Female-specific long-term blood pressure regulation: Modeling and analysis

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1 Introduction

Hypertension is a global health challenge: it affects one billion people and is estimated to account for more than 60% of all cases or types of cardiovascular disease. Interestingly, women have lower blood pressure than men before menopause but higher afterwards. Yet, hypertensive men and women are typically treated using the same approach. In part due to our insufficient knowledge regarding sex-specific blood pressure regulation mechanisms, fewer women achieve blood pressure control compared to men under treatment, even though compliance and treatment rates are higher in women [2]. These data highlight the critical need to better understand the mechanisms of blood pressure control in both sexes and cast doubt on the current "one size fits all" therapeutic approach.

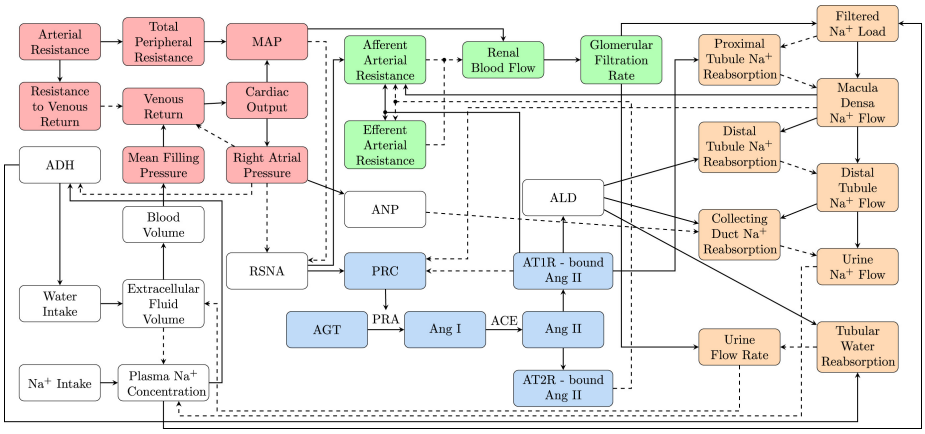


Figure 1: Flowchart of the model developed in [6].

Through mathematical modeling and simulations, the authors in [6] have identified which factors contribute to the sexual dimorphism in response to antihypertensive therapies targeting the renin angiotensin system (RAS). They have

developed a sex-specific blood pressure regulation model that includes sex differences in the renin-angiotensin system (RAS), baseline adosterone level, and the reactivity of renal sympathetic nervous activity (RSNA) as depicted in Fig. 1. A novel aspect of the model is the representation of sex-specific vasodilatory effect of the bound angiotensin II type two receptor (AT2R-bound Ang II) on renal vascular resistance. Sex-specific model parameters were identified by fitting reaction rate constants separately to normotensive RAS hormone levels for men and women in steady state. However, **the model has two major drawbacks**:

- It does not account for dynamic changes in hormones, particularly estradiol (E_2) and progesterone (P_4) levels, throughout the female life span.
- It does not take into account other mechanisms that influence vasodilation, e.g. proper endothelial function or dysfunction.

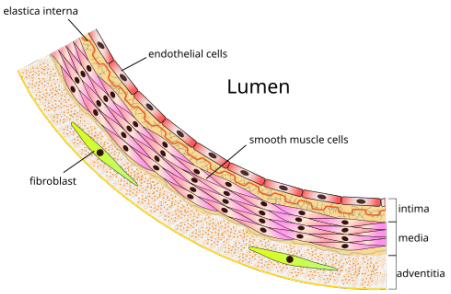
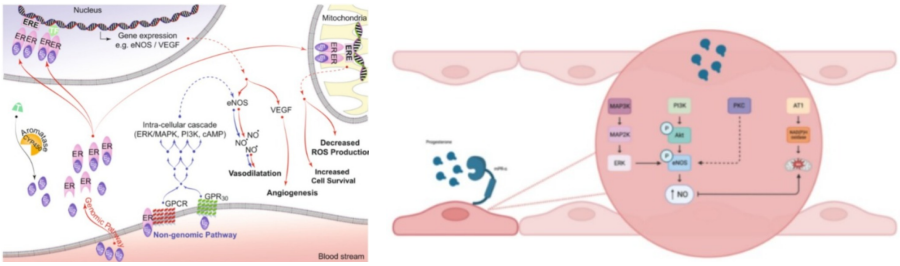


Figure 2: Vessel walls. Figure taken from [1].

The endothelium is a thin layer of single flat (squamous) cells that line the interior surface of blood vessels (and lymphatic vessels), see Fig. 2. Endothelial cells are involved in many aspects of vessel function, including blood clotting, inflammation, angiogenesis (i.e. formation of new blood vessels), and blood pressure control through vasoconstriction and vasodilation. Vasodilation works to decrease vascular resistance and blood pressure through relaxation of smooth muscle cells within the vessel walls. Endothelial dysfunction, or the loss of proper endothelial function, is a hallmark for vascular diseases. Impaired endothelial function, causing hypertension and thrombosis, is often seen in patients with coronary artery disease, diabetes mellitus, hypertension, hypercholesterolemia, as well as in smokers. One of the main mechanisms of endothelial dysfunction is the decrease of nitric oxide (NO) production. Nitric oxide is biosynthesized endogenously from L-arginine, oxygen, and NADPH by various nitric oxide synthase (NOS) enzymes. The endothelium uses nitric oxide to signal the surrounding smooth muscle to relax, resulting in vasodilation and increasing blood flow. Once nitric oxide is converted to nitrates and nitrites by oxygen and water, cell signaling is deactivated.

E_2 and P_4 have been linked to the bio-availability of NO; their cellular mechanisms of actions and pathways have been characterized (Fig. 3). However,

there are contradictory results on their interactions with NO due to the nature of the experiments. Many experiments that discuss the cardio-protective role of E_2 and P_4 are performed in postmenopausal women during Hormonal Replacement Therapy (HRT), which differs from the actions from endogenous produced hormones [3, 8]. Such experiments lead to contradictory conclusions regarding premenopausal women. The extrapolation from one group to the other does not hold, since the body undergoes systemic changes during peri-menopause, including loss of sex hormone receptors [**?**]. Recently, angiotensin II has also been linked to NO; thus, to endothelial function [4]. This would complete a feedback loop that is still not included, between the model developed in [6] and arterial resistance.



(a) E_2 pathway. (b) P_4 pathway.

Figure 3: Schematic diagrams of pathways for E_2 (left, from [3]) and P_4 (right, from [8].

To close this gap, this thesis aims at constructing a dynamic mathematical model based on physiological descriptions and first principles to explore the interactions between E_2, P_4, NO and vasodilation for cases where experimental findings are still contradictory. The **specific aims** are:

- To obtain a minimal sex-specific model for blood pressure regulation by applying model reduction techniques to remove the sub-models for renal hemodynamics (green nodes) and renal Na^+ handling and urine production (orange nodes) from the model by Leete et al. [6].
- To study the effect of healthy menstrual cycles and post-menopausal hormone levels on blood pressure regulation by relating the sex-specific parameters to dynamic changes in E_2 and P_4 hormone levels.
- To include the vasodilatory effect of NO into the model by extending it with a sub-model for endothelial function depending on E_2 and P_4.

2 Workplan

- **Task 1 (months 1-3): Implementation of a minimal model**
  As a first step, the model by Leete et al. [6] needs to be re-implemented

since the authors did not publish their source code. In a second step, model reduction techniques [7] will be applied to obtain a minimal model that still contains variables that describe cardiovascular function and the RAS.

- **Task 2 (months 4-6): Model analysis and simulations**
  First, interaction points with E_2 and P_4 will be identified based on a literature review. The focus will be on parameters that Leete et al. [6] have identified as being sex-specific. Hill kinetics will be implemented to include stimulatory and inhibitory effects of E_2 and P_4 on these parameters. Finally, dynamic hormone input curves for E_2 and P_4 in pre- and post-menopausal women will be used to run model simulations and to analyze the results.

- **Task 3 (months 7-9): Model extension**
  Based on the schematic diagrams in [3] and [8] (Fig. 3), an ordinary differential equation model for the cellular signaling pathways leading to NO production and degradation will be constructed, based on models suggested by [5]. The effects of E_2 and P_4 will be included in this model based on mechanisms described in literature. Finally, the output of this model (NO) will be coupled to the model from task 1 by being included into the equation for arterial resistance (as vasodilation decreases arterial resistance).

The remaining 3 months will be spent on finalizing the writing of the thesis. No new results will be genrated in this time.

References

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