Aging-Shifted Prostaglandin Profile in Endothelium as a Factor in Cardiovascular Disorders

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1. Introduction

Cardiovascular disorders, including atherosclerosis, coronary artery disease, heart failure, and hypertension, remain the leading cause of death worldwide [1]. These diseases are among several pathological conditions that are associated with aging [2–4], and age is a primary risk factor for their development [5, 6]. Endothelium is a thin layer of epithelial cells which line the interior of lymph and blood vessels and is a major component of the vascular wall. One important contributor to the development of cardiovascular diseases is a dysfunctional endothelium. Endothelial dysfunction is considered a fair predictor of cardiovascular diseases [4, 7–11].

Furchgott and Zawadzki unequivocally demonstrated that the endothelium is required for normal vessel relaxation [12]. Besides inducing relaxation, normal and healthy endothelium regulates vessel wall permeability, blood flow, vascular tone, and structure and exerts anticoagulant and fibrinolytic properties [13]. Aging adversely affects these normal functions of the endothelium, enhancing vasospasm and thrombosis, leading to eventual cardiovascular diseases [4, 14–16]. Age-impaired vascular relaxation has been shown in different human vascular beds including brachial artery, aorta, coronary artery, carotid, and mesenteric microvessels [14–21]. In line with these reports, additional evidence has been obtained in different vascular beds of animals including dogs [2, 22], rats [2, 23–32], and mice [33, 34]. This reduced relaxation is accompanied with increased blood pressure [35–39]. Elevated blood pressure is an important cardiovascular risk factor that can eventually lead to heart failure.

Normal endothelial function is regulated by a controlled balance between endothelium-dependent relaxing factors and endothelium-dependent contracting factors. The main vasoactive factors released by endothelial cells are nitric oxide (NO) and cyclooxygenase- (COX-) derived eicosanoids [4, 40, 41]. NO production has been shown to be reduced with aging [42–45]. There is less information on how eicosanoids change in the endothelium with age. It is also not well understood how changes in eicosanoid profile might contribute to endothelium dysfunction. Nevertheless, accumulating evidence indicates that the age-related changes in endothelial eicosanoids contribute to endothelium dysfunction and to the development of age-associated cardiovascular diseases.

In endothelium, there are six primary cyclooxygenase-(COX-) derived eicosanoids, prostaglandin H2 (PGH2), prostaglandin I2 (PGI2, prostacyclin), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α), prostaglandin D2 (PGD2), and thromboxane A2 (TxA2) (Figure 1). These eicosanoids are local hormones that are synthesized by virtually all mammalian tissues [46] and act at or near their
sites of synthesis in both autocrine and paracrine fashion. They trigger a vast array of biological signals, among which are vasodilation, vasoconstriction, and platelet aggregation [47–49]. In fact, the eicosanoids were the first identified endothelium-derived vasoactive factors [50, 51]. Although there is conflicting evidence [52–54], the majority of the literature shows that PGI2 and PGD2 are vasodilators [55–59], whereas PGH2, PGF2α, and TxA2 are vasoconstrictors and/or platelet aggregation inducers [53, 54, 60–66]. PGE2 can induce vasodilation [47, 67–70] or vasoconstriction [53, 54, 71–73], depending on the vascular bed and concentration [74, 75]. In healthy endothelium, these vasodilators and vasoconstrictors, coexisting with other vasoactive factors, are held in balance to maintain normal vascular functions. The aging process shifts this balanced profile toward a proconstrictive mediator profile [76, 77]. In this paper, we summarize and discuss how endothelium-derived eicosanoid profile changes with age and how those changes might contribute to age-associated endothelial dysfunction.

There is limited data on how eicosanoids change in humans [4], and most experiments have been conducted in animal models and most commonly in rat [2]. Rats of 1.5–2 months or less are considered immature, rats of 3–6 months are considered young adult, and rats of approximately 24 months or more are considered aged, though there are differences between strains [2].

2. Cyclooxygenases and PGH2

There are two isoforms of the cyclooxygenases (COX1 and COX2) encoded by two different genes. Both COX1 and COX2 are expressed in the endothelial and vascular smooth muscle cells, and the expression levels are 20-fold higher in endothelial cells than in smooth muscle cells [78]. In endothelium, both of the COX enzymes are constitutively expressed [79, 80]. However, they are also inducible, for instance, by shear stress [79–81]. Endothelial cells express COX1 preferentially over COX2 [82, 83].

In human mesenteric microvessels of individuals greater than 80 years of age, COX1 levels are 50% increased, while COX2 levels are slightly decreased [21]. In normotensive rats, both COX1 and COX2, in either whole vascular tissue or endothelial cells from vasculatures, are increased with aging from 1-fold to 5-fold [29, 42, 63, 84–86]. Comparable effects of aging on COX1 and COX2 expression levels have been observed in mice [33, 34]. At similar ages, COX1 or COX2 measurement, measured at the mRNA or protein levels, is almost doubled in the aorta of spontaneous hypertensive rats (SHRs) as compared to normotensive control Wistar-Kyoto (WKY) rats [63, 84, 87, 88]. Similar increases in COX1 and COX2 were observed in Nω-nitro-L-arginine methyl ester (L-NAME-) induced hypertensive rats as compared to control Sprague-Dawley rats [89]. Increased COX2 was also reported in the renal artery of hypertensive patients [89]. These data indicate that there are age-associated increases in COX1 and COX2 levels, as well as an association between elevated COX1/COX2 levels, in both animal models and human studies, and clinical cardiovascular disorders.

Upon stimulation, arachidonic acid (AA) is released from the cell membrane to the cytosol where it is enzymatically converted to PGH2 by COX1 and COX2. Subsequently, PGH2 is transformed to PGI2, PGE2, PGD2, PGF2α, and TxA2. These substances, as well as untransformed PGH2, are released out of endothelial cells and into the circulation, where they interact with their receptors localized on the smooth muscle cell surface and trigger vasoactive signals.

2.2 COX1 and COX2 expression in aging

The expression of COX1 and COX2 is increased with aging, measured at the mRNA or protein levels, is almost doubled in the aorta of spontaneous hypertensive rats (SHRs) as compared to normotensive control Wistar-Kyoto (WKY) rats [63, 84, 87, 88]. Similar increases in COX1 and COX2 were observed in Nω-nitro-L-arginine methyl ester (L-NAME-) induced hypertensive rats as compared to control Sprague-Dawley rats [89]. Increased COX2 was also reported in the renal artery of hypertensive patients [89]. These data indicate that there are age-associated increases in COX1 and COX2 levels, as well as an association between elevated COX1/COX2 levels, in both animal models and human studies, and clinical cardiovascular disorders.
COX2 are the upstream contributors of PGI2 synthesis [80, 102–104]. PGI2 is synthesized by its terminal specific PGI2 synthase (PGIS) [105, Figure 1]. PGIS colocalizes with COX1 in endothelial cells [106]. In endothelium, PGIS is by far the most abundant PG terminal synthase, with its expression level 5–100-fold higher than the other PG terminal synthases [54, 64, 65, 84]. Accordingly, PGI2 is the most abundant endothelial eicosanoid, with expression levels 10–100-fold higher than that of the other eicosanoids in humans [107, 108] and in animals [54, 97, 109, 110].

PGI2 triggers potent vasodilation [51, 57] by interacting with the PGI2 receptor (IP) (Figure 1), which located in smooth muscle cells [108, 111]. The vasodilation effect of PGI2 has also been shown in pig coronary arteries at low concentrations [58]. At higher concentrations PGI2 may induce vasoconstriction [32, 54, 64]. PGI2 cannot cause vasoconstriction until its concentration reached 1 μM or higher. 1 μM is 1000-fold higher than the endogenous concentration of PGI2, which is in the 0.2–1 nM range [112]. Even at elevated concentrations, PGI2 is a weak vasoconstrictor and induces modest tension in the rat aorta [32, 54, 64]. Modest vasoconstrictive effects of PGI2 may emanate from weak cross-activation of TP, which can induce vasoconstriction [49]. At lower concentrations, PGI2, especially endogenous PGI2, is a vasodilator. In addition, PGI2 is the most potent endogenous anticoagulant agent [113]. The vasodilation and anticoagulation effects of PGI2 have been confirmed by a recent report showing that IP deletion in mice results in hypertension and reduced anticoagulation activity [114].

In human blood, PGI2, measured as PGA12, is 400 pg/mL in new born infants, 230 pg/mL in infants, 150 pg/mL in adolescents, and 85 pg/mL in adults [112]. Age-associated PGI2 decline is also observed in urine of humans [115, 116]. The endothelium is the main site for PGI2 synthesis [50, 51]. Although there has been no report on PGI2 production in isolated human vessels, PGI2 levels were reported to decline in cultured human vascular endothelial cells during serial passage [117–119]. Based on these reports, one would expect that PGIS in endothelium decreases with age. Yet there have been no reports evaluating age-associated PGIS changes in the human endothelium. In the endothelial cells from rat aorta, there is a slight and insignificant age-associated decrease in PGIS mRNA [84]. However, additional evidence shows that mRNA or protein of PGIS is 2–4-fold higher in aorta or coronary arteries of aged normotensive rats [85, 86, 110, 120] suggesting that lower PGI levels may be caused by increased PGI2 degradation with age, rather than the change in PGI2 synthesis. In fact, there is no apparent correlation between circulating PGI2 level with level of endothelial PGIS, suggesting the necessity of investigation of the effects of age on the metabolism/degradation of PGI2. More work is needed to determine whether circulating PGI2 correlates to endothelial PGI2 and to clarify the effects of age on PGI2 in the endothelium and in the circulation. Age-associated reduction in IP level has been consistently reported in rats [84, 85]. The reduced IP is expected to lead to reduced sensitivity to PGI2 effects. Consistently, dilation in response to PGI2 is significantly blunted in aged humans as determined by forearm blood flow measurements [121].

Reports on the change in PGI2 or PGIS under pathological conditions, such as hypertension, are contradictory. While one group reported a 50% reduction in PGI2 in SHR aorta as compared to WKY aorta [96], another group reported insignificant differences in PGI2 levels in SHR and WKY rats [64, 65]. In addition, Tang and Vanhoutte reported that PGI2 mRNA is 4-fold higher in the endothelial cells of SHR aorta than in WKY aorta [84]. These limited and inconsistent reports indicate a need for more complete and thorough investigations into how aging affects PGI2, its synthase, receptor, and metabolism. Moreover, clarifying PGI2 effects in the development of cardiovascular disorders in animal models and in humans could be of potential therapeutic significance.

4. PGE2

Prostaglandin E2 (PGE2) is the most abundant prostaglandin in the human body. In endothelium, however, its level is lower than that of PGI2, in line with a lower expression level of the corresponding synthases, which are 5–100-fold lower than PGIS [54, 64, 65, 84]. There are three types of known PGE2 synthases (PGESs), the cytosolic PGES (cPGES) and two forms of membrane PGES, mPGES1 and mPGES2 [122, Figure 1]. cPGES is constitutively expressed and functionally coupled to COX1 [122, 123]. mPGES1 is inducible and functionally coupled with COX2 [124] and is the major PGE2 synthase responsible for PGE2 production [123]. In endothelium, the expression levels of the PGESs are comparable to other PG synthases [54, 64, 65, 84]. Consistently, the amount of PGE2 in endothelium is comparable to other PGs, but lower than the amount of PGI2 [54, 97, 107–110, 125]. In further accord, the contribution of PGE2 to endothelium-dependent vasoaction is marginal [84, 125]. Chen et al. showed that deletion of mPGES1 in mice resulted in abolished production of PGE2 but did not affect blood pressure [114]. Yang, on the other hand, showed that mPGES1 deletion in mice resulted in exaggerated hypertensive in response to high salt and angiotensin II infusion [126], suggesting that mPGES1 may be an important physiological regulator of blood pressure. While the role of mPGES1 in blood pressure regulation is debatable, mPGES1 is implicated in atherosclerosis. Deletion of mPGES1 in mice retards atherosclerosis development [127].

PGE2 acts through four PGE2 receptors (EP1, EP2, EP3, and EP4), which are mainly located in the smooth muscle cells in the vessels [125, 128, Figure 1]. Activation of EP1 and EP3 receptors induces calcium mobilization/release and inhibits adenyl cyclase release, which triggers vasoconstriction [111, 129]. In contrast, activation of EP2 and EP4 receptors stimulates adenyl cyclase and induces cyclic adenosine monophosphate release, which triggers vasorelaxation [111, 129]. The vascular actions of PGE2 are complex, due to the opposing vasoactions triggered by the binding of PGE2 to the variant PGE2 receptors. Depending on the circumstances, PGE2 may be vasodilating [47, 67–70] or vasoconstricting [53, 54, 71–73]. In addition to the distributions
of different PGE$_2$ receptors expressed in the vascular system, PGE$_2$ concentration is also important. This complexity likely explains the reported inconsistent effects of mPGES1 deletion on blood pressure [114, 126]. PGE$_2$ has a biphasic effect on human blood platelet aggregation. At low concentrations (0.01–1 μM), it potentiates platelet aggregation, and, at higher concentrations (10 μM), it inhibits ADP- and collagen-induced aggregation in platelet rich plasma [71, 130–132]. The endogenous PGE$_2$ concentration is below 1 μM [133], making PGE$_2$ a stimulator of atherosclerosis. Thus, reduced PGE$_2$ level by mPGES1 deletion retards atherosclerosis development [127].

There is little information available on age-related changes in any of the PGESs, PGE$_2$, or EPs. A recent report by Tang and Vanhoutte revealed that while cPGES and mPGES1 in the aorta endothelial cells are insignificantly higher in aged rats, mRNA of mPGES2 is 5-fold higher [84], which can presumably result in higher level of PGE$_2$. PGE$_2$ secreted from coronary arteries is increased in aged rat as compared to young rats [120]. Expression of EP1–4 increased with age, with EP4 elevated 2-fold in endothelial cells from rats of 72 weeks as compared with rats of 36 weeks [84]. Since vasodilation depends on the ligand and the type of receptors, age-increased PGE$_2$ and EP4 are assumed to predispose to increased vasodilation. Further investigation is required to determine the effect of age-related changes in PGE$_2$ and its synthases and receptors in different vascular beds and on relaxation/constriction of vasculatures.

5. PGF$_{2α}$

There are two isomers of prostaglandin F$_{2α}$. One is PGF$_{2α}$, and the other is 9α, 11β-PGF$_{2}$ [134–137]. They are transformed from PGH$_2$ by the membrane-associated 9,11-endoperoxide reductase and from PGD$_2$/PGE$_2$ by cytosolic PGD$_2$ 11-ketoreductase/PGE$_2$ 9-ketoreductase, respectively [138, Figure 1]. In endothelium, the level of PGF$_{2α}$ is similar to that of PGE$_2$, but much lower than that of PGIL$_{1}$ [54, 97, 107–110, 125], corresponding to low abundance of PGF$_{2α}$ cognate synthase (PGFS) in the endothelium [54, 64, 65, 84].

PGF$_{2α}$ has its own specific receptor (FP), which is expressed in endothelium and in vascular smooth muscle cells [139–143, Figure 1]. PGF$_{2α}$ can also interact with TP [54]. Interaction between PGF$_{2α}$ and its receptor generates calcium release and triggers potent vasoconstriction [144–148]. Deletion of FP reduces arterial blood pressure and delays atherogenesis in hyperlipidemic mice [149]. PGF$_{2α}$ has also been indicated in promoting cardiac hypertrophy [150–152]. Although PGF$_{2α}$ is a potent vasoconstrictor, the contribution of PGF$_{2α}$ to endothelium-dependent contractions is minimal in most cases due to its relatively low abundance in the endothelium [54, 97, 107–110, 125].

Information on the effects of aging on PGF$_{2α}$ is limited. PGFS mRNA was doubled in the endothelial cells from aged rat aorta as compared to that from young rat aorta [84]. Consistently, PGF$_{2α}$ is 2-fold higher in the aorta of aged rats versus young rats [110, 148]. Change in FP mRNA in the endothelial cells of rat aorta with age, however, is insignificant [84]. Basal PGF$_{2α}$ is slightly higher in the aorta of SHRs than that of WKY rats, but the difference is increased upon acetylcholine stimulation [54]. Research needs to be conducted to obtain more complete information on age-associated changes in PGF$_{2α}$ in humans and the effects of those changes on the development of cardiovascular disorders.

6. PGD$_2$

PGD$_2$ is synthesized by two PGD$_2$ synthases (PGDSs) encoded by two unrelated genes. One is hematopoietic PGDS (H-PGDS), and the other is lipocalin-type enzyme (L-PGDS) [138, Figure 1]. Both can be upregulated in response to an increase in fluid shear stress [153]. In most of the vasculatures, the level of PGD$_2$ is very low or undetectable in some vascular beds [74], due to the low level of PGDSs [54, 64, 65, 84].

PGD$_2$ has multiple receptors [154]. However, two PGD$_2$ receptors (DP1 and DP2) have been most widely studied (Figure 1). Besides playing an important role in the central nervous and immune systems [154], PGD$_2$ has functions in the vasculature. PGD$_2$ can elicit endothelium-dependent relaxation through receptor activation [59] and acts as a vasodilator [155, 156]. On the other hand, it can also act as a bronchoconstrictor [157–159]. Finally, PGD$_2$ is an anti-coagulant [160–163].

There is only one report on the effect of aging on PGDS and DP. While aging had no effect on L-PGDS, it caused a 5-fold increase in H-PGDS mRNA in aged rat aorta endothelial cells [84]. Age had no apparent effect on DP [84]. H-PGDS is 3-fold higher in aorta endothelial cells from SHRs versus WKY rats [84]. Age had no apparent effect on DP [84]. H-PGDS is 3-fold higher in aorta endothelial cells from SHRs versus WKY rats [84]. In the smooth muscle cells from the same aorta preparations, DP mRNA was measured to be 3-fold higher in SHRs as compared with WKY rats [84].

7. TxA$_2$

TxA$_2$ is mainly produced in the platelets [100, 101]. It is also synthesized in the vasculature, the endothelium, and smooth muscles by TxA$_2$ synthase (TXS) [49, Figure 1]. However, the amount of TxA$_2$ in the endothelium is much lower than the amount of PGI$_2$ [54, 97, 107–110, 125]. Consistently, the expression level of the TXS is much lower than that of PGIS [54, 64, 65, 84].

There are two types of TxA$_2$ receptors (TP) denoted, TPa and Tpb. TP interacts with TxA$_2$ and other PGs, although TxA$_2$ is the most potent agonist [54, 164, Figure 1]. TP appears to be the main receptor of PGH$_2$ [25, 26, 90–97]. Deletion of TP receptors has provided insights into their physiological function. For example, TP knockout mice exhibit decreased vascular proliferation and platelet activation in response to intimal lesions [165]. These animals also experience delays in atherogenesis [166]. TP deletion also prevents angiotensin-II- and L-NAME-induced hypertension and associated cardiac hypertrophy [167].

TxA$_2$ elicits diverse physiological/pathophysiological reactions, including platelet aggregation and vascular smooth muscle contraction [49]. Activation of platelet aggregation
Table 1: Age-associated changes in PGs and TxA₂ and their synthases and receptors.

| Entity | Tissue                  | Age            | Change | References          |
|--------|-------------------------|----------------|--------|---------------------|
| COX1/2 (hum, r, m) | Mesenteric microvessels | Adult, aged    | Increase | [21, 29, 33, 34, 42, 63, 84–86] |
| PGI₂ (hum) | Blood                  | Adolescent, aged | Decrease | [112, 116] |
| PGIS (r) | Aorta, coronary artery in heart | Adults, aged  | Increase | [85, 86, 110, 120] |
| IP (r) | Aorta                   | Adults, aged    | Decrease | [84, 85, 121] |
| PGE₂ (r) | Coronary artery in heart | Aged         | Increase | [120] |
| cPGES (r), Aorta | Old adult | N/S | | [84] |
| mPGES-1 (r) | Aorta                  | Old adult      | N/S | [84] |
| mPGES-2 (r) | Aorta                  | Old adult      | Increase | [84] |
| EP1–3 (r) | Aorta                  | Old adult      | N/S | [84] |
| EP4 (r) | Aorta                   | Old adult      | Increase | [84] |
| PGE₂α (ham, r) | Aorta | Aged     | Increase | [110, 148] |
| PGFS (r) | Aorta                  | Old adult      | Increase | [84] |
| FP (r) | Aorta                | Old adult      | N/S | [84] |
| PGDS (r) | Aorta                  | Old adult      | Increase | [84] |
| DP (r) | Aorta                  | Old adult      | N/S | [84] |
| TxA₂ (r) | Aorta or mesenteric artery | | Increase | [42, 86, 172] |
| TXS (r) | Aorta                  | Old adult      | Increase | [84] |
| TP (r) | Aorta                  | Old adult      | N/S | [84] |

hum: human; ham: hamster; r: rat; m: mouse; N/S: not significant.

Definition of age groups: human, adolescent, 13–19 years; adult, 20–60 years; aged, >60 years. Hamster, aged, >18 months. Rat, young adult, 3–6 months; old adult, 6–18 months; aged >24 months.

...is thought to be the dominant biological function of TxA₂. TxA₂ causes platelet shape change, aggregation, and secretion, which promotes thrombus formation and thrombosis [168–171]. Thrombosis can cause acute myocardial infarction and atherogenesis [166, 171–174]. TxA₂-induced contraction effects are variable, depending on the specific vascular beds examined and the agent used to induce contraction [116, 175, 176]. The majority of reports coincide with the view that the contraction induced by endothelium-derived TxA₂ is weak, because inhibitors of TXS do not induce relaxation [91, 92, 96, 176]. Contraction effects are likely mediated by TP activated by PGH₂ because inhibitors of PGHSs and TP induce relaxation [91, 92, 96, 175, 176].

Several publications reported a 2–5-fold increase in TxA₂ in aorta or mesenteric arteries of aged rats as compared to that of young rats [42, 86, 172]. Consistently, Tang and Vanhoutte reported a 4-fold increase in TXS mRNA [84]. In contrast, a single investigation of age-dependence of TxA₂ did not find any significant difference in TxA₂ between young and aged rat aortas [110]. Aging did not show any significant effect on rat aorta TP mRNA [84].

An increased production of TxA₂ has been found in patients and animal models of several cardiovascular diseases including unstable angina [177], experimental myocardial ischemia and infarction [178], cerebral vasospasm, pregnancy induced hypertension [179, 180], and congenital heart disease [116]. TxA₂ levels reported in those studies are systemic, rather than endothelial. In endothelium, there is no difference in aorta TxA₂ between SHRs and WKY rats [54, 64, 65, 87]. However, TXS mRNA is doubled in the aorta endothelium of SHRs versus WKY rats [84]. Age-related changes in TP have not been found [84, 181].

In summary (Table 1), aging has been consistently shown to cause severalfold increase in COXs, that is, the synthesis of PGH₂ [29, 42, 63, 84–86]. Aging probably reduces PGI₂, the predominant PG in the endothelium [112, 115–118, 182], though it is not certain and requires more work. Aging has been shown, or has the potential, to change other PGs in the endothelium. However, because the level of PGI₂ is 10–100-fold higher than that of the rest of PGs, the shift of PG profile in the endothelium during aging will be predominantly determined by PGI₂ and untransformed PGH₂. PGI₂ and PGH₂ have opposing effects on vessels and platelets. The net result of the effects of aging will be a shift toward a proconstrictive mediator profile, as shown in Figure 2.

8. Association of Prostaglandin and Cardiovascular Disorders in Aging

Associated with this shift are several cardiovascular disorders including hypertension, atherosclerosis, myocardial ischemia, myocardial infarction, and stroke (Figure 2(b)).
Reduced ratio of PGI$_2$/TxA$_2$ was observed in elderly hypertensive patients [183–186]. Age impaired PGI$_2$ synthesis [84, 187] is associated with hypertension [84], progression of atherosclerotic lesions [188], and increased thrombotic risk and heart failure [189, 190]. In addition, aging not only reduces the expression of IP [84], but also reduces the sensitivity of IP [182, 191]. These factors might contribute to the progression of atherosclerosis, as mice with deleted IP [192, 193] and human patients with a dysfunctional prostacyclin IP receptor mutation [194] show accelerated atherosclerosis [97].

On the other hand, aging induces TXS [84]. Higher concentrations of TxA$_2$ are observed in serum or urine in several age-related and hypertensive diseases [185, 186, 195]. In the atherosclerotic coronary artery, the density of TP receptor is increased [171]. Aging-increased TxA$_2$, together with induced TP in the atherosclerotic coronary artery, accelerates arterial atherosclerosis, leading to myocardial infarction [191]. The TP-mediated signaling can also be triggered by PGH$_2$. Age increases COX1/2 in animals and human [21, 29, 33, 34, 42, 63, 84–86] and thereby increases PGH$_2$ production. Age-increased expression of COX-2 in coronary, carotid, and femoral arteries is associated with human atherosclerosis [196–199].

9. Therapeutics That Modulate Prostaglandins in Cardiovascular Disorders

Because prostaglandins and thromboxane are such important factors in endothelium functions and therefore in the physiology and pathology of the vascular system, numerous pharmacological agents that target these factors have been developed to mitigate cardiovascular diseases. As listed in Table 2, prostacyclin (PGI$_2$) and analogues are used clinically to treat hypertension, especially pulmonary hypertension [75, 200–202]. They are also used to inhibit arterial thrombosis and ameliorate myocardial ischemia [203–207]. Although the vascular actions of PGE$_2$ are complex, PGE$_2$ and analogues are used to reduce blood pressure and to alleviate congestive heart failure [208–210], owing to their ability to stimulate renin release and natriuresis and diuresis [211–213]. PGE$_2$, PGE$_1$, and their analogues are more often used to maintain the patency of the ductus arteriosus in infants with congenital heart disease [214–217]. Antagonists of TXS and TP are potent antithrombosis agents and used to treat atherosclerosis, myocardial ischemia, and stroke [218–227].

The underlying principle of the design of these drugs is to selectively increase the effects of vasodilators and anticoagulators and to selectively reduce the effects of vasoconstrictors and coagulators by modulating the amount of ligands, synthases, or receptors of a specific eicosanoid. Because prostaglandins and thromboxane A$_2$ are from the same precursor but elicit opposing effects, selectivity is crucial in the design of these therapeutics. Nonselective inhibition of the upstream synthases, COX1 and COX2, can result in undesirable side effects including hypertension, manifestation of myocardial ischemia, and increased incidents of acute myocardial infarction and stroke, which occur more often in the elderly [104, 228–230].
Intriguingly, low dose of aspirin, an inhibitor of COX1, is popularly used in the prevention of cardiovascular diseases [231–233]. Aspirin covalently acetylates a specific serine moiety (serine 530 of COX-1 and serine 516 of COX-2) [234, 235], and its binding to COX1 is about 170-fold stronger than that to COX-2 [236]. Thus, aspirin is a covalent inhibitor of COX1 inactivating it irreversibly. TxA2 is mainly produced in platelets [100, 101], whereas PGI2 is mainly produced by endothelial cells [51, 57]. Different from most other cell types, platelets do not possess nuclei, which are required for protein synthesis. While COX1 can be regenerated in other cells, such as endothelial cells, COX1 cannot be regenerated in platelets. Nor can COX1 activity be recovered after inactivation by aspirin. Therefore, low dose of aspirin irreversibly and selectively inhibits TxA2 production in platelets.

However, new platelets are constantly formed, and TxA2 is persistently produced [237], which leads to a need for continuous dosing to constantly inhibit COX1. Aspirin resistance is a common clinical phenomenon [238] and has been observed for more than twenty five years [239]. Aspirin resistant patients, partially due to inherited polymorphisms in COX1 [240, 241], have a nearly 4-fold increase in risk of suffering a vascular event compared with aspirin responders [242–244]. As an alternative to aspirin therapy, antagonists of TXS and TP, which can also be combined with aspirin, have been applied to ameliorate thrombosis and prevent cardiovascular diseases [226].

10. Conclusion and Perspective

The incidence and prevalence of cardiovascular diseases increase with advancing age, to the extent that age has been identified as the dominant risk factor for these pathologies [2, 4–6]. It is well established that PGs are powerful endogenous vasodilators and vasoconstrictors and platelet aggregators, playing important roles in regulating homeostasis in vascular systems. Although limited, the current analysis of the literature suggests that there is a modified PG profile associated with age and indicates that age has significant effects on the abundance of PGs, their synthesis, as well as their signaling transduction pathways. Aging-modulated PG profile offers a potentially important molecular mechanism underlying age-dependent endothelial dysfunction and age-associated cardiovascular diseases. Knowledge of age-associated PGs profile changes can be important for designing new pharmacological interventions to prevent or slow down age-associated cardiovascular diseases. Given their biological roles, improved investigation of age-associated changes in PG synthesis, metabolism, and signaling in all major vascular beds is needed.

It is clearly difficult to obtain human vascular tissues to determine age associated changes. Surrogate tissues and fluids such as human blood or urine are plentiful but are of limited value for assessing tissue-specific effects. Defining the relationship between PGs, particularly PGI2 and PGH2, in vascular tissues and the amounts in blood or urine in animal models could be helpful to interpret PG profiles in humans. Technical challenges exist due to metabolite instability. For example, PGH2 is transformed to other PGs and is biologically important in its own right, but untransformed PGH2 is difficult to measure [98, 245]. The development of user-friendly methods could facilitate acquiring these measurements [91, 98, 245]. For example, PGH2 can be instantly reduced to 12-heptadecatrienoic acid (12-HHT) by FeCl2 [91, 98, 245]. 12-HHT is stable and inactive and measurable [91, 98, 245]. Therefore, total PGH2 can be measured as 12-HHT. A relatively mild reducing agent, SnCl2, can reduce untransformed PGH2 to PGF2α. Untransformed PGH2 can be calculated by subtracting the estimate of PGF2α in samples without SnCl2 from the corresponding estimate in samples with SnCl2 [91, 98, 125]. Alternatively, epidemiological approaches could avoid these technical difficulties and offer valuable genetic information. Haplotype analyses have revealed that several polymorphisms in COX, PGIS, and IP are associated with age and cardiovascular diseases [246–250].

Research on an important aspect of age-associated changes in PGs is largely absent in the literature; that of age-associated effects on PG metabolism. One of the most important features of PGs is rapid clearance. Most PGs are metabolized to inactive forms within 1–3 minutes [119, 251], and consequently their signaling is terminated within that time frame. This is due to an effective and efficient metabolism system mainly composed of prostaglandin transporter (PGT) and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) [252]. Both PGT and 15-PGDH have been shown to regulate PG degradation [245, 253, 254]. Thus far, there have been no reports on the influence of age on PG metabolism.

In conclusion, PGs and TxA2 play critical roles in many important events involved in the normal functions of vascular system, including vasodilation, vasoconstriction, platelet aggregation, and inflammation. Although these eicosanoids were discovered in the 1970s, the research into age-associated shifts of the PG profile has just begun. Age-associated alterations in PG profiles are not only interesting, but also important in defining the molecular mechanisms of age-associated cardiovascular pathological conditions and informing strategic and personalized prevention and cure of those diseases.

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References

[1] http://www.who.int/mediacentre/factsheets/fs317/en/index.html.
[2] J. R. Docherty, “Cardiovascular responses in ageing: a review,” Pharmacological Reviews, vol. 42, no. 2, pp. 103–125, 1990.
[3] A. M. Zeiher, H. Drexler, B. Saurbier, and H. Just, “Endothelium-mediated coronary blood flow modulation in humans: effects of age, atherosclerosis, hypercholesterolemia, and hypertension,” Journal of Clinical Investigation, vol. 92, no. 2, pp. 652–662, 1993.
[4] R. P. Brandes, I. Fleming, and R. Busse, “Endothelial aging,” Cardiovascular Research, vol. 66, no. 2, pp. 286–294, 2005.

[5] E. G. Lakatta and D. Levy, “Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a “set up” for vascular disease,” Circulation, vol. 107, no. 1, pp. 139–146, 2003.

[6] P. M. Rothwell, A. J. Coull, E. Silver et al., “Population-based study of rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study),” Lancet, vol. 366, no. 9499, pp. 1773–1783, 2005.

[7] L. Jayakody, T. Kappagoda, M. P. Senaratne, and A. B. Thomson, “Impairment of endothelium-dependent relaxation: an early marker for atherosclerosis in the rabbit,” British Journal of Pharmacology, vol. 94, no. 2, pp. 335–346, 1988.

[8] H. L. Elliott, “Endothelial dysfunction in cardiovascular disease: risk factor, risk marker, or surrogate end point?” Journal of Cardiovascular Pharmacology, vol. 32, supplement 3, pp. S74–S77, 1998.

[9] R. Fathi, B. Haluska, N. Iseb, L. Short, and T. H. Marwick, “The relative importance of vascular structure and function in predicting cardiovascular events,” Journal of the American College of Cardiology, vol. 43, no. 4, pp. 616–623, 2004.

[10] G. B. Mancini, “Vascular structure versus function: is endothelial dysfunction of independent prognostic importance or not?” Journal of the American College of Cardiology, vol. 43, no. 4, pp. 624–628, 2004.

[11] M. D. Herrera, C. Mingorance, R. Rodriguez-Rodriguez, and M. Alvarez de Sotomayor, “Endothelial dysfunction and aging: an update,” Ageing Research Reviews, vol. 9, no. 2, pp. 142–152, 2010.

[12] R. F. Furchgott and J. V. Zawadzki, “The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine,” Nature, vol. 288, no. 5879, pp. 373–376, 1980.

[13] J. Davignon and P. Ganz, “Role of endothelial dysfunction in atherosclerosis,” Circulation, vol. 109, no. 23, pp. III27–III32, 2004.

[14] D. S. Celermajer, K. E. Sorensen, D. J. Spiegelhalter, D. Georgakopoulos, J. Robinson, and J. E. Deanfield, “Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women,” Journal of the American College of Cardiology, vol. 24, no. 2, pp. 471–476, 1994.

[15] S. Taddei, A. Virdis, P. Mattei et al., “Aging and endothelial function in normotensive subjects and patients with essential hypertension,” Circulation, vol. 91, no. 7, pp. 1981–1987, 1995.

[16] S. Taddei, A. Virdis, P. Mattei et al., “Hypertension causes premature aging of endothelial function in humans,” Hypertension, vol. 29, no. 3, pp. 736–743, 1997.

[17] K. Egashira, T. Inou, Y. Hirooka et al., “Effects of age on endothelium-dependent vasodilation of resistance coronary artery by acetylcholine in humans,” Circulation, vol. 88, no. 1, pp. 77–81, 1993.

[18] C. F. König and T. F. Lüscher, “Different mechanisms of endothelial dysfunction with aging and hypertension in rat aorta,” Hypertension, vol. 25, no. 2, pp. 194–200, 1995.

[19] M. Gerhard, M. A. Roddy, S. J. Creager, and M. A. Creager, “Aging progressively impairs endothelium-dependent vasodilation in forearm resistance vessels of humans,” Hypertension, vol. 27, no. 4, pp. 849–853, 1996.

[20] I. Eskurza, K. D. Monahan, J. A. Robinson, and D. R. Seals, “Effect of acute and chronic ascorbic acid on flow-mediated dilatation with sedentary and physically active human ageing,” Journal of Physiology, vol. 556, no. 1, pp. 315–324, 2004.

[21] L. Rodriguez-Mañas, S. Vallejo, P. López-Dóriga et al., “Endothelial dysfunction in aged humans is related with oxidative stress and vascular inflammation,” Aging Cell, vol. 8, no. 3, pp. 226–238, 2009.

[22] I. Shimizu and N. Toda, “Alterations with age of the response to vasodilator agents in isolated mesenteric arteries of the beagle,” British Journal of Pharmacology, vol. 89, no. 4, pp. 769–778, 1986.

[23] H. Moritoki, E. Hosoki, and Y. Ishida, “Age-related decrease in endothelium-dependent dilator response to histamine in rat mesenteric artery,” European Journal of Pharmacology, vol. 126, no. 1–2, pp. 61–67, 1986.

[24] K. Hongo, T. Nakagomi, N. F. Kassell et al., “Effects of aging and hypertension on endothelium-dependent vascular relaxation in rat carotid artery,” Stroke, vol. 19, no. 7, pp. 892–897, 1988.

[25] M. R. Hynes and S. P. Duckles, “Effect of increasing age on the endothelium-mediated relaxation of rat blood vessels in vitro,” Journal of Pharmacology and Experimental Therapeutics, vol. 241, no. 2, pp. 387–392, 1987.

[26] T. Koga, Y. Takata, K. Kobayashi, S. Kishihata, Y. Yamashita, and M. Fujishima, “Age and hypertension promote endothelium-dependent contractions to acetylcholine in the aorta of the rat,” Hypertension, vol. 14, no. 5, pp. 542–548, 1989.

[27] J. Atkinson, R. Tatchum-Talom, and C. Capdeville-Atkinson, “Reduction of endothelial function with age in the mesenteric arterial bed of the normotensive rat,” British Journal of Pharmacology, vol. 111, no. 4, pp. 1184–1188, 1994.

[28] M. Tominaga, K. Fujii, I. Abe, Y. Takata, K. Kobayashi, and M. Fujishima, “Hypertension and aging impair acetylcholine-induced vasodilation in rats,” Journal of Hypertension, vol. 12, no. 3, pp. 259–268, 1994.

[29] K. G. Stewart, Y. Zhang, and S. T. Davidge, “Aging increases PGHS-2-dependent vasoconstriction in rat mesenteric arteries,” Hypertension, vol. 35, no. 6, pp. 1242–1247, 2000.

[30] M. Y. Abeywardena, L. T. Jablonskis, and R. J. Head, “Age and hypertension-induced changes in abnormal contractions in rat aorta,” Journal of Cardiovascular Pharmacology, vol. 40, no. 6, pp. 930–937, 2002.

[31] J. M. Muller-Delp, S. A. Spier, M. W. Ramsey, and M. D. Delp, “Aging impairs endothelium-dependent vasodilation in rat skeletal muscle arterioles,” American Journal of Physiology, vol. 283, no. 4, pp. H1662–H1672, 2002.

[32] E. Gomez, C. Schwendemann, S. Roger et al., “Aging and prostacyclin responses in aorta and platelets from WKY and SHR rats,” American Journal of Physiology, vol. 295, no. 5, pp. H2198–H2211, 2008.

[33] M. E. Gendron, N. Thorin-Trescases, L. Villeneuve, and E. Thorin, “Aging associated with mild dyslipidemia reveals that COX-2 preserves dilation despite endothelial dysfunction,” American Journal of Physiology, vol. 292, no. 1, pp. H431–H458, 2007.

[34] M. E. Gendron and E. Thorin, “A change in the redox environment and thromboxane A2 production precede endothelial dysfunction in mice,” American Journal of Physiology, vol. 293, no. 4, pp. H2508–H2515, 2007.

[35] C. C. Haudenschild, M. F. Prescott, and A. V. Chobanian, “Aortic endothelial and subendothelial cells in experimental...
hypertension and aging,” Hypertension, vol. 3, no. 3, pp. 148–153, 1981.

[36] C. C. Haudenschild and A. V. Chobanian, “Blood pressure lowering diminishes age-related changes in the rat aortic intima,” Hypertension, vol. 6, no. 2, pp. 1-62-1-68, 1984.

[37] E. E. Soltis, “Effect of age on blood pressure and membrane-dependent vascular responses in the rat,” Circulation Research, vol. 61, no. 6, pp. 889–897, 1987.

[38] T. Koga, Y. Takata, K. Kobayashi, S. Takishita, Y. Yamashita, and M. Fujishima, “Ageing suppresses endothelium-dependent relaxation and generates contraction mediated by the muscarinic receptors in vascular smooth muscle of normotensive Wistar-Kyoto and spontaneously hypertensive rats,” Journal of Hypertension, vol. 6, no. 4, pp. S243–S245, 1988.

[39] Y. Iwama, T. Kato, M. Muramatsu et al., “Correlation with blood pressure of the acetylcholine-induced endothelium-derived contracting factor in the rat aorta,” Hypertension, vol. 19, no. 4, pp. 326–332, 1992.

[40] A. U. Ferrari, A. Radaelli, and M. Centola, “Aging and the cardiovascular system,” Journal of Applied Physiology, vol. 95, no. 6, pp. 2591–2597, 2003.

[41] R. L. Matz and R. Andriantsitohaina, “Age-related endothelial dysfunction: potential implications for pharmacotherapy,” Drugs and Aging, vol. 20, no. 7, pp. 527–550, 2003.

[42] R. L. Matz, M. A. de Sotomayor, C. Schott, J. C. Stoclet, and R. Andriantsitohaina, “Vascular bed heterogeneity in age-related endothelial dysfunction with respect to NO and eicosanoids,” British Journal of Pharmacology, vol. 131, no. 2, pp. 303–311, 2000.

[43] M. Barton, F. Cosentino, R. P. Brandes, P. Moreau, S. Shaw, and T. F. Lüscher, “Anatomic heterogeneity of vascular aging: role of nitric oxide and endothelin,” Hypertension, vol. 30, no. 4, pp. 817–824, 1997.

[44] I. Fleming and R. Busse, “NO: the primary EDRF,” Journal of Molecular and Cellular Cardiology, vol. 31, no. 1, pp. 5–14, 1999.

[45] M. R. Tschudi, M. Barton, N. A. Bersinger et al., “Effect of age on kinetics of nitric oxide release in rat aorta and pulmonary artery,” Journal of Clinical Investigation, vol. 98, no. 4, pp. 899–905, 1996.

[46] W. L. Smith, “Localization of enzymes responsible for prostaglandin formation,” in Handbook of Eicosanoids: Prostaglandins and Related Lipids, A. L. Wmils, Ed., vol. IA, pp. 175–184, CRC Press, Boca Raton, Fla, USA, 1987.

[47] J. R. Weeks, “Prostaglandins,” Annual Review of Pharmacology, vol. 12, pp. 317–336, 1972.

[48] R. I. Clyman, F. Mauray, C. Roman, and A. M. Rudolph, “PGE2 is a potent vasodilator of the lamb duc tus arteriosus than is either PG12 or 6 keto PGF1α,” Prostaglandins, vol. 16, no. 2, pp. 259–264, 1978.

[49] N. Nakahata, “Thromboxane A2; physiology/pathophysiology, cellular signal transduction and pharmacology,” Pharmacology and Therapeutics, vol. 118, no. 1, pp. 18–35, 2008.

[50] S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, “An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation,” Nature, vol. 263, no. 5579, pp. 663–665, 1976.

[51] S. Moncada, A. G. Herman, E. A. Higgs, and J. R. Vane, “Differential formation of prostacyclin (PGX or PG12) by layers of the arterial wall. An explanation for the anti-thrombotic properties of vascular endothelium,” Thrombosis Research, vol. 11, no. 5, pp. 323–344, 1977.

[52] S. P. Williams, G. W. Dorn 2nd, and R. M. Rapoport, “Prostaglandin I2 mediates contraction and relaxation of vascular smooth muscle,” American Journal of Physiology, vol. 267, no. 2, pp. H796–H803, 1994.

[53] R. M. Rapoport and S. P. Williams, “Role of prostaglandins in acetylcholine-induced contraction of aorta from spontaneously hypertensive and Wistar-Kyoto rats,” Hypertension, vol. 28, no. 1, pp. 64–75, 1996.

[54] P. Gluais, M. Lonchamp, J. D. Morrow, P. M. Vanhouotte, and M. Feletou, “Acetylsalicylic-induced endothelium-dependent contractions in the SHR aorta: the Janus face of prostacyclin,” British Journal of Pharmacology, vol. 146, no. 6, pp. 834–845, 2005.

[55] S. Bunting, S. Gryglewski, S. Moncada, and J. R. Vane, “Areal walls generate from prostaglandin endoperoxides a substance (prostaglandin X) which relaxes strips of mesenteric and coeliac arteries and inhibits platelet aggregation,” Prostaglandins, vol. 12, no. 6, pp. 897–913, 1976.

[56] R. R. Gorman, F. A. Fitzpatrick, and O. V. Miller, “Reciprocal regulation of human platelet cAMP levels by thromboxane A2 and prostacyclin,” Advances in Cyclic Nucleotide Research, vol. 9, pp. 597–609, 1978.

[57] S. Moncada and J. R. Vane, “The role of prostacyclin in vascular tissue,” Destiny’s Federal Procedure, vol. 38, no. 1, pp. 66–71, 1979.

[58] H. Shimokawa, N. A. Flavahan, R. R. Lorenz, and P. M. Vanhouotte, “Prostacyclin releases endothelium-derived relaxing factor and potentiates its action in coronary arteries of the pig,” British Journal of Pharmacology, vol. 95, no. 4, pp. 1197–1203, 1988.

[59] D. Abram, D. R. Varma, and S. Chemtob, “Regulation of prostaglandin vasomotor effects and receptors in choroidal vessels of newborn pigs,” American Journal of Physiology, vol. 272, no. 3, pp. R995–R1001, 1997.

[60] Z. S. Katusic, J. T. Shepherd, and P. M. Vanhouitte, “Endothelium-dependent contractions to calcium ionophore A23187, arachidonic acid and acetylsalicylic in canine basilar arteries,” Stroke, vol. 19, no. 4, pp. 476–479, 1988.

[61] H. Shirahase, H. Usui, K. Kurahashi, M. Fujiwara, and K. Fukui, “Endothelium-dependent contraction induced by nicotine in isolated canine basilar artery-possible involvement of a thromboxane A2 (TXA2) like substance,” Life Sciences, vol. 42, no. 4, pp. 437–445, 1988.

[62] S. Taddei and P. M. Vanhouitte, “Role of endothelin in endothelin-evoked contractions in the rat aorta,” Hypertension, vol. 21, no. 1, pp. 9–15, 1993.

[63] T. Ge, H. Hughes, D. C. Junquero, K. K. Wu, P. M. Vanhouitte, and C. M. Boulanger, “Endothelium-dependent contractions are associated with both augmented expression of prostaglandin H synthase-1 and hypersensitivity to prostaglandin H2 in the SHR aorta,” Circulation Research, vol. 76, no. 6, pp. 1003–1010, 1995.

[64] P. Gluais, J. Paysant, C. Badier-Commander, T. Verbeuren, P. M. Vanhouitte, and M. Félotou, “In SHR aorta, calcium ionophore A2-3187 releases prostacyclin and thromboxane A2 as endothelium-derived contracting factors,” American Journal of Physiology, vol. 291, no. 5, pp. H2255–H2264, 2006.

[65] P. Gluais, P. M. Vanhouitte, and M. Félotou, “Mechanisms underlying ATP-induced endothelium-dependent contractions in the SHR aorta,” European Journal of Pharmacology, vol. 556, no. 1–3, pp. 107–114, 2007.

[66] A. Hirao, K. Kondo, N. Inui, K. Umemura, K. Ohashi, and H. Watanabe, “Cyclooxygenase-dependent vasoconstricting
factor(s) in remodelled rat femoral arteries,” *Cardiovascular Research*, vol. 79, no. 1, pp. 161–168, 2008.

[67] J. Nakano, R. B. McClay, and A. V. Francan, “Circulatory and pulmonary airway responses to different mixtures of prostaglandins E2 and F2α in dogs,” *European Journal of Pharmacology*, vol. 24, no. 1, pp. 61–66, 1973.

[68] G. J. Dusting and J. R. Vane, “Some cardiovascular properties of prostacyclin (PGI2) which are not shared by PGE2,” *Circulation Research*, vol. 46, no. 6, pp. 1183–1187, 1980.

[69] J. Carter, J. A. Reynoldsdon, and G. D. Thorburn, “The effects of certain vasodilating prostaglandins on the coronary and hindlimb vascular beds of the conscious sheep,” *Comparative Biochemistry and Physiology*, vol. 83, no. 2, pp. 401–406, 1986.

[70] U. Neisius, R. Olsson, R. Rukwied, G. Lischetzki, and M. Schmelz, “Prostaglandin E2 induces vasodilation and pruritus, but no protein extravasation in atopic dermatitis and controls,” *Journal of the American Academy of Dermatology*, vol. 47, no. 1, pp. 28–32, 2002.

[71] S. J. Gray and S. Heptinstall, “The eukaryotic nitric oxide synthase,” *Journal of Cardiovascular Pharmacology*, vol. 257–264, 2000.

[72] M. Wang, A. M. Zukas, Y. Hui, E. Ricciotti, E. Puré, and X. Norel, “Prostanoid receptors in the human vascular wall," *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 62, no. 3, pp. 161–167, 2000.

[73] D. W. Kawka, O. Oueltel, P. O. Hétu, I. I. Singer, and D. Rendeau, “Double-label expression studies of prostacyclin synthase, thromboxane synthase and COX isoforms in normal aortic endothelium,” *Biochimica et Biophysica Acta*, vol. 1711, no. 1, pp. 45–54, 2007.

[74] E. H. Tang and P. M. Vanhoutte, “Gene expression changes of prostanoid synthases in endothelial cells and prostanoid receptors in vascular smooth muscle cells caused by aging and hypertension,” *Physiological Genomics*, vol. 32, no. 3, pp. 409–418, 2008.

[75] Y. Numaguchi, M. Harada, H. Osanai et al., “Altered gene expression of prostacyclin synthase and prostacyclin receptor in the thoracic aorta of spontaneously hypertensive rats," *Cardiovascular Research*, vol. 41, no. 3, pp. 682–688, 1999.

[76] K. B. Kang, M. A. Rajanayagam, A. van der Zyp, and H. Majewski, “A role for cyclooxygenase in aging-related changes of β-adrenoceptor-mediated relaxation in rat aortas," *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 375, no. 4, pp. 273–281, 2007.

[77] D. A. Graham and J. W. Rush, “Cyclooxygenase and thromboxane/prostaglandin receptor contribute to aortic endothelium-dependent dysfunction in aging female spontaneously hypertensive rats," *Journal of Applied Physiology*, vol. 107, no. 4, pp. 1059–1067, 2009.

[78] W. T. Wong, X. Y. Tian, F. P. Leung et al., “Bone morphogenic protein-4 impairs endothelial function through oxidative stress-dependent cyclooxygenase-2 upregulation: implications on hypertension," *Circulation Research*, vol. 107, no. 8, pp. 984–991, 2010.

[79] C. Qu, S. W. Leung, P. M. Vanhoutte, and R. Y. Man, “Chronic inhibition of nitric-oxide synthase potentiates endothelium-dependent contractions in the rat aorta by augmenting the expression of cyclooxygenase-2," *Journal of Pharmacology and Experimental Therapeutics*, vol. 334, no. 2, pp. 373–380, 2010.

[80] T. Kato, Y. Iwama, K. Okumura, H. Hashimoto, T. Ito, and T. Satake, "Prostaglandin H2 may be the endothelium-derived contracting factor released by acetylcholine in the aorta of the rat," *Hypertension*, vol. 15, no. 5, pp. 475–481, 1990.

[81] P. J. Pagano, L. Lin, W. C. Sessa, and A. Nasjletti, "Arachidonic acid elicits endothelium-dependent release from the rabbit aorta of a constrictor prostaglandin resembling prostaglandin endoperoxides," *Circulation Research*, vol. 69, no. 2, pp. 396–405, 1991.

[82] F. X. Dai, J. Skopec, A. Diederich, and D. Diederich, "Prostaglandin H2 and thromboxane A2 are contractile factors in intrarenal arteries of spontaneously hypertensive rats," *Hypertension*, vol. 19, no. 6, pp. 795–798, 1992.

[83] K. Shimizu, M. Muramatsu, Y. Kakegawa et al., "Role of prostaglandin H2 as an endothelium-derived contracting factor in diabetic state," *Diabetes*, vol. 42, no. 9, pp. 1246–1252, 1993.

[84] K. C. Kent, L. J. Collins, F. T. Schwerin, M. K. Raychowdhury, and J. A. Ware, "Identification of functional PGH2/TxA2 oxide synthase are selectively up-regulated by steady laminar shear stress," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 19, pp. 10417–10422, 1996.
prostaglandin E₂, ” *Arthritis Research and Therapy*, vol. 7, no. 3, pp. 114–117, 2005.

[125] M. Camacho, J. López-Belmonte, and L. Vila, ”Rate of vasoconstrictor prostaglandins released by endothelial cells depends on cyclooxygenase-2 expression and prostaglandin I synthase activity,” *Circulation Research*, vol. 83, no. 4, pp. 353–365, 1998.

[126] T. Yang, ”Microsomal prostaglandin E synthase-1 and blood pressure regulation,” *Kidney International*, vol. 72, no. 3, pp. 274–278, 2007.

[127] M. Wang, A. M. Zukas, Y. Hui, E. Ricciotti, E. Puré, and G. A. FitzGerald, ”Deletion of microsomal prostaglandin E synthase-1 augments prostacyclin and retards atherogenesis,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 39, pp. 14507–14512, 2006.

[128] Y. Sugimoto and S. Narumiya, ”Prostaglandin E receptors,” *Journal of Biological Chemistry*, vol. 282, no. 16, pp. 11613–11617, 2007.

[129] A. Alfranca, M. A. Iníguez, M. Fresno, and J. M. Redondo, ”Prostanoi signal transduction and gene expression in the endothelium: role in cardiovascular diseases,” *Cardiovascular Research*, vol. 70, no. 3, pp. 446–456, 2006.

[130] H. Shio, J. Shaw, and P. Ramwell, ”Relation of cyclic AMP to the release and actions of prostaglandins,” *Annals of the New York Academy of Sciences*, vol. 185, pp. 327–335, 1971.

[131] E. W. Salzman, P. C. Kensler, and L. Levine, ”Cyclic 3’ ,5’-adenosine monophosphate in human blood platelets. IV. Regulatory role of cyclic AMP in platelet function,” *Annals of the New York Academy of Sciences*, vol. 201, pp. 61–71, 1972.

[132] H. J. Weiss, A. L. Willis, D. Kuhn, and H. Brand, ”Prostaglandin E₂, potentiation of platelet aggregation induced by LASS endoperoxide: absent in storage pool disease, normal after aspirin ingestion,” *British Journal of Haematology*, vol. 32, no. 2, pp. 257–272, 1976.

[133] A. Morimoto, K. Morimoto, T. Watanabe, Y. Sakata, and N. Murakami, ”Does an increase in prostaglandin E₂ in the blood circulation contribute to a febrile response in rabbits?” *Brain Research Bulletin*, vol. 29, no. 2, pp. 189–192, 1992.

[134] S. Bergstрем, R. Rybage, B. Samuelsson, and J. Sjöveall, ”Prostaglandins and related factors. 15. The structures of prostaglandin E₁, F₁-α, and F₁-β,” *The Journal of Biological Chemistry*, vol. 238, pp. 3555–3564, 1963.

[135] M. J. Dun, J. F. Liar, and E. Dry, ”Basal and stimulated rates of renal secretion and excretion of prostaglandins E₂, Falpaha, and 13, 14-dihydro-15-keto Falpaha in the dog,” *Kidney International*, vol. 13, no. 2, pp. 36–43, 1978.

[136] T. E. Liston and L. J. Roberts II, ”Transformation of prostaglandin D₂ to 9α,11β-(15S)-trihydroxyprosta-(5Z,13E)-dien-1-οic acid (9α,11β-prostaglandin F₂): a unique biologically active prostaglandin produced enzymatically in vivo in humans,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 82, no. 18, pp. 6030–6034, 1985.

[137] C. R. Beasley, C. Robinson, and R. L. Featherstone, ”9α,11β-prostaglandin F₂, a novel metabolite of prostaglandin D₂ is a potent contractile agonist of human and guinea pig airways,” *Journal of Clinical Investigation*, vol. 79, no. 3, pp. 978–983, 1987.

[138] R. J. Helliwell, L. F. Adams, and M. D. Mitchell, ”Prostaglandin synthases: recent developments and a novel hypothesis,” *Prostaglandins Leukotrienes and Essential Fatty Acids*, vol. 70, no. 2, pp. 101–113, 2004.

[139] M. Fukunaga, N. Makita, L. J. Roberts 2nd, J. D. Morrow, K. Takahashi, and K. F. Badr, ”Evidence for the existence of F₂-isoprostane receptors on rat vascular smooth muscle cells,” *American Journal of Physiology*, vol. 264, no. 6, pp. C1619–C1624, 1993.

[140] M. Abramovitz, Y. Boie, T. Nguyen et al., ”Cloning and expression of a cDNA for the human prostanoyl FP receptor,” *Journal of Biological Chemistry*, vol. 269, no. 4, pp. 2632–2636, 1994.

[141] S. Lake, H. Gullverg, J. Wahlqvist et al., ”Cloning of the rat and human prostaglandin F₂ alpha receptors and the expression of the rat prostaglandin F₂ alpha receptor,” *FEBS Letters*, vol. 355, no. 3, pp. 317–325, 1994.

[142] K. Sakamoto, T. Ezashi, K. Miwa et al., ”Molecular cloning and expression of a cDNA of the bovine prostaglandin F₂ alpha receptor,” *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*, vol. 23, pp. 259–261, 1995.

[143] Y. Sugimoto, K. Hasumoto, T. Namba et al., ”Cloning and expression of a cDNA for mouse prostaglandin F₂ receptor,” *Journal of Biological Chemistry*, vol. 269, no. 2, pp. 1356–1360, 1994.

[144] J. Csepli and A. I. Csapo, ”The effect of the prostaglandin F₂α analogue ICI 81008 on uterine small arteries and on blood pressure,” *Prostaglandins*, vol. 10, no. 4, pp. 689–697, 1975.

[145] A. N. Hata and R. M. Breyer, ”Pharmacology and signaling of prostaglandin receptors: multiple roles in inflammation and immune modulation,” *Pharmacology and Therapeutics*, vol. 103, no. 2, pp. 147–166, 2004.

[146] E. M. Smyth, T. Grosser, M. Wang, Y. Yu, and G. A. FitzGerald, ”Prostanoids in health and disease,” *Journal of Lipid Research*, vol. 50, pp. S423–428, 2009.

[147] S. L. Wong, F. P. Leung, P. Vanhouotte, and Y. Huang, ”Endothelium-dependent contractions in hamster aorta: the essential role of COX-2 and prostaglandin-2α,” *Basic, Basic and Clinical Pharmacology and Toxicology*, vol. 102, pp. 15–15, 2008.

[148] S. L. Wong, F. P. Leung, C. W. Lau et al., ”Cyclooxygenase-2-derived prostaglandin F₂α mediates endothelium-dependent contractions in the aorta of hamsters with increased impact during aging,” *Circulation Research*, vol. 104, no. 2, pp. 228–235, 2009.

[149] Y. Yu, M. B. Lucitt, J. Stubbe et al., ”Prostaglandin F₂α elevates blood pressure and promotes atherosclerosis,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 19, pp. 7985–7990, 2009.

[150] J. W. Adams, D. S. Migita, M. K. Yu et al., ”Prostaglandin F₂α stimulates hypertrophic growth of cultured neonatal rat ventricular myocytes,” *Journal of Biological Chemistry*, vol. 271, no. 2, pp. 1179–1186, 1996.

[151] J. Lai, H. Jin, R. Yang et al., ”Prostaglandin F₂α induces cardiac myocyte hypertrophy in vitro and cardiac growth in vivo,” *American Journal of Physiology*, vol. 271, no. 6, pp. H2197–H2208, 1996.

[152] K. Pöncke, C. Giessler, M. Grapow et al., ”FP-receptor mediated trophic effects of prostanoids in rat ventricular cardiomyocytes,” *British Journal of Pharmacology*, vol. 129, no. 8, pp. 1723–1731, 2000.

[153] Y. Taba, T. Sasaguri, M. Miyagi et al., ”Fluid shear stress induces lipocalin-type prostaglandin D₂ synthase expression in vascular endothelial cells,” *Circulation Research*, vol. 86, no. 9, pp. 967–973, 2000.

[154] R. L. Jones, M. A. Giembycz, and D. F. Woodward, ”Prostanoid receptor antagonists: development strategies and
disease,” Archives of Disease in Childhood, vol. 60, no. 11, pp. 1025–1030, 1985.

[217] E. D. Silove, J. Y. Coe, M. F. Shiu et al., “Oral prostaglandin E2 in ductus-dependent pulmonary circulation,” Circulation, vol. 63, no. 3, pp. 682–688, 1981.

[218] G. I. Fiddler and P. Lumley, “Preliminary clinical studies with thromboxane synthase inhibitors and thromboxane receptor blockers. A review,” Circulation, vol. 81, supplement I, no. 1, pp. I–69–I–78, 1990.

[219] E. W. Jones, S. R. Cockbill, A. J. Cowley et al., “Effects of dazoxiben and low-dose aspirin on platelet behaviour in man,” British Journal of Clinical Pharmacology, vol. 15, supplement 1, pp. 395–41S, 1983.

[220] M. A. Villalobos, J. P. de La Cruz, R. Escalante, M. M. Arrebola, A. Guerrero, and F. Sánchez de la Cuesta, “Effects of camonagrel, a selective inhibitor of platelet thromboxane synthase, on the platelet-subendothelium interaction,” Pharmacology, vol. 69, no. 1, pp. 44–50, 2003.

[221] S. J. Coker and J. R. Parratt, “The effects of dazoxiben on arrhythmias and ventricular fibrillation induced by coronary, artery occlusion and reperfusion,” British Journal of Clinical Pharmacology, vol. 15, supplement 1, pp. 875–95S, 1983.

[222] S. J. Coker, “Further evidence that thromboxane exacerbates arrhythmias: effects of UK38485 during coronary artery occlusion and reperfusion in anaesthetized greyhounds,” Journal of Molecular and Cellular Cardiology, vol. 16, no. 7, pp. 633–641, 1984.

[223] G. G. Neri Serneri, S. Coccheri, E. Marubini, and F. Violi, “Picotamide, a combined inhibitor of thromboxane A2 synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: the DAVID study,” European Heart Journal, vol. 25, no. 20, pp. 1845–1852, 2004.

[224] A. Vetrano, M. Milani, and G. Corsini, “Effects of aspirin or picotamide, an antithromboxane agent, in combination with low-intensity oral anticoagulation in patients with acute myocardial infarction: a controlled randomized pilot trial,” Giornale Italiano di Cardiologia Journal, vol. 29, no. 5, pp. 524–528, 1999.

[225] M. Cocozza, T. Picano, U. Oliviero, N. Russo, V. Coto, and M. Milani, “Effects of picotamide, an antithromboxane agent, on carotid atherosclerotic evolution: a two-year, double-blind, placebo-controlled study in diabetic patients,” Stroke, vol. 26, no. 4, pp. 597–601, 1995.

[226] M. G. Hennerici, M. L. Bots, I. Ford, S. Laurent, and P. J. Touboul, “Rationale, design and population baseline characteristics of the PERFORM Vascular Project: an ancillary study of the Prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack (PERFORM) trial,” Cardiovascular Drugs and Therapy, vol. 24, no. 2, pp. 175–180, 2010.

[227] S. Simonet, J. I. Descombes, M. O. Vallez et al., “S 18886, a new thromboxane (TP)-receptor antagonist is the active isomer of S 18204 in all species, except in the guinea-pig,” Advances in Experimental Medicine and Biology, vol. 433, pp. 173–176, 1997.

[228] A. G. Johnson, T. V. Nguyen, and R. O. Day, “Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis,” Annals of Internal Medicine, vol. 121, no. 4, pp. 289–300, 1994.

[229] S. K. Swan, D. W. Rudy, K. C. Lasseter et al., “Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet: a randomized, controlled trial,” Annals of Internal Medicine, vol. 133, no. 1, pp. 1–9, 2000.

[230] C. J. Hawkey, G. M. Hawkey, S. Everitt, M. M. Skelly, W. A. Stack, and D. Gray, “Increased risk of myocardial infarction as first manifestation of ischaemic heart disease and nonselective nonsteroidal anti-inflammatory drugs,” British Journal of Clinical Pharmacology, vol. 61, no. 6, pp. 730–737, 2006.

[231] S. Husain, N. P. Andrews, D. Mulcahy, J. A. Panza, and A. A. Quyyumi, “Aspirin improves endothelial dysfunction in atherosclerosis,” Circulation, vol. 97, no. 8, pp. 716–720, 1998.

[232] V. Fuster, M. L. Dyken, P. S. Vokonas, and C. Hennekens, “Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group,” Circulation, vol. 87, no. 2, pp. 659–675, 1993.

[233] Antiplatelet Trials Collaboration, “Collaborative overview of randomized trials of antiplatelet therapy: I prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients,” British Medical Journal, vol. 308, no. 6921, pp. 81–106, 1994.

[234] G. J. Roth and P. W. Majerus, “The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particular fraction protein, Annual Review of Pharmacology and Toxicology,” The Journal of Clinical Investigation, vol. 56, no. 3, pp. 624–632, 1975.

[235] P. J. Loll, D. Picot, and R. M. Garavito, “The structural basis of aspirin activity inferred from the crystal structure of inactivated prostaglandin H2 synthase,” Nature Structural & Molecular Biology, vol. 2, no. 8, pp. 637–643, 1995.

[236] J. R. Vane, Y. S. Bakhle, and R. M. Botting, “Cyclooxygenases 1 and 2,” Annual Review of Pharmacology and Toxicology, vol. 38, pp. 97–120, 1998.

[237] P. Pignatelli, S. di Santo, F. Barilla, C. Gaudio, and F. Violi, “Multiple anti-atherosclerotic treatments impair aspirin compliance: effects on aspirin resistance,” Journal of Thrombosis and Haemostasis, vol. 6, no. 10, pp. 1832–1834, 2008.

[238] J. Dawson, T. Quinn, M. Rafferty et al., “Aspirin resistance and compliance with therapy,” Cardiovascular Therapeutics, vol. 29, no. 5, pp. 301–307, 2011.

[239] G. Di Minno, “Aspirin resistance and platelet turnover: a 25-year old issue,” Nutrition, Metabolism and Cardiovascular Diseases, vol. 21, no. 8, pp. 542–545, 2011.

[240] A. Szczeklik, J. Musiał, A. Undas, and M. Sanak, “Aspirin resistance,” Journal of Thrombosis and Haemostasis, vol. 3, no. 8, pp. 1655–1662, 2005.

[241] T. Goodman, A. Ferro, and P. Sharma, “Pharmacogenetics of aspirin resistance: a comprehensive systematic review,” British Journal of Clinical Pharmacology, vol. 66, no. 2, pp. 222–331, 2008.

[242] G. Krasopoulos, J. S. Brister, W. S. Beattie, and M. R. Buchan, “Aspirin ‘resistance’ and risk of cardiovascular morbidity: systematic review and meta-analysis,” British Medical Journal, vol. 336, no. 7637, pp. 195–198, 2008.

[243] J. D. Snoep, M. M. Hovens, J. C. Eikenboom, J. G. van der Bom, and M. V. Huisman, “Association of laboratory-defined aspirin resistance with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis,” Archives of Internal Medicine, vol. 167, no. 15, pp. 1593–1599, 2007.

[244] J. W. Eikelboom, J. Hirsh, J. I. Weitz, M. Johnston, Q. Yi, and S. Yusuf, “Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular
death in patients at high risk for cardiovascular events,” 
*Circulation*, vol. 105, no. 14, pp. 1650–1655, 2002.

[245] H. H. Tai, H. Cho, M. Tong, and Y. Ding, “NAD+-linked 15-
hydroxyprostaglandin dehydrogenase: structure and biologi-
cal function,” *Current Pharmaceutical Design*, vol. 12, no. 8, 
pp. 955–962, 2006.

[246] M. E. Rudock, Y. Liu, J. T. Ziegler et al., “Association of poly-
morphisms in cyclooxygenase (COX)-2 with coronary and 
carotid calcium in the Diabetes Heart Study,” *Atherosclerosis*, 
vol. 203, no. 2, pp. 459–465, 2009.

[247] J. Helmersson, J. Arnlöv, T. Axelsson, and S. Basu, “A poly-
morphism in the cyclooxygenase 1 gene is associated with 
decreased inflammatory prostaglandin F2α formation and 
lower risk of cardiovascular disease,” *Prostaglandins Leuko-
trienes and Essential Fatty Acids*, vol. 80, no. 1, pp. 51–56, 
2009.

[248] T. Nakayama, “Prostacyclin synthase gene: genetic polymor-
phisms and prevention of some cardiovascular diseases,” 
*Current Medicinal Chemistry: Cardiovascular and Hematolog-
ical Agents*, vol. 3, no. 2, pp. 157–164, 2005.

[249] J. Stitham, A. Stojanovic, and J. Hwa, “Impaired receptor 
binding and activation associated with a human prostacyclin 
receptor polymorphism,” *Journal of Biological Chemistry*, vol. 
277, no. 18, pp. 15439–15444, 2002.

[250] R. N. Lemaitre, K. Rice, K. Marciant et al., “Variation in 
eicosanoid genes, non-fatal myocardial infarction and is-
chemic stroke,” *Atherosclerosis*, vol. 204, no. 2, pp. e58–e63, 
2009.

[251] M. Hamberg and B. Samuelsson, “On the metabolism of 
prostaglandins E 1 and E 2 in man,” *Journal of Biological 
Chemistry*, vol. 246, no. 22, pp. 6713–6721, 1971.

[252] R. Nomura, R. Lu, M. L. Pucci, and V. L. Schuster, “The two-step model of prostaglandin signal termination: in 
vitro reconstitution with the prostaglandin transporter and 
prostaglandin 15 dehydrogenase,” *Molecular Pharmacology*, 
vol. 65, no. 4, pp. 973–978, 2004.

[253] H. Y. Chang, J. Locker, R. Lu, and V. L. Schuster, “Failure of 
postnatal ductus arteriosus closure in prostaglandin trans-
porter-deficient mice,” *Circulation*, vol. 121, no. 4, pp. 529– 
536, 2010.

[254] Y. Chi, J. Min, J. F. Jasmin, M. P. Lisanti, Y. T. Chang, and V. 
L. Schuster, “Development of a high affinity inhibitor of the 
prostaglandin transporter PGT,” *Journal of Pharmacology and 
Experimental Therapeutics*, vol. 339, no. 2, pp. 529–536, 2011.