Research Article / Araştırma Makalesi

How Do Paroxetine and Citalopram Affect the Force of Contraction in Endothelially Investigated and Damaged Aortic Tissue?

Endoteli Sağlam ve Hasarlı Aort Dokusunda Paroksetin ve Sitalopram Kasılma Kuvvetini Nasıl Etkiler?

Raviye ÖZEN KOCA [1], Zülfikare Işık SOLAK GÖRMÜŞ [1], Hatice SOLAK [2], Gülnur AKDOĞAN [1]

[1]Department of Physiology, Necmettin Erbakan University, Faculty of Medicine, Konya, TÜRKİYE
[2]Department of Physiology, Kütahya Health Sciences University, Faculty of Medicine, Kütahya, TÜRKİYE

Abstract

Background: Depression is common in patients with cardiovascular disease. Clinical data on the potential cardiovascular effects of the most commonly used antidepressant drugs, serotonin reuptake inhibitors (SSRI), are controversial. The present study aimed to compare the effects of citalopram and paroxetine on muscle contraction in endothelial intact and damaged aortic tissues of rats.
Materials and Methods: Thoracic aortic tissue sections were removed from 12 male Wistar Albino rats divided into Healthy Endothelium Aorta Paroxetine (HEParox), Damaged Endothelium Aorta Paroxetine (DEParox), Healthy Endothelium Aorta Citalopram (HECital), Damaged Endothelium Aorta Citalopram (DECital) groups. The tissues were placed in the isolated organ bath system. Maximum contraction was obtained by adding 10^{-6} M phenylephrine (PE) to the endothelium intact groups. Endothelial damage was created in the aorta sections in the endothelium damaged groups and 10^{-6} M PE was given. After controlling the endothelial damage by adding 10^{-6} M acetylcholine (Ach), a second dose of PE was added and maximum contractions were recorded. When the contractions reached a plateau, cumulative doses of 10^{-8} – 10^{-3} M paroxetine and citalopram were added to the relevant groups. Muscle tension parameters occurring 10 minutes before PE addition, 10 minutes after addition, and 5 minutes after each drug dose were evaluated. Statistical analyses of the study were performed with the R 4.3.1 program.
Results: Paroxetine and citalopram caused significantly different time-dependent changes in aortic contraction, with citalopram exerting a stronger inhibitory effect than paroxetine in both healthy and damaged endothelium ($p < .001$). When the change in tension values over time was compared in pairs within the group, significant differences were detected ($p < .05$). When the tension values over time were compared between the groups, significant differences were detected ($p < .001$).
Conclusions: Paroxetine and citalopram produced a dose-dependent suppressed contractile response in endothelial-intact aortic tissue. In endothelial-damaged aortic tissue, only citalopram produced a suppressed contractile response. This result demonstrates that citalopram is endothelium-independent, whereas paroxetine is endothelium-dependent. More research is needed on the safety and efficacy of frequently preferred SSRI antidepressant drugs such as paroxetine and citalopram in cardiovascular disease conditions.

Keywords: Aorta, Cardiovascular, Contraction, Paroxetine, Citalopram.

Öz

Amaç: Depresyon kardiyovasküler hastalığı olanlarda yaygın olarak görülmektedir. En sık kullanılan antidepresan ilaçlar olan serotonin geri alım inhibitörlerinin (SSRI'lar) potansiyel kardiyovasküler etkilerine ilişkin klinik veriler tartışmalıdır. Mevcut çalışmada sitalopram ve paroksetinin sıçanların endotel sağlam ve hasarlı aort dokularındaki kas kontraksiyonuna etkilerinin karşılaştırılması hedeflenmiştir.
Materyal ve Metod: Endotel Sağlam Aort Paroksetin (HEParox), Endotel Hasarlı Aort Paroksetin (DEParox), Endotel Sağlam Aort Sitalopram (HECital), Endotel Hasarlı Aort Sitalopram (DECital) grubu olarak ayrılan 12 adet erkek Wistar Albino cinsi sıçandan torasik aort doku kesitleri çıkarıldı. Dokular izole organ banyosu sistemine yerleştirildi. Endotel sağlam gruplara 10^{-6} M fenilefrin (PE) uygulanarak maksimum kasılma elde edildi. Endotel hasarlı gruplardaki aort kesitlerine endotel hasarı oluşturulup 10^{-6} M PE verildi. 10^{-6} M asetilkolin (Ach) uygulanarak endotel hasarı kontrol edildikten sonra ikinci doz PE uygulanarak maksimum kasılmalar kaydedildi. Kasılmalar plato çizince ilgili gruplara 10^{-8} – 10^{-3} M paroksetin ve sitalopram dozları kümülatif olarak uygulandı. PE verilmeden önceki 10. dakika ile verildikten sonraki 10. dakika ve her ilaç dozu uygulamasından sonraki 5 dakikalık sürede meydana gelen kas gerim parametreleri değerlendirildi. Çalışmanın istatistiksel analizleri R 4.3.1 programıyla gerçekleştirildi.
Bulgular: Paroksetin ve sitalopram aort kasılmasında zamana bağlı önemli ölçüde farklı değişikliklere neden oldu; sitalopram, hem sağlıklı hem de hasarlı endotelde paroksetinden daha güçlü bir inhibitör etki gösterdi ($p < .001$). Gerim değerlerinin zamana göre değişimi grup içinde ikişerli karşılaştırıldığında anlamlı farklılıklar saptandı ($p < .05$). Zaman içi gerim değerleri gruplar arasında karşılaştırıldığında anlamlı farklılıklar tespit edildi ($p < .001$).
Sonuç: Paroksetin ve sitalopram endoteli sağlam aort dokusunda doza bağlı baskılanmış bir kontraktil yanıt meydana getirmiştir. Endoteli hasarlı aort dokusunda ise yalnız sitalopram baskılanmış bir kontraktil yanıt meydana getirmiştir. Bu sonuç sitalopramın endotelden bağımsız, paroksetinin ise endotele bağımlı bir şekilde etkinlik gösterdiğini ortaya koymaktadır. Paroksetin ve sitalopram gibi sık tercih edilen SSRI türü antidepresan ilaçların kardiyovasküler hastalık durumlarındaki kullanımlarının güvenliği ve etkinliği hakkında daha fazla araştırmaya ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Aort, Kardiyovasküler, Kasılma, Paroksetin, Sitalopram

Corresponding Author / Sorumlu Yazar

Raviye Ozen Koca MD, PhD
Department of Physiology, Necmettin Erbakan University, Faculty of Medicine, Konya, TÜRKİYE

E-mail: raviyeozen@gmail.com

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Introduction

Cardiovascular diseases (CVD) pose a significant burden on public health systems, especially in elderly, mostly because this patient group often has multiple comorbidities (1). CVD refers to age-related electrical and functional changes in the heart, including systolic and diastolic dysfunctions and arrhythmias (2).

Depression is highly prevalent in patients with CVD. One in every five patients with coronary artery disease or heart failure is depressed. CVD and depression profoundly affect overall quality of life, even more so for heart failure patients. CVD patients are more depressed than the general population. Depressed individuals are more likely to eventually develop CVD and also have a higher mortality rate than general population. CVD patients who are also depressed have poorer outcomes than non-depressed patients. Both behavioral and biological mechanisms have been investigated as potential pathways linking depression to CVD risk. Regarding hypertension, some studies suggest that depression may increase cardiovascular risk by reducing nocturnal blood pressure drop (3).

Major depression or worsening of previous mood disorders is a common adverse outcome of coronary heart disease (CHD), heart failure, and cardiac revascularization procedures (4). Despite the proven effects of antidepressant treatment in patients with heart disease, the use of some antidepressants has been shown to be associated with adverse cardiac and noncardiac events that can lead to decreased patient survival as well as increased mortality and morbidity (5). Focusing specifically on newer generations of antidepressants, some notable adverse events have been reported, emphasizing individualization of treatment to minimize these side effects (6).

Although many pharmacological and behavioral therapies are available to treat depression, it is not yet clear which treatments are best for reducing the risk of CVD and depression-related death. It is increasingly important to identify alternative treatments that directly target the impaired pathways in patients with both CVD and depressive symptoms (7). The effects of depression on the cardiovascular system include positive chronotropic effects, increased blood pressure, cardiac arrhythmia, platelet aggregation, and negative effects on inflammation. Antidepressants used in the treatment of depression have been shown to reduce the risk of developing CHD (8).

Depression is common in older adults and individuals with CVD. Although selective serotonin reuptake inhibitors have been shown to be generally safe for treating depression in these patients, it is important to identify additional antidepressants when selective serotonin reuptake inhibitors are not effective. Each medication has different recommended uses, dosing intervals, cardiovascular effects, general advantages and disadvantages. However, with careful administration and attention to the potential adverse reactions of each medication, selective serotonin reuptake inhibitor antidepressants can provide safe and effective alternatives for older adults and patients with cardiovascular disease (9). There are no adequate studies to evaluate the safety of antidepressants in patients with cardiovascular disease or those at high risk. More research is needed on the safety and efficacy of paroxetine and citalopram, which are frequently preferred in the treatment of SSRI family, for use in CVD. The aim of the current project is to investigate the effects of citalopram and paroxetine, which are known to be widely used antidepressants in the management of depression and anxiety, on contractile force in endothelial-damaged and healthy rat aortic tissue.

Materials and Methods

This study was approved by the Necmettin Erbakan University Experimental Medicine Application and Research Center Experimental Animals Local Ethics Committee (date: 20.02.2025; decision number: 2025-021). 12 male Wistar Albino rats (250-300 gr) aged 12 weeks were included in the research. The rats were kept in an environment with 12 hours of light and darkness, 24ºC room temperature and 55-60% humidity. The animals were given ad-libitum standard rat food and fresh water throughout the experiment.

Isolated Organ Bath Experiments

Cervical dislocation was applied to the experimental animals under anesthesia. Then, the thoracic aorta was rapidly isolated and placed in Krebs solution. Krebs solution is used to preserve the vitality of the tissues in the isolated organ bath system. Krebs solution is a solution that provides the physiological conditions in vivo to a certain extent in vitro. Its content allows smooth muscle cells to maintain their contractility properties at an optimal level in vitro. The content of the Krebs-Henseleit solution to be used in the experiments is as follows (in mM): $NaHCO_3$ 25.0, NaCl 118.2, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.3, $MgSO_4$ 1.2 and glucose 11.7 (pH 7.4). After cleaning of tissue and blood residues, the aorta was divided into 3-4 mm long rings. The rings were placed in the transverse plane by attaching them to the isolated organ bath hooks containing Krebs solution, thermoregulated at 37°C and continuously gassed (95% O_2 and 5% CO_2), and the tension was set at 2 grams. Changes in the isometric tension of aortic rings were recorded using a force-shifting transducer. After the tissues were hung, they were washed for 45 minutes at 15-minute intervals to wait for the effect of the anesthetic agents to decrease. Contractions were recorded by added phenylephrine (PE 10^{-6} M) to the isolated organ bath chambers. Endothelial damage was created in the aorta sections in the "Endothelial Damage" groups. After controlling the endothelial damage by adding acetylcholine (Ach) 10^{-6} M, the damaged strips were washed for 15 minutes to reduce the effect of the anesthetic agents and a second dose of PE was added to record the contractions. When the contraction plateaued after PE was added to the aorta sections, cumulative doses of 10^{-8} – 10^{-3} M paroxetine and citalopram were added to the relevant groups. Muscle tension parameters were evaluated during the 10^{th} minute before PE was added,

the 10th minute after it was added and the 5-minute period after each drug dose (10, 11).

Formation of Experimental Groups

Group 1 (Healthy Endothelium Aorta Paroxetine Group - HEParox): Phenylephrine (PE 10^{-6} M) was added to the isolated organ bath chambers and contractions were recorded. When contraction plateaued after PE 10^{-6} M was added to aortic sections, 10^{-8} – 10^{-3} M paroxetine doses were added cumulatively. Muscle tension parameters were evaluated 10 minutes before and after PE 10^{-6} M addition, and after each drug dose addition.

Group 2 (Damaged Endothelium Aorta Paroxetine Group - DEParox): Mechanical endothelial damage was created in aortic sections. PE was added to the isolated organ bath chambers and contractions were recorded. Then, after controlling the endothelial damage by adding acetylcholine (Ach 10^{-6} M), a second dose of PE 10^{-6} M was added and contractions were recorded. After PE 10^{-6} M was added to aortic slices, when contraction plateaued, cumulative doses of 10^{-8} – 10^{-3} M paroxetine were added. Muscle tension parameters were evaluated 10 minutes before and after PE addition, and after each drug dose addition.

Group 3 (Healthy Endothelium Aorta Citalopram Group - HECital): PE 10^{-6} M was applied to the isolated organ bath chambers and contractions were recorded. When the contraction plateaued after PE 10^{-6} M was added to the aortic sections, 10^{-8} – 10^{-3} M citalopram doses were added cumulatively. Muscle tension parameters were evaluated 10 minutes before and after PE 10^{-6} M addition, and after each drug dose addition.

Group 4 (Damaged Endothelium Aorta Citalopram Group - DECital): Mechanical endothelial damage was created in the aortic sections. PE was applied to the isolated organ bath chambers and contractions were recorded. Then, after controlling the endothelial damage by adding Ach 10^{-6} M, a second dose of PE 10^{-6} M was added and contractions were recorded. When the aortic sections reached a plateau in contraction after PE 10^{-6} M addition, 10^{-8} – 10^{-3} M citalopram doses were added cumulatively. Muscle tension parameters were evaluated 10 minutes before and after PE 10^{-6} M addition, and after each drug dose addition.

Statistical Analysis

Statistical analyses were performed using the SPSS software. Within-group comparisons of muscle tension values at different time points were conducted using repeated-measures ANOVA, followed by Bonferroni post hoc tests to identify specific differences. Between-group comparisons at each drug concentration were evaluated using two-way ANOVA with interaction effects, and Tukey's post hoc tests were applied where appropriate. Numerical variables were expressed as mean ± standard error (Mean ± SE), while qualitative variables were presented as frequencies and percentages. A p-value of less than 0.05 was considered statistically significant.

Results

Rat aortic tissue contractions were recorded in an isolated organ bath and normalized by dividing by dry tissue weight (mg). Data were evaluated statistically (Figure 1, Figure 2). There were significant differences between groups in terms of time-dependent change in tension values ($p < .001$) (Figure 1). When the healthy endothelium groups were compared among themselves; the contraction values recorded in the HEParox group at doses of 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} were significantly higher than the HECital group ($p < .001$) (Figure 1). When the endothelial damaged groups were compared among themselves; the contraction values recorded at doses of 10^{-8} ($p < .05$), 10^{-7} ($p < .005$), 10^{-6} ($p < .001$), 10^{-5} ($p < .001$), 10^{-4} ($p < .001$) and 10^{-3} ($p < .001$) in the DEParox group were found to be significantly higher than in the DECital group (Figure 1).

When the change in tension values according to time was compared in pairs within the group;

In the HECital group; the tension value before the 10^{-6} PE dose was recorded significantly lower than after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} citalopram doses ($p < .001$). The tension value after the dose of 10^{-6} citalopram was recorded significantly lower than before the addition of 10^{-6} PE ($p < .001$), after the addition of 10^{-6} PE ($p < .05$) and after the doses of 10^{-8} citalopram ($p < .05$). The tension value after the dose of 10^{-5} citalopram was recorded significantly lower than before and after the addition of 10^{-6} PE ($p < .001$) and after the doses of 10^{-8} citalopram ($p = .001$). The tension value after the dose of 10^{-4} citalopram was recorded significantly lower than before and after the addition of 10^{-6} PE, after the doses of 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} citalopram ($p < .001$) The tension value at the 10^{-3} citalopram dose was recorded significantly lower than before the 10^{-6} PE, after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} citalopram ($p < .001$) (Figure 1, Figure 2A).

In the DECital group; the tension value before the 10^{-6} PE dose was found to be significantly lower than after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} doses ($p < .001$). The tension value after the 10^{-6} citalopram dose was found to be significantly lower than before 10^{-6} PE ($p < .001$), after 10^{-6} PE ($p < .005$) and 10^{-8} ($p < .05$) doses. The tension value after 10^{-5} citalopram dose was found to be significantly lower than the tension before the 10^{-6} PE ($p < .001$), after 10^{-6} PE ($p < .001$), 10^{-8} ($p < .001$), 10^{-7} ($p < .001$) and 10^{-6} ($p = .01$) citalopram doses. The tension value after the 10^{-4} dose was found to be significantly lower than the tension before the 10^{-6} PE, after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} citalopram doses ($p < .001$). The tension value after the 10^{-3} dose was found to be significantly lower than the tension before the 10^{-6} PE dose, after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} ($p < .001$) and 10^{-4} ($p = .001$) citalopram doses (Figure 1, Figure 2B).

In the HEParox group; the tension value before the 10^{-6} PE was significantly lower than that after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} paroxetine doses ($p < .001$).

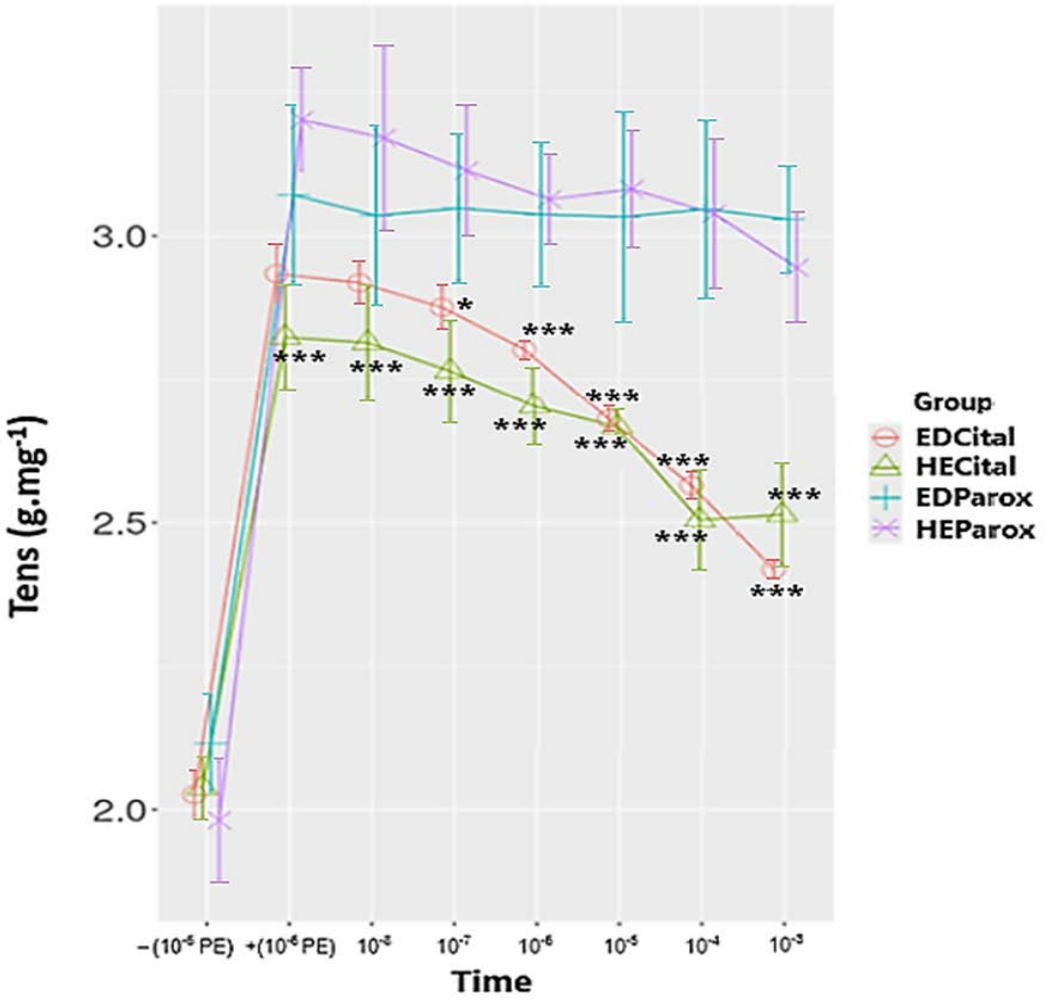

Figure 1. Tension changes in tissues in response to Paroxetine (Parox) and Citalopram (Cital) added to groups.
Significant differences were found between the groups in terms of time-dependent change in tension values ($p < .001$). When tension values over time were compared between all groups, significant differences were found ($p < .001$). –(10^{-6} PE): Basal; +(10^{-6} PE): Tension values recorded in the 10-minute period after administration of 10^{-6} M PE; 10^{-8} – 10^{-3}: Tension values recorded in the 5-minute periods after cumulative doses of Paroxetine (10^{-8} to 10^{-3} M) were administered to health and damaged endothelium Paroxetine groups, and cumulative doses of Citalopram (10^{-8} to 10^{-3} M) were administered to healthy and damaged endothelium Citalopram groups. At +(10^{-6} PE) dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-8} dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-7} dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-6} dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-5} dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-4} dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-3} dose, HECital contraction is significantly lower than HEParox ($p < .001$). At 10^{-7} dose, EDCital contraction is significantly lower than EDParox ($p < .05$). At 10^{-6} dose, EDCital contraction is significantly lower than EDParox ($p < .001$). At 10^{-5} dose, EDCital contraction is significantly lower than EDParox ($p < .001$). At 10^{-4} dose, EDCital contraction is significantly lower than EDParox ($p < .001$). At 10^{-3} dose, EDCital contraction is significantly lower than EDParox ($p < .001$). *$p < .05$, ***$p < .001$. EDCital, Endothelium Damaged Aorta Citalopram Group; HECital, Healthy Endothelium Aorta Citalopram Group; EDParox, Endothelium Damaged Aorta Paroxetine Group; HEParox, Healthy Endothelium Aorta Paroxetine Group.

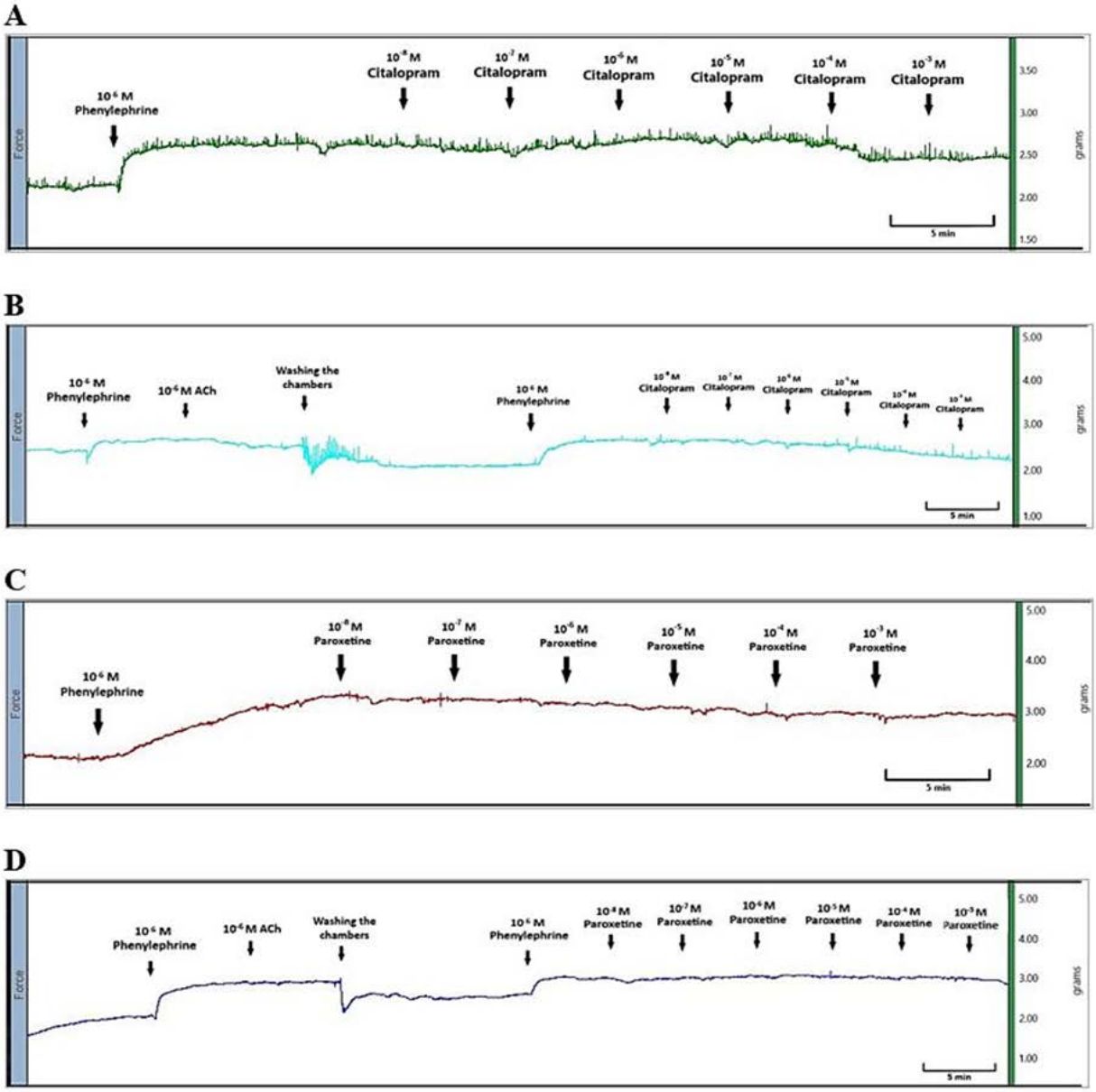

Figure 2. A, Healthy endothelium aorta citalopram group; B, Endothelium damaged aorta citalopram group; C, Healthy endothelium aorta paroxetine group; D, Endothelium damaged aorta paroxetine group

The tension value after the 10^{-6} paroxetine dose was significantly lower than before the 10^{-6} PE ($p < .001$), after the 10^{-6} PE ($p < .005$) and 10^{-8} doses ($p < .05$). The tension value after the 10^{-5} paroxetine dose was significantly lower than that before the 10^{-6} PE ($p < .001$) and after the 10^{-6} PE ($p = .01$) doses. The tension value after the 10^{-4} paroxetine dose was significantly lower than the tension caused by paroxetine before the 10^{-6} PE ($p < .001$), after the 10^{-6} PE ($p< .001$) and 10^{-6} ($p < .005$) doses. The tension value after the 10^{-3} paroxetine dose was found to be significantly lower than before the 10^{-6} PE, after the 10-6 PE, and 10^{-8}, 10^{-7}, 10^{-6} ($p< .001$) and 10^{-5} ($p< .005$) doses (Figure 1, Figure 2C).

In the DEParox group; the tension value before the 10^{-6} PE was recorded significantly lower than after the 10^{-6} PE, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} and 10^{-3} paroxetine doses ($p < .001$). No significant difference was found in other pairwise time comparisons ($p > .05$) (Figure 1, Figure 2D).

When comparing groups over time, statistically significant differences in aortic contraction were observed at all time points following PE (10^{-6}) and drug administration (10^{-8}–10^{-3}) ($p < .001$) (Figure 1). Specifically, following the 10^{-6} PE dose, contractions in the DECital group were significantly lower than those in the HEParox group ($p < .001$), and those in the HECital group were significantly lower than in both the DEParox ($p < .001$) and HEParox groups ($p < .001$). Similar patterns were observed after each subsequent drug dose, with the DECital and HECital groups consistently exhibiting

significantly lower contraction values compared to the DE-Parox and HEParox groups (p-values ranging from < .001 to .05), indicating a consistent and marked difference in vascular reactivity dependent on drug type and endothelial integrity

Discussion

Individuals with depressive disorders exhibit a higher prevalence of hypertension compared to the general population, despite some reports suggesting an association between depression and hypotension. This discrepancy may be partly explained by the influence of antidepressant medications, which can alter blood pressure regulation through their actions on adrenergic, serotonergic, histaminergic, dopaminergic, and cholinergic systems (12). Antidepressant treatment may, in certain cases, lead to a hypertensive crisis, especially as a component of serotonin syndrome, which is often accompanied by neuromuscular, cognitive, and autonomic disturbances.

Given the uncertainty around antidepressants effects on blood pressure, clinicians should assess patients' cardiovascular status before treatment. Antidepressant drugs may alter blood pressure patterns and potentially interact with antihypertensive therapies, which makes careful monitoring and thoughtful prescribing essential (12). It is therefore recommended to exercise caution when initiating antidepressant treatment and to routinely check for hypertension (13). Selective serotonin reuptake inhibitors (SSRIs), which are among the most commonly used antidepressants, have shown mixed results in terms of their cardiovascular effects. SSRIs generally have minimal effects on the autonomic nervous system and relatively mild effects on blood pressure. This makes them a safer choice for older individuals and patients with cardiovascular disease. However, beyond their central action of inhibiting the serotonin reuptake transporter in the brain, SSRIs also reduce peripheral serotonin (5-hydroxytryptamine, 5-HT) levels by blocking its uptake into platelets. Furthermore, evidence suggests that SSRIs may promote the development of atherosclerosis and thereby increase the likelihood of acute cardiovascular events through mechanisms that are not directly related to 5-HT depletion (14).

Paroxetine is one of the well-known types of SSRIs and its cardiovascular effects have been investigated in several studies. Paroxetine has been shown to affect heart rate in patients with major depressive disorder (15). Conversely, some studies have demonstrated that paroxetine may exert beneficial effects on cardiac hypertrophy, dysfunction, and fibrosis induced by hypertension in animal models. This medication has been shown to attenuate sympathetic overactivity and enhance the responsiveness of adrenergic receptors to catecholamines. In particular, paroxetine therapy inhibits the epinephrine-induced expression of genes associated with hypertrophy and fibrosis, as well as the internalization of beta-1 adrenergic receptors in cardiomyocytes. Among hypertensive patients with comorbid depression, those receiving paroxetine exhibited less severe cardiac remodeling when compared to individuals treated with other antidepressant agents. Paroxetine blocks G protein-coupled receptor kinase 2 (GRK2)-mediated adrenergic receptor beta 1 activation and internalization in the context of hypertension. This increases adrenergic receptor beta sensitivity and partially reduces cardiac hypertrophy (16).

Increased expression of GRK2 has been implicated in the development of various cardiovascular disorders, including myocardial infarction (MI). Although paroxetine is known to inhibit GRK2, evidence supporting its protective effects following MI remains limited. One experimental study using an animal model of MI explored the potential cardioprotective properties of paroxetine and found that pretreatment with the drug helped mitigate post-MI cardiac remodeling. This was achieved through modulation of fibrotic, inflammatory, and angiogenic pathways. These findings suggest that paroxetine may hold therapeutic promise as a cardioprotective agent by attenuating adverse structural and molecular changes in the heart following MI (17).

Pulmonary hypertension is often accompanied by right ventricular (RV) failure, which remains a major contributor to both morbidity and mortality. In a study utilizing a rat model of pulmonary hypertension, the impact of paroxetine on RV performance was assessed. Treatment with paroxetine led to marked improvements in RV systolic function, demonstrated by significant increases in stroke volume, cardiac output, and ejection fraction. Notably, these improvements occurred without substantial changes in RV hypertrophy, myosin heavy chain or titin isoform transitions, or levels of fibrosis. The enhancement in systolic function is thought to be primarily related to the antioxidant properties of paroxetine (18). There is also evidence linking depression to the pathogenesis of atherosclerosis. One experimental study investigated the comparative effects of escitalopram—a selective serotonin reuptake inhibitor (SSRI) with antihyperlipidemic properties—and atorvastatin in a rat model of high-fat diet-induced atherosclerosis. Escitalopram, the S-enantiomer of citalopram, was administered for six weeks. The treatment was associated with notable reductions in serum total cholesterol, triglycerides, low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL), alongside a decrease in malondialdehyde levels. In parallel, a significant increase in high-density lipoproteins (HDL) was observed compared to the untreated atherosclerosis group. These findings indicate that escitalopram can attenuate atherosclerotic progression, supporting its potential suitability as an antidepressant in elderly populations (19). Another study explored the role of the serotonin transporter (SERT) in regulating contractile responses to 5-hydroxytryptamine (5-HT) in the pulmonary arteries of rats, and how this regulation is influenced by chronic hypoxia. The SERT inhibitor citalopram was used to evaluate its effects on 5-HT-induced vasoconstriction in isolated pulmonary artery segments and compared

to responses in systemic arteries. Results showed that citalopram enhanced 5-HT-induced contractions specifically in intralobar pulmonary arteries. Interestingly, this potentiation was found to be endothelium-dependent under normoxic conditions but shifted to an endothelium-independent mechanism following chronic hypoxic exposure. These observations suggest that SERT activity plays a role in modulating local 5-HT concentrations near vasoconstrictive receptors in the pulmonary vasculature. The data suggest that, in contrast to normoxic rats, in pulmonary arteries from hypoxic rats the SERT responsible for this effect is not located in the endothelium but rather is likely located in smooth muscle. The data are consistent with reports that hypoxia in the pulmonary circulation induces/upregulates SERT and thus increases 5-HT uptake in vascular smooth muscle. The findings may have implications for the use of SERT inhibitors recommended for the treatment of pulmonary hypertension (20).

Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening condition that carries a high risk of morbidity and mortality. Some earlier studies have proposed a potential link between maternal use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy and an elevated risk of developing PPHN. Contemporary data indicate that SSRI exposure in utero is associated with a statistically increased risk of PPHN. Nevertheless, the overall clinical relevance of this risk appears limited and is generally considered to be outweighed by the therapeutic advantages of treating maternal perinatal depression. Since untreated perinatal depression is itself linked to negative outcomes for both the mother and the fetus, the increased risk of PPHN does not, in most cases, warrant cessation of antidepressant treatment. Ongoing research is warranted in this area, especially in light of the rising rates of maternal depression and the corresponding increase in antidepressant use during pregnancy (21).

In the context of pulmonary hypertension, both serotonin (5-hydroxytryptamine, 5-HT) transport and receptor-mediated mechanisms may be upregulated, contributing to heightened vasoconstriction in the pulmonary arteries. One investigation evaluated how inhibitors of the serotonin transporter (SERT) and antagonists of 5-HT receptors influence 5-HT-induced vasoconstrictive responses in pulmonary vasculature. Findings from this study revealed that SERT inhibitors like citalopram can exacerbate pulmonary vasoconstriction. However, this effect was mitigated when co-administered with 5-HT(1B) receptor antagonists. Notably, a synergistic effect was observed between the actions of 5-HT(1B) receptor blockade and SERT inhibition, suggesting a potential therapeutic approach for modulating serotonin-induced pulmonary vascular responses (22).

SSRIs exhibit cardioprotective effects. One study investigated whether SSRIs regulate endothelial cell expression of vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM-1) and adhesiveness to U937 monocytes. The effects of citalopram, fluvoxamine and fluoxetine were evaluated in human aortic endothelial cells. It has been reported that SSRIs may exhibit anti-inflammatory activity on endothelial cells and reduce circulating VCAM-1 and ICAM-1 in vivo, which may be a mechanism that partially mediates cardioprotective effects (23). In another study that included patients with major depression who had psychotic symptoms, it was reported that 6 months of antidepressant treatment with citalopram and risperidone improved endothelial function and improved arterial stiffness (24). Since it is known that hypertension, one of the most important risk factors for the development of CVD, has a two-way interaction with depression, the effects of citalopram administration in the management of hypertension were also examined. A randomized clinical trial was conducted in 72 patients with concomitant depression and hypertension, and beneficial effects of citalopram in lowering blood pressure were observed (25).

In addition to selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and citalopram, the effects of other antidepressants on both skeletal and smooth muscle function have been investigated using isolated organ bath models. Agomelatine, an SSRI with melatonergic activity, was shown to inhibit myometrial contractions in a dose-dependent manner (26). Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has been demonstrated to significantly alter contractile parameters of isolated rat diaphragm muscle in a dose-dependent fashion (27). These findings emphasize the importance of assessing both central and peripheral effects of antidepressants across various muscle tissues, particularly in patients with comorbid conditions.

Paroxetine, whose efficacy was studied in aortic tissue, was shown to attenuate the decreased relaxation response in diabetes-induced endothelial dysfunction (28). Another study on aortic tissue found a decreased vasoconstrictor response in adult rat offspring exposed to maternal fluoxetine during pregnancy and lactation (29).

In the present study, the contraction patterns resulting from cumulative paroxetine and citalopram applications in healthy and damaged endothelial aortic tissues were examined, and significant differences were detected between the groups and in the within-group values ($p < 0.05$). In healthy endothelial aortic tissues, both paroxetine and citalopram administration caused an inhibitory effect on PE-induced contractions. However, the contractile inhibition in the HE-Cital group was significantly more pronounced than in the HEParox group, indicating that citalopram may have a stronger vasodilator effect compared to paroxetine. In aortic tissues with damaged endothelium, it was noted that citalopram administration caused an inhibitory effect on PE-induced contractions; but paroxetine administration did not cause any significant change in contraction values. This suggests that the efficacy of citalopram is endothelium-independent, whereas paroxetine is endothelium-dependent. Paroxetine probably through a nitric oxide-mediated mec-

hanism. In a similar study, it was shown that sertraline, another type of SSRI, inhibited phenylephrine-induced contractions in isolated rat thoracic aortic tissue and that this effect may be mediated by nitric oxide (10). In a separate study, agomelatine, another SSRI antidepressant, was shown to cause a dose-dependent nitric oxide-dependent inhibition of intact rat thoracic aortic tissue contraction (30). Another study found that amitriptyline, fluoxetine and tranylcypromine caused inhibition of rat aortic tissue contractions, probably by activation of the NO-cGMP pathway (31). On the other hand, a study on patients with major depression reported that decreased nitric oxide production, which contributes to increased cardiovascular risk, was reversed by paroxetine administration (32). Although all these study results and the findings of the current study support the idea that the suppressive effect of paroxetine on tissue contraction may be endothelium-mediated; it is not clear by which mechanism citalopram causes a stronger inhibitory effect than paroxetine.

Limitations

This study has several limitations. All experiments were conducted in vitro using isolated rat aortic tissue, which may not fully replicate the complex in vivo vascular environment or systemic pharmacokinetics of SSRIs. Only male Wistar Albino rats were used, limiting the generalizability of the findings to female subjects. The study did not investigate the underlying molecular mechanisms responsible for the observed endothelium-dependent and -independent effects. These findings should be further expanded with in vivo studies with larger and gender-balanced samples.

Conclusion

This study demonstrates that both paroxetine and citalopram suppress phenylephrine-induced contractions in endothelium-intact rat aortic tissue in a dose-dependent manner. Notably, only citalopram retained its inhibitory effect in endothelium-damaged tissue, suggesting an endothelium-independent mechanism of action. In contrast, paroxetine's vascular effects appear to be endothelium-dependent, potentially involving nitric oxide pathways. These findings provide novel insights into the differential vascular actions of SSRIs and highlight the importance of endothelial integrity in their vascular response. Clinically, it appears likely that use of both drugs will increase coronary and peripheral blood flow, providing beneficial effects in depression-related cardiovascular disease. However, much more research is needed to better understand the effects of these drugs in clinical practice.

Ethical Approval: *This study was approved by the Necmettin Erbakan University Experimental Medicine Application and Research Center Experimental Animals Local Ethics Committee (date: 20.02.2025; decision number: 2025-021).*

Author Contributions:
Concept: R.Ö.K., Z.I.S.G., H.S., G.A.;
Literature Review: R.Ö.K., G.A.;
Design: R.Ö.K., Z.I.S.G., H.S., G.A.;
Data acquisition: R.Ö.K., G.A.;
Analysis and interpretation: R.Ö.K., Z.I.S.G., H.S., G.A.;
Writing manuscript: R.Ö.K., G.A.;
Critical revision of manuscript: R.Ö.K., Z.I.S.G.
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