (2008) 459–468.
[68] C. Metais, J. Li, M. Simons, F.W. Sellke, Serotonin-induced coronary contraction increases after blood cardioplegia-reperfusion: role of COX-2 expression, Circulation 100 (19) (1999) II328–II334.
[69] N. Sekiguchi, F. Umeda, M. Masakado, Y. Ono, T. Hashimoto, H. Nawata, Immunohistochemical study of prostacyclin-stimulating factor (PSF) in the diabetic and atherosclerotic human coronary artery, Diabetes 46 (10) (1997) 1627–1632.
[70] K. Schror, The effect of prostaglandins and thromboxane A2 on coronary vessel tone–mechanisms of action and therapeutic implications, Eur. Heart J. 14 (1993) 34–41.
[71] S.D. Katugampola, A.P. Davenport, Thromboxane receptor density is increased in human cardiovascular disease with evidence for inhibition at therapeutic concentrations by the AT(1) receptor antagonist losartan, (2001), Br. J. Pharmacol. 134 (7) (2001) 1385–1392.
[72] M. Ruel, T.A. Khan, P. Voisine, C. Bianchi, F.W. Sellke, Vasomotor dysfunction after cardiac surgery, Eur. J. Cardiothorac. Surg. 26 (5) (2004) 1002–1014.
[73] J. Feng, Y. Liu, R.T. Clements, Calcium-activated potassium channels contribute to human coronary microvascular dysfunction after cardioplegic arrest, Circulation 118 (14) (2008) S46–51.
[74] J. Feng, Y. Liu, K.R. Khabbaz, Endothelin-1-induced contractile responses of human coronary arterioles via endothelin-A receptors and PKC-alpha signaling pathways, Surgery 147 (6) (2010) 798–804.
[75] S.M. Nouraei, A. Gholipour Baradari, A. Emami Zeydi, Does early post-operative administration of aspirin influence the risk of bleeding after Coronary artery bypass graft surgery? A prospective observational study, Med. Arch. 69 (6) (2015) 381–383.
[76] S.S. Aboul-Hassan, T. Stankowski, J. Marczak, R. Cichon, What is the impact of preoperative aspirin administration on patients undergoing coronary artery bypass grafting, Interact. Cardiovasc. Thorac. Surg. 24 (2) (2016) 280–285.
[77] L.D. Hillis, P.K. Smith, J.L. Anderson, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J. Thorac. Cardiovasc. Surg. 143 (1) (2012) 4–34.
[78] H. Wu, J. Wang, H. Sun, Preoperative continuation of aspirin therapy may improve perioperative saphenous venous graft patency after off-pump coronary artery bypass grafting, Ann. Thorac. Surg. 99 (2) (2015) 576–580.
[79] J. Dunning, S. Das, What is the optimal dose of aspirin after discharge following coronary bypass surgery, Interact. Cardiovasc. Thorac. Surg. 2 (4) (2003)

427–430.
[80] P. Achouh, R. Boutekadjirt, D. Toledano, Long-term (5- to 20-year) patency of the radial artery for coronary bypass grafting, J. Thorac. Cardiovasc. Surg. 140 (1) (2010) 73–79.
[81] N. Zimmermann, E. Gams, T. Hohlfeld, Aspirin in coronary artery bypass surgery: new aspects of and alternatives for an old antithrombotic agent, Eur. J. Cardiothorac. Surg. 34 (1) (2008) 93–108.
[82] S. Goldman, J. Copeland, T. Moritz, Internal mammary artery and saphenous vein graft patency. Effects of aspirin, Circulation 82 (5) (1990) IV237–242.
[83] K. Berg, M. Langaas, M. Ericsson, Acetylsalicylic acid treatment until surgery reduces oxidative stress and inflammation in patients undergoing coronary artery bypass grafting, Eur. J. Cardiothorac. Surg. 43 (6) (2013) 1154–1163.
[84] E. Tuleja, F. Mejza, A. Cmiel, A. Szczeklik, Effects of cyclooxygenases inhibitors on vasoactive prostanoids and thrombin generation at the site of microvascular injury in healthy men, Arterioscler. Thromb. Vasc. Biol. 23 (6) (2003) 1111–1115.
[85] P.A. Kyrle, H.G. Eichler, U. Jager, K. Lechner, Inhibition of prostacyclin and thromboxane A2 generation by low-dose aspirin at the site of plug formation in man in vivo, Circulation 75 (5) (1987) 1025–1029.
[86] J.M. Gerrard, S. Taback, S. Singhroy, In vivo measurement of thromboxane B2 and 6-keto-prostaglandin F1 alpha in humans in response to a standardized vascular injury and the influence of aspirin, Circulation 79 (1) (1989) 29–38.
[87] G.A. Braden, H.R. Knapp, G.A. FitzGerald, Suppression of eicosanoid biosynthesis during coronary angioplasty by fish oil and aspirin, Circulation 84 (2) (1991) 679–685.
[88] G.A. FitzGerald, J.A. Oates, J. Hawiger, Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man, J. Clin. Invest. 71 (3) (1983) 676–688.
[89] R.H. Boger, S.M. Bode-Boger, P. Kramme, D. Tsikas, F.M. Gutzki, J.C. Frolich, Effect of captopril on prostacyclin and nitric oxide formation in healthy human subjects: interaction with low dose acetylsalicylic acid, Br. J. Clin. Pharmacol. 42 (6) (1996) 721–727.
[90] S.M. Bode-Boger, R.H. Boger, M. Schubert, J.C. Frolich, Effects of very low dose and enteric-coated acetylsalicylic acid on prostacyclin and thromboxane formation and on bleeding time in healthy subjects, Eur. J. Clin. Pharmacol. 54 (9–10) (1998) 707–714.
[91] F. Catella-Lawson, M.P. Reilly, S.C. Kapoor, Cyclooxygenase inhibitors and the antiplatelet effects of aspirin, N. Engl. J. Med. 345 (25) (2001) 1809–1817.
[92] G.J. Roth, D.C. Calverley, Aspirin, platelets, and thrombosis: theory and practice, Blood 83 (4) (1994) 885–898.
[93] B.F. McAdam, F. Catella-Lawson, I.A. Mardini, S. Kapoor, J.A. Lawson, G.A. FitzGerald, Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2, Proc. Natl. Acad. Sci. U. S. A. 96 (1) (1999) 272–277.
[94] F. Catella-Lawson, B. McAdam, B.W. Morrison, Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids, J. Pharmacol. Exp. Ther. 289 (2) (1999) 735–741.
[95] Y. Yu, E. Ricciotti, R. Scalia, et al., Vascular COX-2 modulates blood pressure and thrombosis in mice, Sci. Transl. Med. 4 (132) (2012) 132ra54.
[96] F. Lenfant, F. Tremollieres, P. Gourdy, J.F. Arnal, Timing of the vascular actions of estrogens in experimental and human studies: why protective early, and not when delayed, Maturitas 68 (2) (2011) 165–173.
[97] T.H. Jones, Testosterone deficiency: a risk factor for cardiovascular disease, Trends. Endocrinol. Metab. 21 (8) (2010) 496–503.
[98] O.M. Reslan, R.A. Khalil, Vascular effects of estrogenic menopausal hormone therapy, Rev. Recent. Clin. Trials. 7 (1) (2012) 47–70.
[99] H. Seeger, A.O. Muec, Effects of dydrogesterone on the vascular system, Gynecol. Endocrinol. 23 (1) (2007) 2–8.
[100] S. Wu, X. Weng, Regulation of atrial natriuretic peptide, thromboxane and prostaglandin production by androgen in elderly men with coronary heart disease, Chin. Med. Sci. J. 8 (4) (1993) 207–209.
[101] R.C. Christian, P.Y. Liu, S. Harrington, M. Ruan, V.M. Miller, L.A. Fitzpatrick, Intimal estrogen receptor (ER)beta, but not ERalpha expression, is correlated with coronary calcification and atherosclerosis in pre- and postmenopausal women, J. Clin. Endocrinol. Metab. 91 (7) (2006) 2713–2720.
[102] A. Sobrino, P.J. Oviedo, S. Novella, Estradiol selectively stimulates endothelial prostacyclin production through estrogen receptor-{alpha}, J. Mol. Endocrinol. 44 (4) (2010) 237–246.
[103] K.M. Egan, J.A. Lawson, S. Fries, COX-2-derived prostacyclin confers atheroprotection on female mice, Science 306 (5703) (2004) 1954–1957.
[104] A.O. Mueck, H. Seeger, D. Wallwiener, Medroxyprogesterone acetate versus norethisterone: effect on estradiol-induced changes of markers for endothelial function and atherosclerotic plaque characteristics in human female coronary endothelial cell cultures, Menopause 9 (4) (2002) 273–281.
[105] P. Akarasereenont, K. Techatraisak, A. Thaworn, S. Chotewuttakorn, The induction of cyclooxygenase-2 by 17beta-estradiol in endothelial cells is mediated through protein kinase C, Inflamm. Res. 49 (9) (2000) 460–465.
[106] A.C. Calkin, K. Sudhir, S. Honisett, M.R. Williams, T. Dawood, P.A. Komesaroff, Rapid potentiation of endothelium-dependent vasodilation by estradiol in postmenopausal women is mediated via cyclooxygenase 2, J. Clin. Endocrinol. Metab. 87 (11) (2002) 5072–5075.
[107] R.C. Tostes, D. Nigro, Z.B. Fortes, M.H. Carvalho, Effects of estrogen on the vascular system, Braz. J. Med. Biol. Res. 36 (9) (2003) 1143–1158.
[108] J.A. Ospina, D.N. Krause, S.P. Duckles, 17beta-estradiol increases rat cerebrovascular prostacyclin synthesis by elevating cyclooxygenase-1 and prostacyclin synthase, Stroke 33 (2) (2002) 600–605.
[109] E.C. Turner, B.T. Kinsella, Estrogen increases expression of the human prostacyclin receptor within the vasculature through an ERalpha-dependent mechanism, J. Mol. Biol. 396 (3) (2010) 473–486.
[110] H.M. Reid, B.T. Kinsella, Prostacyclin receptors: transcriptional regulation and novel signalling mechanisms, Prostaglandins Other Lipid. Mediat. 121 (2015) 70–82.
[111] C. Seillan, C. Ody, F. Russo-Marie, D. Duval, Differential effects of sex steroids on prostaglandin secretion by male and female cultured piglet endothelial cells, Prostaglandins 26 (1) (1983) 3–12.
[112] A. Kano, Effects of 17 beta-estradiol on the responses to vasoactivators and electrical transmural stimulation in isolated dog arteries, Nihon. Hoigaku. Zasshi. 43 (5) (1989) 407–415.
[113] R.E. White, G. Han, C. Dimitropoulou, Estrogen-induced contraction of coronary arteries is mediated by superoxide generated in vascular smooth muscle, Am. J. Physiol. Heart. Circ. Physiol. 289 (4) (2005) H1468–1475.
[114] H. Teoh, A. Quan, R.Y. Man, Acute impairment of relaxation by low levels of testosterone in porcine coronary arteries, Cardiovasc. Res. 45 (4) (2000) 1010–1018.
[115] H. Teoh, A. Quan, S.W. Leung, R.Y. Man, Differential effects of 17beta-estradiol and testosterone on the contractile responses of porcine coronary arteries, Br. J. Pharmacol. 129 (7) (2000) 1301–1308.
[116] A.H. Chester, C. Jiang, J.A. Borland, M.H. Yacoub, P. Collins, Oestrogen relaxes human epicardial coronary arteries through non-endothelium-dependent mechanisms, Coron. Artery. Dis. 6 (5) (1995) 417–422.
[117] J.D. Kalenic, R.J. Ramirez, S. Einzig, W.A. Neal, H.A. Omar, Estrogen-induced relaxation in bovine coronary arteries in vitro: evidence for a new mechanism, W. V. Med. J. 96 (6) (2000) 617–621.
[118] D. Otter, C. Austin, Effects of 17beta-oestradiol on rat isolated coronary and mesenteric artery tone: involvement of nitric oxide, J. Pharm. Pharmacol. 50 (5) (1998) 531–538.
[119] D.M. Kelly, T.H. Jones, Testosterone: a vascular hormone in health and disease, J. Endocrinol. 217 (3) (2013) 47–71.
[120] K.M. English, R.D. Jones, T.H. Jones, A.H. Morice, K.S. Channer, Testosterone acts as a coronary vasodilator by a calcium antagonistic action, J. Endocrinol. Invest. 25 (5) (2002) 455–458.
[121] K.M. English, R.D. Jones, T.H. Jones, A.H. Morice, K.S. Channer, Aging reduces the responsiveness of coronary arteries from male Wistar rats to the vasodilatory action of testosterone, Clin. Sci. (Lond.) 99 (1) (2000) 77–82.
[122] T.M. Chou, K. Sudhir, S.J. Hutchison, Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo, Circulation 94 (10) (1996) 2614–2619.
[123] E. Yildirim, K. Erol, The effects of testosterone on isolated sheep coronary artery, Anadolu. Kardiyol. Derg. 11 (4) (2011) 343–350.
[124] P. Yue, K. Chatterjee, C. Beale, P.A. Poole-Wilson, P. Collins, Testosterone relaxes rabbit coronary arteries and aorta, Circulation 91 (4) (1995) 1154–1160.
[125] R.D. Jones, T. Hugh Jones, K.S. Channer, The influence of testosterone upon vascular reactivity, Eur. J. Endocrinol. 151 (1) (2004) 29–37.
[126] C.M. Webb, J.G. McNeill, C.S. Hayward, D. de Zeigler, P. Collins, Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease, Circulation 100 (16) (1999) 1690–1696.
[127] T. Yazawa, S. Kawabe, M. Kanno, Androgen/androgen receptor pathway regulates expression of the genes for cyclooxygenase-2 and amphiregulin in periovulatory granulosa cells, Mol. Cell. Endocrinol. 369 (1–2) (2013) 42–51.
[128] V.G. Marrachelli, F.J. Miranda, J.M. Centeno, Role of NO-synthases and cyclooxygenases in the hyperreactivity of male rabbit carotid artery to testosterone under experimental diabetes, Pharmacol. Res. 61 (1) (2010) 62–70.
[129] S.B. Eivers, B.T. Kinsella, Regulated expression of the prostacyclin receptor (IP) gene by androgens within the vasculature: combined role for androgens and serum cholesterol, Biochim. Biophys. Acta 1859 (10) (2016) 1333–1351.
[130] T. Inoue, Y. Eguchi, T. Matsumoto, Lipocalin-type prostaglandin D synthase is a powerful biomarker for severity of stable coronary artery disease, Atherosclerosis 201 (2) (2008) 385–391.
[131] T. Osanai, K. Okumura, Lipocalin-type PGD synthase as a novel biomarker for coronary vasospasm, Circ. J. 75 (4) (2011) 784–785.
[132] T. Matsumoto, Y. Eguchi, H. Oda, Lipocalin-type prostaglandin D synthase is associated with coronary vasospasm and vasomotor reactivity in response to acetylcholine, Circ. J. 75 (4) (2011) 897–904.
[133] G. Yang, L. Chen, An update of microsomal prostaglandin E synthase-1 and PGE2 receptors in cardiovascular health and diseases, Oxid. Med. Cell. Longev. 2016 (2016) 5249086.
[134] G. Ozen, G. Topal, I. Gomez, Control of human vascular tone by prostanoids derived from perivascular adipose tissue, Prostaglandins Other Lipid. Mediat. 107 (2013) 13–17.
[135] G. Ozen, A. Daci, X. Norel, G. Topal, Human perivascular adipose tissue dysfunction as a cause of vascular disease: focus on vascular tone and wall remodeling, Eur. J. Pharmacol. 766 (2015) 16–24.
[136] Y. Eguchi, N. Eguchi, H. Oda, Expression of lipocalin-type prostaglandin D synthase (beta-trace) in human heart and its accumulation in the coronary circulation of angina patients, Proc. Natl. Acad. Sci. U. S. A. 94 (26) (1997) 14689–14694.
[137] E. Erez, A. Erman, E. Snir, Thromboxane production in human lung during cardiopulmonary bypass: beneficial effect of aspirin, Ann. Thorac. Surg. 65 (1) (1998) 101–106.
[138] G.C. Davies, M. Sobel, E.W. Salzman, Elevated plasma fibrinopeptide A and thromboxane B2 levels during cardiopulmonary bypass, Circulation 61 (4) (1980) 808–814.
[139] M.E. Faymonville, G. Deby-Dupont, R. Larbuisson, Prostaglandin E2, prostacyclin,

and thromboxane changes during nonpulsatile cardiopulmonary bypass in humans, J. Thorac. Cardiovasc. Surg. 91 (6) (1986) 858–866.
[140] W.D. Watkins, M.B. Peterson, D.L. Kong, Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow, J. Thorac. Cardiovasc. Surg. 84 (2) (1982) 250–256.
[141] T. Inoue, K. Takayanagi, S. Morooka, Serum prostaglandin D synthase level after coronary angioplasty may predict occurrence of restenosis, Thromb. Haemost. 85 (1) (2001) 165–170.
[142] P.D. Hirsh, L.D. Hillis, W.B. Campbell, B.G. Firth, J.T. Willerson, Release of prostaglandins and thromboxane into the coronary circulation in patients with ischemic heart disease, N. Engl. J. Med. 304 (12) (1981) 685–691.
[143] D. Prisco, P.G. Rogasi, M. Matucci, R. Abbate, G.F. Gensini, G.G. Serneri, Increased thromboxane A2 generation and altered membrane fatty acid composition in platelets from patients with active angina pectoris, Thromb. Res. 44 (1) (1986) 101–112.
[144] F. Santilli, G. Davi, S. Basili, Thromboxane and prostacyclin biosynthesis in heart failure of ischemic origin: effects of disease severity and aspirin treatment, J. Thromb. Haemost. 8 (5) (2010) 914–922.