



Review

The hypertensive potential of estrogen: An untold story

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ABSTRACT

Cardiovascular disease (CVD) is the major cause of morbidity and mortality worldwide. The implication of estrogen in this disease has been extensively studied. While the vast majority of published research argue for a cardioprotective role of estrogen in vascular inflammation such as in atherosclerosis, the role of estrogen in hypertension remains far from being resolved. The vasorelaxant effect of estrogen has already been well-established. However, emerging evidence supports a vasoconstrictive potential of this hormone. It has been proposed that the microenvironment dictates the effect of estrogen-induced type 1 nitric oxide synthase-1 (nNOS) on vasotone. Indeed, depending on nNOS product, nitric oxide or superoxide, estrogen can induce vasodilation or vasoconstriction, respectively. In this review, we discuss the evidence supporting the vasorelaxant effects of estrogen, and the molecular players involved. Furthermore, we shed light on recent reports revealing a vasoconstrictive role of estrogen, and speculate on the underlying signaling pathways. In addition, we identify certain factors that can account for the discrepant estrogenic effects. This review emphasizes a yin-yang role of estrogen in regulating blood pressure.

1. Introduction

Cardiovascular disease (CVD) continues to be the world's leading cause of debility and mortality [1]. According to the World Health Organization (WHO), CVD accounts for 31% of annual global deaths [2]. Common risk factors for CVDs include smoking, unhealthy diet, diabetes mellitus, hyperlipidemia and hypertension [3]. The latter is considered a major contributor to CVD-associated morbidity and mortality [4].

The American College of Cardiology and American Heart Association (ACC/AHA) define hypertension as systolic blood pressure (SBP) above 130 mm Hg or diastolic blood pressure (DBP) above 80 mm Hg [5]. It affects 1.13 billion people and accounts for 9.4 million deaths per year [2], with an expected increase in prevalence by 30 percent by 2025 [6]. Hypertension is more common in low- and middle-income countries [2], where access to healthcare is limited and lifestyle facilitates its development [7].

Hypertension is mostly asymptomatic [8], but it sets the stage for several debilitating diseases. These include CVDs, cerebrovascular

accidents (CVAs), retinal vascular disorders and hypertensive renal disease [9], most of which are associated with high mortality and morbidity [10]. Thus, it is no surprise that hypertension is referred to as the 'silent killer' [8].

Hypertension induces arterial remodeling, where small vessels undergo wall thickening and lose their elasticity in a process called arteriosclerosis, leading to the so termed 'target organ damage' [11]. In brain arteries, arteriosclerosis narrows the lumen and hardens the vessel wall, resulting in ischemic or hemorrhagic stroke [12]. It also damages coronary vessels, which can progress to a myocardial infarction (MI) [13]. Renally, arteriosclerosis stiffens the nephron, also called nephrosclerosis [14], impeding filtration, which in turn leads to electrolyte imbalances and volume overload [15]. Hypertensive retinopathy is another manifestation of arteriosclerosis, in which retinal vessels are damaged, causing blurry vision and even blindness [16]. Moreover, these vessels can leak and allow fluid to build up behind the retina, resulting in retinal detachment and acute blindness [17].

17 β -estradiol (E₂), estrone (E₁) and estriol (E₃) constitute an endogenous group of sex steroid hormones called estrogens [18]. E₂ is the

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predominant and most biologically active form [18]. It executes its physiologic effects via two members of the nuclear receptor superfamily, estrogen receptor- α (ER- α) and - β (ER- β) [19]. Both receptors are structurally similar but differ in their DNA-binding and ligand-binding domains, leading to different transcriptional activation programs [20]. E₂ binding to and signaling through ER homo- or heterodimers elicit a genomic effect. Additionally, they activate several signal transduction pathways, such as extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38 mitogen-activated protein kinase (p38 MAPK) and phosphoinositide 3-kinase-serine/threonine-specific kinase B (PI3K/AKT) [21]. E₂ can also rapidly mediate non-genomic actions by activating plasma membrane bound estrogen receptors, called G protein-coupled estrogen receptor (GPER, formerly known as GPR30) [22,23]. GPER can activate multiple downstream signaling cascades, like PI3K/AKT and MAPK [24,25].

Historically, E₂ has been described as a vasorelaxant [26–28], but recent observations argue for a vasoconstrictive effect of the hormone. In this review, we highlight the emerging role of estrogen as a vasoconstrictive agent. We also speculate on the molecular players that may be involved in the underlying mechanism.

2. Vasorelaxant effects of estrogen

The vasoprotective role of estrogen has been extensively documented. As a result, prior to menopause, females have less incidence of CVDs than age-matched men [29]. The cardioprotective sexual dimorphism is evident in many cardiovascular disorders. Indeed, when compared to men, premenopausal women show better endurance to ischemia and reperfusion during open-heart surgery [30,31]. In addition, females show significantly more adaptive cardiac remodeling in response to aortic stenosis, while males show upregulated inflammatory and fibrotic markers and genes [32].

With regards to blood pressure (BP), a lower incidence of hypertension is observed in premenopausal women [33,34]. With aging, BP increases in both sexes, but postmenopausal women have a more abrupt increase [35], encompassing 75 percent of women above 60 [36]. Accordingly, older women tend to have a higher BP than men of similar age group [35]. This discrepancy between the BP of pre- and postmenopausal women prompted scientists to focus on the potential benefits of estrogen in the context of hypertension. In the context of hypertension, estrogen's hypotensive role has been classically attributed to the following observations (Fig. 1):

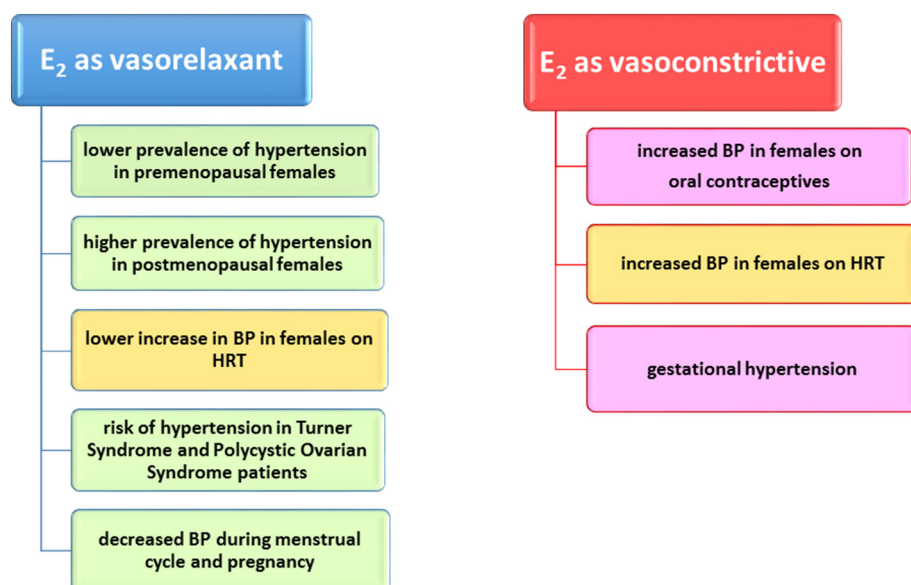


Fig. 1. Various clinical observations supporting either the vasorelaxant or the vasoconstrictive effect of estrogen. Several observations support the well-established role of estrogen. These include lower prevalence of hypertension in premenopausal females and higher prevalence of the disease in postmenopausal females. Decreased blood pressure in during menstrual cycle and during the first two trimesters of pregnancy further support a vasorelaxant role of the hormone. In addition, Turner Syndrome and Polycystic Ovarian Syndrome patients, characterized by low estrogen level, are at higher risk of hypertension. Elevated blood pressure in females on oral contraceptives and pregnancy-induced hypertension support a vasoconstrictive role of estrogen. Blood pressure in post-menopausal females on ERT is still a matter of controversy

2.1. Hypertension in females as compared to males

The prevalence of hypertension is generally lower in premenopausal women compared to age-matched men [33]. It was reported that the average SBP and DBP in males under 60 is higher than females by 6-7 and 3-5 mm Hg respectively [37–39]. This gender-related difference was traditionally correlated to the difference in blood estrogen concentration between the two groups [35,38]. In this respect, estrogen was labeled as hypotensive.

Interestingly, sexual dimorphism in BP is observed in animals as well. For instance, male rats, including Dahl salt-sensitive rats [40,41], deoxycorticosterone acetate-salt hypertensive rats [42], spontaneously hypertensive rats and New Zealand genetically hypertensive rats have higher BP as compared to their corresponding female rats [43–46].

On the other hand, the incidence of CVDs is higher in postmenopausal women when compared to age-matched men [33,47]. While this may appear contradictory to the notion that women are generally at lower risk of dying from hypertension-related CVDs [48], it is noteworthy to mention that these “women” included both pre- and post-menopausal groups, i.e. estrogen-replete and deplete subjects, respectively. Indeed, 41% of postmenopausal women are at risk of being hypertensive [49], with a similar DBP to age-matched men, but higher SBP [50].

2.2. Hypertension in premenopausal versus postmenopausal females

Conventional and ambulatory evaluations of BP in women have shown that postmenopausal women have an SBP higher by 4-5 mm Hg compared to premenopausal and perimenopausal women [51–54]. However, a recent study reported that the values of SBP and DBP are significantly higher in postmenopausal females as compared to premenopausal ones [55]. Cross-sectional studies have also shown that menopause, including surgical menopause [56], increases the risk of hypertension by 2-fold even after adjustment for age and body mass index (BMI) [57,58]. These observations confirm a correlation between serum estrogen level and hypertension in females. This is in addition to reports showing that postmenopausal women show a non-dipping pattern of BP. Normally, a 10% circadian decrease in BP is observed between day and night, a decrease referred to as BP dipping. Postmenopausal women, however, tend to show less than 10% decline in their nocturnal BP [59].

2.3. Hypertension in postmenopausal females on hormone replacement therapy (HRT)

The effect of HRT on CVDs remain controversial, as this effect mainly depends on the HRT preparation and HRT initiation time since menopause [60]. However, many observational studies established that postmenopausal women on HRT have a lower rate of CVDs than those who are not [61]. This can be partially explained by the smaller increase in SBP in females on HRT compared to their counterpart [62,63]. It was also reported that postmenopausal women administered with E₂ have lower daytime and nocturnal SBP and DBP when compared to placebo-treated women [64]. A recent meta-review has shown that transdermal estrogen has a beneficial effect on BP of postmenopausal females [65].

2.4. Hypertension in females with Turner syndrome and polycystic ovarian syndrome (PCOS)

In addition to menopause, there are other cases where a decrease in estrogen levels may be associated with hypertension. Females with Turner syndrome or PCOS, both of which are characterized by low estrogen levels [66,67], are at higher risk of developing hypertension [66–69]. Moreover, a study has shown that there is a negative correlation between estrogen and DBP in females with Turner Syndrome [70]. This implies a beneficial effect of estrogen on BP in these patients.

2.5. Blood pressure during menstrual cycle and pregnancy

The BP-lowering potential of estrogen can also be inferred from its effect during the menstrual cycle and pregnancy. In the menstrual cycle, BP is lower during the luteal phase, when estrogen levels peak, than in the follicular phase when these levels drop [71,72]. In pregnancy, BP decreases during the first and the second trimesters [73], in concomitance with an increase in estrogen [74].

3. Estrogen's vasorelaxant direct effect on the arterial wall: signaling molecules

Estrogen grants protective effects to the cardiovascular system, particularly to the vasculature. Whereas the anti-inflammatory role of estrogen in atherosclerosis has been well established [75,76], the role of estrogen in hypertension is beginning to be cemented. Emerging evidence from experimental and clinical research points to both vasodilatory and vasoconstrictive effects of estrogen.

E₂, the most active endogenous estrogen in premenopausal women, has been documented to induce vasodilation through several molecular pathways [77]. While estrogen's hypotensive effect is mainly through the release of vasodilators from the endothelium [78], it can also lead to vasculature relaxation in an endothelium-independent manner [79]. A myriad of agents are responsible for estrogen's vasodilatory effects. Below we discuss the most important ones (Fig. 2).

3.1. Nitric oxide

Nitric oxide (NO) is one of the most well-studied and canonical estrogen-induced vasodilators [80]. Indeed, it has been demonstrated that inhibiting nitric oxide synthase (NOS) attenuates the vasodilatory effect of E₁ in phenylephrine-contracted Wistar rat aortic ring [81]. Similarly, another study shows that E₂ induces vasorelaxation in porcine coronary arteries through NO [82]. E₂ was reported to increase endothelial nitric oxide synthase (eNOS) activity in ovariectomized diabetic rat model [78]. It also upregulates eNOS expression via cytosolic ER-mediated genomic effect or membranous ER signaling and the consequential activation of the PI3K/cyclic adenosine monophosphate (cAMP) pathway [75,80,83]. In addition to being a vasodilator, this cAMP exerts many biological effects on arteriolar smooth muscle cells

[84–88].

Further evidence, however, shows that estrogen's vasodilatory effect can be elicited in the absence of the endothelium as well, supporting a direct effect of estrogen on vascular smooth muscle cells (VSMCs). Indeed, estrogen can cause production of NO in VSMCs themselves [89]. This is attained mainly via lowering VSMCs' intracellular levels of calcium (Ca²⁺), which can be the result of diminishing Ca²⁺ influx or stimulating Ca²⁺ efflux [89]. The VSMC-produced NO, in turn, stimulates potassium (K⁺) channels, whose opening further leads to decreased intracellular Ca²⁺, further propagating vascular relaxation [90]. Darkow *et al.* show that estrogen can induce the relaxation of endothelium-denuded porcine coronary arteries through local production of cyclic guanosine monophosphate (cGMP) and NO, which then open large-conductance Ca²⁺ and voltage-activated K⁺ channels (BKCa) [91].

However, NO appears to be dispensable for estrogen-mediated vasodilation in several cases. For example, a study shows that NO inhibition does not affect estrogen-induced relaxation of resistance sized mesenteric arteries in spontaneously hypertensive rats (SHRs) [92]. Additionally, estrogen was able to induce vasorelaxation of de-endothelialized serotonin-precontracted male rat aortic strips via the inhibition of serotonin-induced Src kinase, which is NO-independent [79].

3.2. Carbon monoxide

In addition to NO, carbon monoxide (CO) is considered a potent endothelial-derived vasorelaxant. The role of CO in estrogen-induced vasorelaxation was reported by Pósa *et al* [93]. This group showed that heme oxygenase-generated CO contribute to estrogen-induced vasodilation of ovariectomized rat aorta. They also demonstrate that estrogen induce vasorelaxation in a hydroxide (HO⁻)-CO-NO signaling pathway [93].

3.3. Cyclic nucleotides

Inhibition of cAMP and cGMP production has no effect on E₂-induced vasorelaxation of mesenteric arteries of SHRs [94]. However, in response to estrogen, cGMP plays a key role in the relaxation of porcine coronary artery [91], including endothelial-denuded ones [95]. Moreover, in endothelin-1 (ET-1)-stimulated aortic rings of Wistar rats, estrogen causes relaxation via a mechanisms that depends on guanylate cyclase (GC) [81]. Additionally, cAMP bridges GPER-mediated relaxation [96], especially in porcine coronary artery [97]. It is proposed that cAMP activates both protein kinase A (PKA) and exchange protein activated by cAMP (EPAC) in a synergistic manner to dephosphorylate myosin light chain (MLC) and induce vascular relaxation [97]. However, further experimentation is warranted to better elucidate the interplay between EPAC and PKA in modulating estrogen's cardiovascular effects.

3.4. Mitogen-activated protein kinases

MAPKs are key signaling molecules involved in a plethora of cellular processes. However, their role in estrogen-induced vasorelaxation is still not fully elucidated. Two recent studies show discrepant results in this respect. The vasorelaxant effect of E₁ on rat aortic rings was not affected by ERK1/2 or p38 inhibition [81]. This indicates that MAPKs do not play a role in estrogen-induced vasorelaxation. It is reported, however, that inhibiting ERK1/2 potentiates ER agonist-induced relaxation of ET-1-constricted porcine coronary artery [97]. This suggests that estrogen inhibits ERK1/2 to achieve part of its vasodilatory effect. On the other hand, a study has shown that ERK1/2 mediate the rapid, non-genomic vasorelaxation of E₂ and ER- α agonist [98].

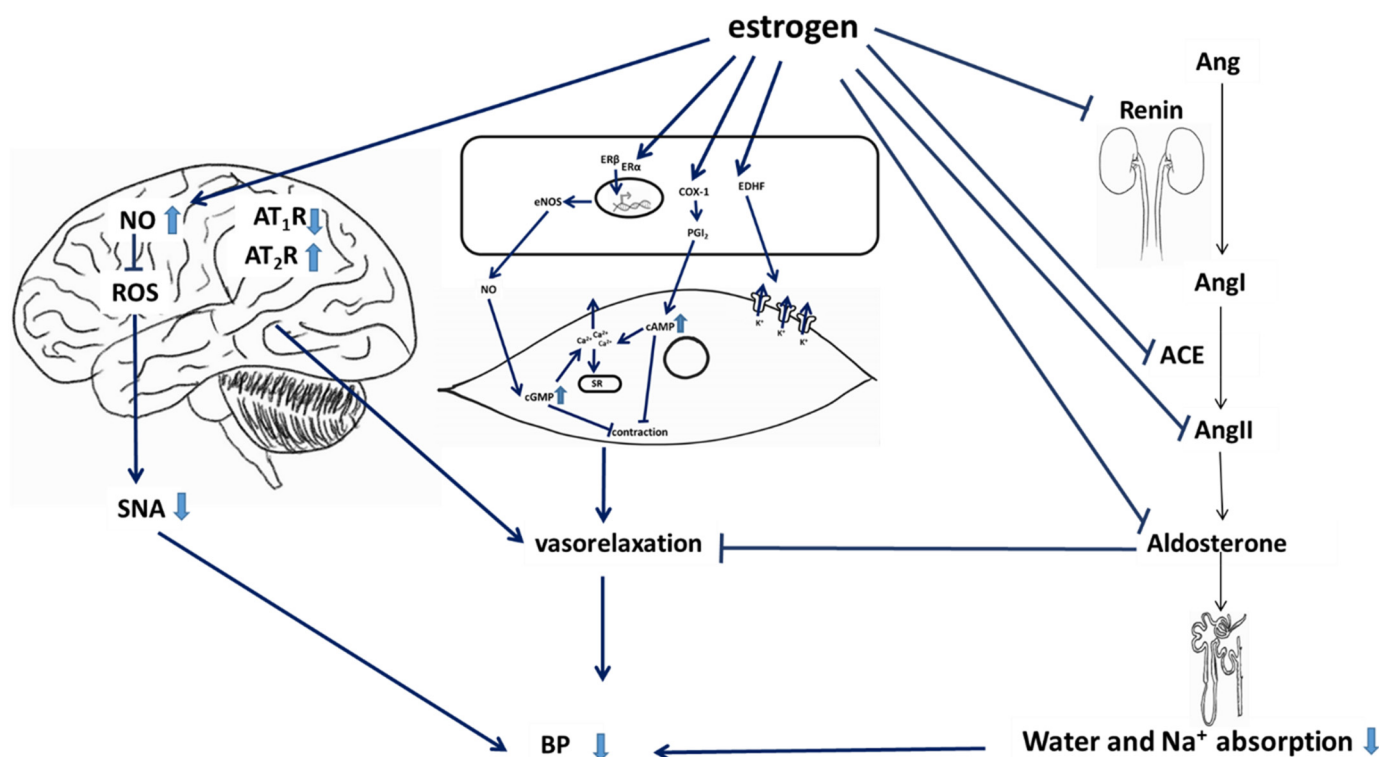


Fig. 2. Signaling pathways mediating estrogen-induced vasorelaxation. Estrogen works on three different lines to elicit its hypotensive effect. First, it decreases the sympathetic nervous action (SNA) by increasing NO production and AT₂R expression. In addition, estrogen attenuates AT₁R expression and ROS production. At the level of the RAAS, estrogen attenuates Renin and ACE activities, leading to decreased AngII and aldosterone levels. Estrogen also attenuates water and sodium absorption in the kidneys. At the level of blood vessels, estrogen binds to its receptors on endothelial cell, leading to eNOS transcription, and thus NO release. In addition, estrogen stimulates COX-1-mediated PGI₂ release, which decreases intracellular Ca²⁺. In addition, estrogen induces EDHF release, causing K⁺ through their corresponding channels. These events lead to membrane hyperpolarization and consequently vasorelaxation.

3.5. Phosphoinositide 3-Kinase-serine/threonine-specific Kinase B

The role of PI3K in vasorelaxation is well-established. In estrogen-induced relaxation, De Oliveira *et al.* report that E₁ induces relaxation of phenylephrine-contracted rat aortic rings in PI3K/Akt-dependent manner [81]. Particularly, PI3K/Akt activate eNOS, leading to the release of endothelial NO, which in turn increases vascular cGMP and leads to vasorelaxation [81]. This pathway has been shown in action in response to an estrogen-receptor agonist in phenylephrine-contracted resistant mesenteric arteries too [99].

3.6. Protein Kinase G

The role of protein kinase G (PKG) in mediating the effects of estrogen remains controversial. PKG is activated by the second messenger cGMP, which is produced by soluble GC [100]. The interaction between E₂ and PKG has been investigated for years. Earlier studies showed that E₂-induced vasorelaxation of mesenteric arteries in SHR was not affected by cGMP or PKG inhibition [94]. However, these findings are yet to be conclusive, especially that PKG was reported to be a key mediator of estrogen-induced arterial vasodilation in ApoE^{-/-} mice [101]. In fact, it has been demonstrated that estrogen activates PKG, which in turn stimulates the production of hydrogen sulfide (H₂S), a potent vasodilator that decreases BP [94,102]. Further studies are thus warranted to conclusively determine the interplay between estrogen and PKG in regulating vasotone.

4. Estrogen's vasorelaxant effect: Roles of the Renin-Angiotensin-Aldosterone System (RAAS) and the central nervous system (CNS)

4.1. Effect on RAAS

Vasoconstriction, and by extension BP, are regulated by more than just local metabolites. A vital component of the recipe for BP maintenance is the RAAS. RAAS involves renin, an enzyme released by the renal juxtaglomerular apparatus, and angiotensinogen (AGT), a protein synthesized in the liver. Renin proteolyzes AGT to angiotensin I (Ang I), which in turn is activated by angiotensin converting enzyme (ACE), that is found in lungs and kidneys, to angiotensin II (Ang II) [103]. Ang II binds to Ang II type 1 receptor (AT1R), resulting in a cacophony of physiologic changes that eventually lead to elevation in BP [103]. These physiologic changes include vasoconstriction, sympathetic nervous system (SNS) stimulation, increased sodium reabsorption at the nephron and the release of aldosterone and anti-diuretic hormone (ADH) from adrenal and pituitary glands respectively [103–105]. Moreover, prolonged activation of AT1R is associated with pathologic processes, like arteriosclerosis and atherosclerosis [106].

The interaction between estrogen and RAAS is intricate. An initial glance at the literature suggests a RAAS-activating role of estrogen. This is inferred from postmenopausal women who have a less responsive RAAS to orthostatic stress than premenopausal females [107], and the decreased expression of AT1R and ACE in ovariectomized animals [108,109]. Additionally, estrogen has been shown to increase plasma renin activity, AGT, Ang I and Ang II [107,108,110,111]. Nevertheless, estrogen seems to have a hypotensive role through RAAS. Indeed, evidence shows that despite increasing RAAS substrates, E₂ downregulates AT1R and stimulates the expression of Ang II type 2 receptor (AT2R) instead [108], which has vasorelaxant and natriuretic effects

[106,108], both of which drop BP. E₂ also induces renal and cerebral expression of angiotensin converting enzyme 2 (ACE2) [108,112], which catalyzes the conversion of Ang II to angiotensin 1-7 (Ang 1-7) [113]. Ang 1-7 is a peptide that causes vasodilation and natriuresis renally [106], and attenuates SNS centrally [112], reducing BP. On the other hand, hypoestrogenism in menopause causes increased AT1R to AT2R ratio [106,108], hence the observed postmenopausal hypertension.

4.2. Effect on CNS

Activation of the SNS increases CO and TPR and acutely raises BP; however, the role of the SNS in the long-term control remains under investigation [114]. Joyner *et al.* investigated the relationship between SNS and chronic BP maintenance. Their work showed a proportional relationship between SNS and TPR of young men, tapered by an inversely proportional relationship with CO and vascular adrenergic insensitivity. They also demonstrated that with age, men's BP increases alongside an increase in sympathetic neuronal activity (SNA). Interestingly, premenopausal women showed no relationship between their BP and SNA due to the notion that β_2 -adrenergic receptor (β_2 -AR)-mediated vasodilation makes this relation; this trait is lost after menopause [115]. Consequentially, postmenopausal women ended up with both an increased SNA and a stronger association between elevated BP and SNS than in men [115]. This result goes in concordance with Chobanian *et al.*'s work, in which postmenopausal females had higher SBP than age-matched men [50]. Furthermore, the loss of vasodilation by β_2 -AR activation post menopause indicates a substantial role for estrogen in this mechanism. This is confirmed by other studies showing that low-dose E₂ reduced sympathetic effect on vessels and by extension BP in rats with postmenopausal hypertension [116]. This is also in accordance with other reports indicating that 17 β -estradiol-evoked vasodilation in renal and mesenteric arteries is diminished and may be masked by β_2 -AR-mediated vasodilation [117].

The extent of estrogen's influence on SNS goes beyond regulating its effect on vascular tone. Centrally, SNA is controlled by several cerebral regions, like the subfornical organ (SFO), paraventricular nucleus (PVN) and the rostral ventral lateral medulla (RVLM), all of which express ERs [118]. Intracerebroventricular infusion of propyl-pyrazoletriol, a selective ER- α agonist, ordiarylpropionitrile, a selective ER- β agonist, alleviated hypertension in ovariectomized rats [119]. In addition, silencing these receptors in the cerebroventricular region augmented hypertension in intact female rats. These results confirm a central hypotensive role of estrogen mediated by both ER subtypes the brain regions that control BP. Subsequent studies have localized ER- β to PVN and RVLM and ER- α to SFO [119,120], but there is a need for further investigation into the pathways each ER subtype indwells.

5. Vasoconstrictive effect of estrogen

Emerging evidence supports a new and rather surprising effect of estrogen, a hypertensive effect. This estrogenic action was principally inferred from the rise of BP in premenopausal women on contraceptives and postmenopausal women on HRT [121–126]. The positive association between hypertension and the third trimester of pregnancy, an estrogen-rich phase, further underpinned the hypertensive role of estrogen [127–129].

Several subsequent reports further validated this effect in animal models. Long-term estrogen exposure lead to increased BP in mice [130]. Similarly, long-term administration of Envoid, an oral contraceptive, significantly increased the BP of ovariectomized female rats [131]. This was the first *in vivo* evidence showing the effect of contraceptives on hypertension. Another study by Fowler *et al.*, confirmed that it is estrogen in contraceptives that is responsible for BP elevation [132]. Later, Byrne *et al.*, showed that administration of ethynylestradiol, a synthetic derivative of E₂, to female Sprague-Dawley rats

induced an increase in BP [133]. In addition, Lew *et al.*, showed that estrogen administration to rats increased their BP by 4 percent [134]. *In vitro* experiments further supported the hypertensive estrogen effect. Estrogen (10–100 nmol/L) was reported to induce contraction of rat aortic VSMCs [135,136]. Also, estrogen increased contractility of VSMCs from Ephrin-B3 knock-out mice [137]. This was confirmed *in vivo*, where ovariectomy lead to normal BP of EFNB3 knock-out female mice [137]. These studies mostly showed a slight but significant increase in BP (1.5–2 mm Hg). However, this slight increase is dangerous since it is associated with the development of serious cardiovascular events [138,139], including coronary atherosclerosis [140].

The emerging vasoconstrictive potential of estrogen stems from the following observations (Fig. 1):

5.1. Hypertension in women on oral contraceptives

Women on oral contraceptives are at a higher risk of developing hypertension [122,141]. In fact, these women showed an increase in both SBP and DBP [132,142–144]. Notably, progesterone in contraceptive pills does not contribute to BP elevation [145–147], implying that it is estrogen in oral contraceptives that exerts their hypertensive effect. This hypertensive effect appears to be estrogen dose-dependent [148,149], since newer preparations of oral contraceptives that have lower estrogen content are associated with lower elevations in BP [38,123]. Conversely, women using preparations containing more than 50 μ g of estrogen have a BP greater than 140/90 mm Hg [150]. It is worth mentioning that upon cessation of estrogenic contraceptives, women returned to normal BP [151–153].

5.2. Hypertension in women on hormone replacement therapy

Postmenopausal women resort to HRT to compensate for the lost estrogen beneficial effects. Indeed, estrogen is assumed to be responsible for reduced cardiovascular events such as aortic stenosis, fibrosis, and ischemia/reperfusion (I/R) injury [80]. However, several studies showed that HRT can lead to an increase in BP in postmenopausal females [125,138], even after adjusting other factors [48]. Specifically, increased SBP was observed in postmenopausal females receiving estrogen plus progestin and estrogen-only hormonal preparations [126,154].

It is worth mentioning that the endothelial integrity of small vessels is compromised in postmenopausal woman [155], which may affect estrogen-induced vasodilation. In addition, menopause-related arterial stiffness favors hypertension [156]. These factors, in addition to the route of HRT, whether oral or transdermal [157], hormonal preparation and method of study may account for the discrepant results of reports assessing the effect of HRT on BP [158].

Observations on the effect of HRT on BP remain controversial. While we earlier discussed the BP-lowering or rising effect of HRT, other significant studies show that HRT does not really have a profound effect on BP, regardless of its formulation. The Women's Health Initiative (WHI) is the largest (16,000 women) randomized, placebo-controlled trial that has evaluated the effect of postmenopausal HRT on cardiovascular outcomes [125]. It reported that at 5.2 years, HRT produced only a small mean increase (1.5 mmHg) in systolic pressure compared with placebo [125]. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, use of ERT with or without progestins did not affect BP at three years among 875 healthy postmenopausal women [159]. In the Kronos Early Estrogen Prevention Study (KEEPS), neither of the two different formulations of HRT evaluated produced any significant change in BP or endothelial function among recently postmenopausal women without high BP at baseline [160].

5.3. Hypertension in pregnant women

Pregnancy-induced hypertension is detected after 20 weeks of

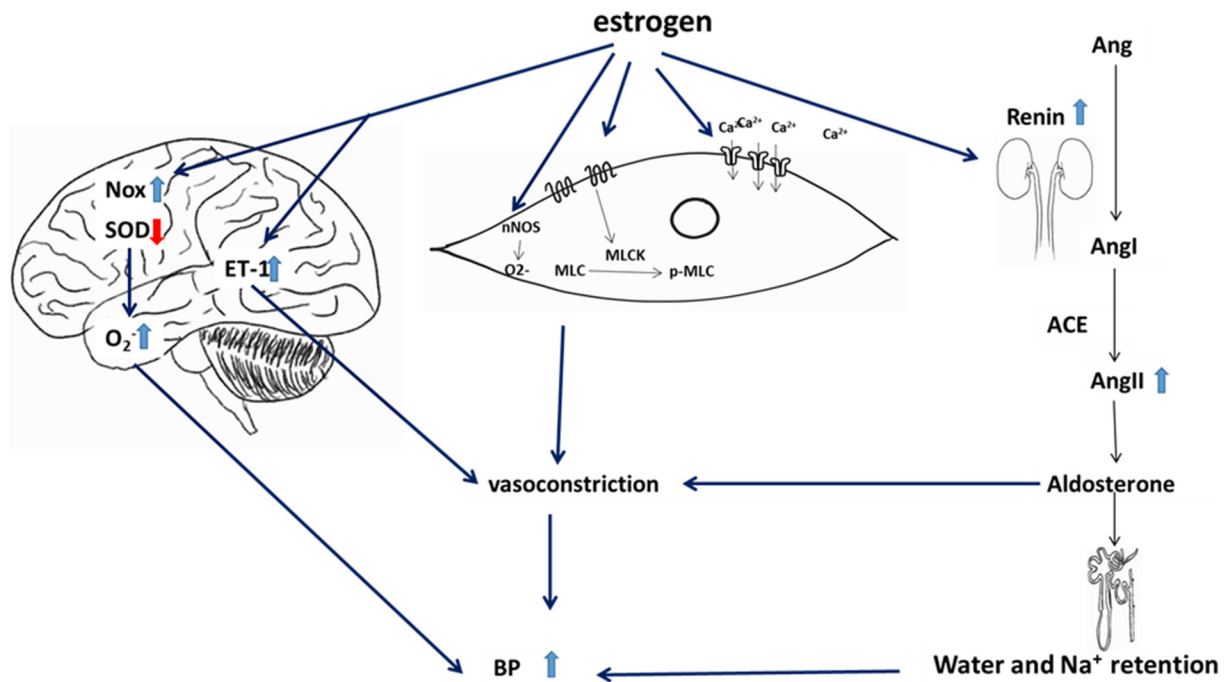


Fig. 3. Putative signaling pathways mediating estrogen-induced vasoconstriction. Estrogen mainly affects three levels, the brain, the RAAS, and the VSMC itself, to induce vasoconstriction. In RVLM, estrogen increases ET-1 leading to vasoconstriction. In addition, estrogen increases Nox or decreases SOD, leading to O_2^- pileup, and consequently increased blood pressure. At the level of the RAAS, estrogen increases the level and the activity of renin, and subsequently level of AgII and aldosterone, leading to increased blood pressure. In the VSMC, estrogen increases cell sensitization to Ca^{2+} , activates MLC, and induces nNOS-released O_2^- . These pathways are known to induce VSMC contraction, and thus vasoconstriction.

gestation and resolves within 12 weeks of delivery [161]. It includes gestational hypertension, preeclampsia (gestational hypertension plus proteinuria) and eclampsia (seizure during or within 24 hours of delivery in preeclamptic woman) [161,162]. Studies show that preeclampsia affects 3 to 7 percent of pregnant women [163], while gestational hypertension takes in almost 6 percent of pregnancies [164]. Since pregnancy is characterized by high estrogen levels, especially towards the last trimester [74,165,166], it may be postulated that increased estrogen levels are associated with gestational hypertension. In fact, estrogen levels increase to their maximum in the last trimester [74], during which the ambulatory blood pressure (ABP) reaches its highest level throughout pregnancy [73].

6. Mechanisms of estrogen-induced vasoconstriction

The mechanism by which estrogen induces vasoconstriction is not fully elucidated yet. However, several research groups proposed possible pathways by which estrogen can induce high BP. These pathways include central actions of estrogen directly on certain brain regions, estrogen modulation of the RAAS system, modulation by calcium channels, or phosphorylation of myosin light chain (MLC) (Fig. 3).

6.1. Brain sites involved in BP regulation

It is well established that the central nervous system regulates BP via sympathetic nervous activity [118]. This activity involves several brain regions, whose neurons express ERs. Thus, the effect of estrogen on BP may be elicited via these neurons [167]. It was suggested that chronic exposure to E_2 lead to a concomitant increase in BP and superoxide species in the rostral ventrolateral medulla (RVLM) of Sprague Dawley female rats [130]. Interestingly, this brain area expresses both ER- α and ER- β and is involved in BP regulation [168]. Moreover, administration of anti-oxidants that lowered superoxide species also reduced BP [130]. Thus, it was postulated that estrogen leads to accumulation of superoxide anions in the RVLM, thereby leading to BP

elevation [130]. The same group later showed that chronic estrogen exposure activated the expression of different sets of genes in RVLM depending on the age of the rat [169]. While chronic estrogen exposure increased the expression of the vasoconstrictor ET-1 in both young and old mice, it upregulated the expression of NADPH oxidases (NOX-1 and NOX-2) in young mice only, while downregulating the expression of superoxide dismutase in old rats [169]. Thus, estrogen exposure may cause hypertension by activating various molecular signaling pathways in the rostral ventrolateral medulla, with ET-1 and O_2^- being common mediators [169], albeit to different extents in young versus aging animals.

6.2. RAAS Activation

The RAAS plays a critical role in fluid homeostasis and BP regulation [105,170–172]. Contextually, estrogen and estrogen-containing contraceptives increased the plasma levels of the renin substrate, angiotensinogen, in studies involving human subjects [172–175]. This increase is often associated with elevation in plasma renin activity and plasma levels of Ag II [105,111,173,176]. It is this activation of RAAS components that is known to increase BP [177,178]. Moreover, *in vivo* studies showed that estrogen (ethynylestradiol) increased SBP of rats. This increase was concomitant with an increase in the activity and levels of renin and Ag II [179]. This indicates a positive relationship between hypertension and RAAS with estrogen [133]. Additionally, inhibition of the RAAS with enalapril, an ACE inhibitor, decreases BP in both males and females of SHR [44]. More importantly, this enalapril partially removes the sex difference-related BP variances [44]. Similarly, suppression of this system prevented contraceptive-induced BP elevation in rats [180].

It is worth mentioning that RAAS inhibition could not completely normalize BP between males and females of SHR, suggesting that other mechanisms contribute to the sex-related hypertension differences [44]. These results were confirmed in another study where ACE inhibitors failed to normalize BP in male SHR, also demonstrating that

pathways different from Ang II contribute to hypertension in these animals [133].

6.3. Calcium channels

The role of calcium channels in arterial vasoreactivity is extensively documented [181–183]. In the context of estrogen-modulated vasoreactivity, a study reports that contraceptive-induced hypertension in rats is mediated by calcium channels [184]. Administration of nifedipine, a L-type calcium channel blocker, significantly inhibited the contraceptive-induced hypertension [184]. This result was further confirmed by another study which showed that calcium channels mediate estrogen-induced vasoconstriction [185]. In fact, it was speculated that estrogen elicited its vasoconstrictive effect via a signaling pathway that increases the sensitivity of Ca^{2+} influx in VSMCs [137].

6.4. Myosin light chain phosphorylation

Phosphorylation of MLC is a key event in VSMC contraction, and consequently vasoconstriction [186,187]. It has been reported that estrogen induces VSMC contraction via phosphorylation of MLC in a time- and concentration-dependent manner [135,136]. Furthermore, MLC played a role in estrogen-induced vasoconstriction and BP elevation, which was attenuated by ovariectomy [137]. It was proposed that estrogen acts via GPER to reduce phosphorylation of myosin light chain kinase (MLCK), leading to MLC phosphorylation and eventually vasoconstriction [137]. This may be supported by the fact that G_{11} , a GPER agonist, induces while G_{15} , a GPER antagonist, inhibits MLC phosphorylation in aortic ring segments [188].

7. Factors affecting estrogen vasoreactivity

An antihypertensive effect of estrogen has been well-established. This was mainly supported by the lower BP in premenopausal women and higher BP in postmenopausal females, as compared to age-matched men [189] [33,36,187]. However, this vasoprotective role of estrogen has been questioned, especially after the women's health initiative (WHI) trials initiated by the National Institutes of Health (NIH), which showed that HRT may increase the risk of CVDs [125,188] [190]. Additionally, the Heart and Estrogen/progestin Replacement Study I (HERS I) and HERS II studies showed that HRT failed to provide any protection against primary or secondary cardiovascular events [191]. In the context of hypertension, the inconsistency in the reports assessing the vasoreactive role of estrogen calls for an urgent inclusion of other factors in future studies so as to arrive at a better understanding of their respective effects in estrogen's vascular effects. Below we discuss some gender- and non-gender-related factors that may contribute to effect of estrogen on BP (Fig. 4).

7.1. Effect of sex chromosome content

In addition to estrogen, gender-based effects in hypertension are also function of sex chromosome genes [192]. Studies revealed that sex-linked genes have a direct effect on hypertension [193]. For example, females with Turner Syndrome, caused by the absence of one X chromosome, are at a higher risk of hypertension [69]. This suggests the presence of pathways coded by sex chromosomal genes that control hypertension in the general population. Therefore, gender-based differences in hypertension may be the result of an intricate relationship between sex hormones, particularly estrogen, and sex chromosomes. To differentiate between the contribution of sex steroid hormones or sex chromosome genes to the sex-related differences such as hypertension, Four Core Genotype mouse models have been developed by Arnols *et al.* These mice are either Sry-deficient or have a Sry transgene autosomally expressed, thus making mice that are XX females, XY males, XY females

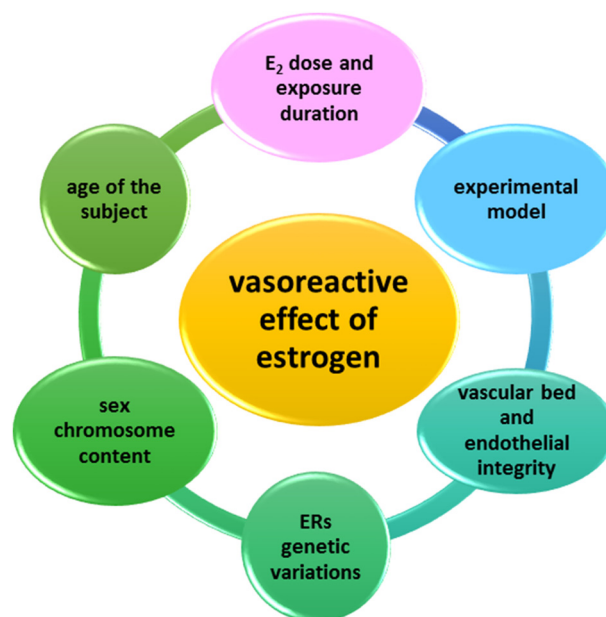


Fig. 4. Factors contributing to estrogen's effect on vasculature. Several factors affect the overall estrogen-induced vasoreactivity. These include estrogen dose and treatment duration, the studied model and its age, endothelial integrity, sex chromosome content and genetic variations in ERs.

or XX males [194]. When steroid hormones were abrogated by castration or ovariectomy, contribution of sex steroids to sex-related differences in these animals can be separated from the contribution made by sex chromosomes genes [194,195]. Using the Four Core Genotype mouse models showed that, so far, there is no clear evidence suggesting that sex chromosomes alone affect CVDs, hypertension included [195].

7.2. Genetic variations in estrogen receptors

Estrogen elicits its vasomotor effects via ER- α , ER- β or GPER, all of which are receptors expressed in the vasculature [196,197]. It has been reported that polymorphisms in ESR1 and ESR2 genes, that encode ER- α and ER- β respectively, contribute to BP regulation, as certain ER genetic variants are associated with hypertension [198,199]. In addition, different ERs show sex-related differential gene expression. The potential differential expression and cellular and intracellular localization ER- α , ER- β or GPER, may, at least partially, explain some of the sex differences in estrogen-induced responses [195]. One more consideration is that ER expression shows age-related changes and could be a source of estrogen response variation between pre- and postmenopausal women [195].

7.3. Vascular bed type and endothelial integrity

One important factor that affects the response to estrogen is the type of vessels used in *ex vivo* experiments, and the type of vascular bed from which VSMCs are extracted for *in vitro* experiments. On the other hand, the endothelium also plays a major role in mediating vascular estrogenic effects. Indeed, endothelial integrity is a major determinant of the hormonal-induced vasoconstrictive or vasorelaxant effect. Wang *et al.*, attribute these discrepancies to the extent of endothelial cell removal in a given experiment [137].

7.4. Estrogen's dose, exposure duration and experimental model used

The dose of estrogen administered to animal models, and the duration of administration significantly affect vasoreactivity in response to estrogen. One study proposes that the reason behind the

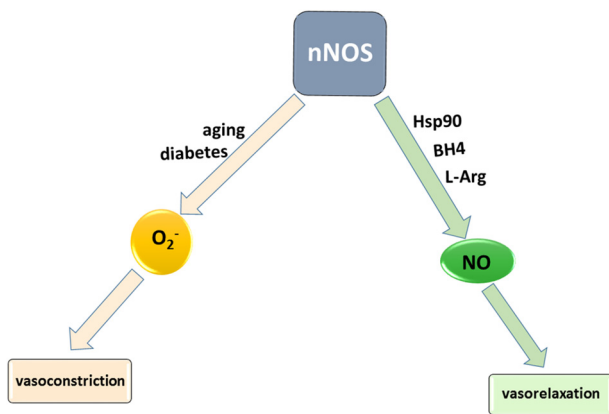


Fig. 5. The nNOS microenvironment in VSMC dictates estrogen vasoreactivity. Owing to its several domains and cofactor-binding sites, nNOS may lead to NO or O_2^- production, depending on its microenvironment. Aging and diabetes favor O_2^- release, leading to vasoconstriction. Cofactors such as Hsp90, BH4, and L-Arg activate the reductase function of nNOS, leading to NOS production, and thus vasorelaxation.

previously established vasorelaxant effect of estrogen and the recently reported vasoconstrictive effects is due to higher dose of estrogen used in earlier studies [200]. Subramanian *et al.* clearly dissects the effect of estrogen dose in estrogen-treated mouse models [130]. The reason behind the discrepancy in their results in cardiovascular parameters, including BP, and results from previous studies is the used estrogen dose. While they used a 20 ng estrogen preparation, previous studies used a 20 fold higher concentration (0.2 to 10 μ g of various estrogenic preparations) [201,202]. Indeed, higher estrogen dose leads to higher serum concentration (190 ± 20 pg/ml), which is far from physiological level of estrogen in female rats (5–140 pg/mL). In this context, it is worth mentioning that pharmacological concentration of estrogen (10–100 nmol/L) used in *in vitro* experiments are far from physiological levels of the hormone (30–1500 pmol/L) [135,136]. In addition, estrogen exposure time adds another level of complexity to vasoreactivity in response to estrogen [130].

One additional contributor to estrogen vasoreactivity may be the animal model used i.e. whether Wistar rats, Sprague-Dawley rats, SHRs, genetic hypertensive rats, or C57BL/6J mice are used. For instance, genetically hypertensive rats needed higher doses of estrogen to increase their BP [134]. At the cellular level, the expression of GPER, which mediates estrogen-induced MLC phosphorylation and thus vasoconstriction, is reduced in cultured VSMCs compared to freshly isolated ones [135]. Thus, the time spent in culture may affect the response of the VSMCs to estrogen.

7.5. Age of the subject

The age of the experimental subject plays a major role in responsiveness to estrogen. The estrogenic response is largely affected by age, both in animal models and in humans [203,204]. For instance, 3-month old normotensive rats exhibited higher BP increase after estrogen treatment than 6-months old rats [205]. Similar pattern of BP change in response to estrogen was observed in genetically hypertensive rats [205]. This indicates that responsiveness to estrogen is more prominent at younger age [134]. It appears that age influences eNOS-dependent estrogen-induced vasodilation [203]. Postmenopausal women receiving acute or chronic estrogen treatment showed an abrogation in the estrogen-induced vasodilatory response; this abrogation was more significant in women of older age or in women who stayed longer without receiving estrogen treatment [203,206]. In addition, estrogen's direct action on the vasculature may be more important in older women because their vascular endothelium becomes increasingly dysfunctional with advanced age [204,206–208]. However, clinically, it is postulated

that the postmenopausal females who were on HRT at a late stage in their lives are at a higher risk of CVDs [209]. This is known as the “windows of opportunity and timing” hypothesis, in which the age of starting HRT affects its risk [22].

7.6. nNOS microenvironment

Recent evidence suggests that estrogen may elicit vasodilation or vasoconstriction of denuded porcine coronary arteries via its novel target, type 1 neuronal NOS (nNOS). nNOS is expressed in VSMCs and is characterized by reductase and oxygenase domains and binding sites for a variety of cofactors [210,211]. Thus, nNOS can lead to NO production or O_2^- production, depending on its microenvironment [185]. Accordingly, estrogen may employ nNOS-derived NO or nNOS-derived O_2^- to induce vasodilation or vasoconstriction, respectively (Fig. 5) [185]. It was later speculated that estrogen-induced vasodilation takes place via ER- α /PI3K/Akt/nNOS/NO signaling pathway [212]. This same pathway may lead to vasoconstriction if nNOS microenvironment was more favorable for O_2^- production, as in the case of diabetes mellitus [212].

Estrogen-induced coronary artery relaxation may also be regulated via another nongenomic pathway involving the chaperone Hsp90 [213]. Interestingly, Hsp90 level was shown to decline with age [212]. This may explain the less potent vasorelaxant effect of estrogen in aged females. In addition, aging leads to decreased levels of L-arginine and tetrahydrobiopterin (BH4), cofactors needed to maintain nNOS in the NO-producing state [214]. Accordingly, aging will aid in nNOS switch to O_2^- release in response to estrogen [185]. This may explain the vasoconstrictive effect of estrogen in HRT [185] (Fig. 5).

8. Conclusion

Taken together, the effect of estrogen on VSMC contractility and ultimately BP is still unresolved. The most explicit example would be the discrepant effect of estrogen on BP during pregnancy. Further studies are needed to clearly identify novel factors affecting vasoreactivity and how they elicit their effects. Similar future studies are needed to better characterize the net vascular effect of estrogen and the factors that determine estrogenic responses. Knowing that awareness and control of hypertension continues to be suboptimal in women [215], these studies aid in a better delineation and guidelines concerning sex and gender in relation to hypertension.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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