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Does Sertraline Affect Contraction in Endothelium Damaged Aorta?

Sertralin, Endotel Hasarlı Aortta Kontraksiyonu Etkiler Mi?

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ÖZET
Amaç: Selektif Serotonin Geri Alım İnhibitorü (SSRI) grubu antidepresanlar kalp hastalarında sık kullanılmaktadır. Çalışmada sertralinin (SE) aort kontraksiyonu üzerine etkilerini sağlıklı/hasarlı sıçan aortu üzerinde araştırmayı amaçladık.
Gereçler ve Yöntem: 24 Wistar albino rat ile grup1-aort-sağlam endotel, grup2-aort-hasarlı endotel oluşturuldu. İzole edilen aort dokuları organ banyolarına yerleştirildi. Aort halkalarının izometrik gerilimindeki değişiklikler kaydedildi. Fenilefrin (PE 10-6M) uygulanması sonrası her iki grupta kasılmalar kaydedildi. Sonrasında grup1'e kümülatif SE 50 mg, (10-9-10-4M) verildi. Grup2'de aort endotel hasarı kontrolü için asetilkolin (Ach 10-6M) uygulanıp bir saat süreyle dokular yıkandı, ikinci doz PE, ardından kümülatif olarak SE verildi (10-9-10-4M), kasılmalar kaydedildi.
Bulgular: Grup1'e kümülatif SE (10-9-10-4M) verildikten sonra ilk üç sertralin dozunda (10-9,10-8,10-7) spontan kasılmalarda belirgin inhibisyon saptandı (p<0.05), kalan sertralin dozlarında kasılma inhibisyonu devam etti. SE 10-6,-5,-4,10-9,-8,-7 kıyaslandığında kontraksiyonlarda inhibisyon oluştu (p<0.005). Grup2'de ikinci PE kasılmalarının inhibisyonu sertralin dozlarından sonra da devam etti, ancak grup1'e göre inhibisyon daha az gözlendi (p<0.05).
Sonuç: SE sıçan izole aortunda PE kaynaklı düz kas kontraksiyonunu inhibe etmiştir. Endotel hasarlı aortta PE kaynaklı düz kas kontraksiyonları daha yavaş inhibe olmuştur. Hasar sonucunda aortta NO salınımı ve NO'ya bağlı vazodilatasyonun azaldığı düşünülmektedir. Sertralinin kardiyovasküler sistem üzerindeki etkilerinin daha net anlaşılabilmesi ileri araştırmalarla mümkün olacaktır.
Anahtar Kelimeler: Aort, endotel, sertralin, kontraksiyon, vazorelaksasyon

ABSTRACT
Aim: Selective Serotonin Reuptake Inhibitor (SSRI) group antidepressants are frequently used in heart patients. In the study, we aimed to investigate the effects of sertraline (SE) on aortic contraction on healthy/damaged rat aorta.
Materials and Methods: Wistar albino rats (24) were divided into group1-aorta-intact endothelium and group2-aorta-damaged endothelium. The isolated aortic tissues were placed in organ baths. Changes in the isometric tension of the aortic rings were recorded. Contractions were recorded in both groups after the application of phenylephrine (PE 10-6M). Afterwards, cumulative sertraline (SE 50 mg) (10-9-10-4M) was given to group 1. In Group 2, to control aortic endothelial damage, acetylcholine (10-6M) was applied and the tissues were washed for an hour, the second dose of PE was given, then SE was given cumulatively (10-9-10-4M), and contractions were recorded.
Results: After cumulative SE (10-9-10-4M) was given to Group 1, a significant inhibition in spontaneous contractions was detected in the first three sertraline doses (10-9,10-8,10-7)(p<0.05), and in the remaining sertraline doses contraction inhibition continued. When comparing SE 10-6,-5,-4 and 10-9,-8,-7 doses, there was inhibition of contractions (p<0.005). In group2, the inhibition of second PE contractions continued after sertraline doses, but the inhibition was observed less than in group1 (p<0.05).
Conclusion: SE inhibited PE-induced smooth muscle contraction in rat isolated aorta. PE-induced smooth muscle contractions were inhibited more slowly in the endothelium-damaged aorta. It is thought that NO release and NO-dependent vasodilation in the aorta decrease as a result of damage. A clearer understanding of the effects of sertraline on the cardiovascular system will be possible with further research.
Keywords: Aorta, endothelium, sertraline, contraction, vasorelaxation

INTRODUCTION

Cardiovascular disease (CVD) and depression stand out as the most common factors impacting quality of life in high-income countries, and it is expected to be so in countries of all income levels by 2030. CVD and depression profoundly impact overall quality of life, particularly for patients with heart failure (1). The prevalence of unknown depression among heart patients has been a subject of study for over 60 years. In a study, it was suggested conducted by Wynn (2), it was suggested that 40% of the patients who were perceived as disabled after a myocardial infarction were experiencing depression, and for many of them this condition had not been previously identified (2). Cay et al. found depression and anxiety symptoms in two-thirds of patients treated for cardiac events (3).

Depression is highly prevalent in patients with CVD and is a predictor of adverse cardiovascular outcomes and increased healthcare costs. One in five patients with coronary artery disease or heart failure experiences depression, which is at least three times higher than in the general population. Heart failure patients with coronary heart disease (CHD) and depressive symptoms have a higher likelihood of having physical limitations and lower quality of life even after considering objective measurements of cardiac function (1). The American Heart Association has issued a scientific statement recommending the elevation of depression to a risk factor status in those who have survived acute coronary syndrome. Although most studies have been conducted in patients with existing CVD, depression has been found to be associated with CHD as well (4).

Both behavioral and biological mechanisms have been researched as potential pathways linking depression to CVD risk. Regarding behavioral factors, depression has been weakly associated with multiple health risk-reducing behaviors, including physical activity, smoking, and adherence to cardiovascular medications, and several studies suggest that these factors mediate the relationship with depression, at least partially (1). Although there are various pharmacological and behavioral therapies available to treat depression, we do not know which treatments are best for reducing the risk of death associated with cardiovascular events and depression. Researchers have conducted numerous randomized controlled trials to test whether improved treatment of depressive symptoms, using cognitive-behavioral therapy, medications, or traditional antidepressant therapies such as combination therapy, can reduce both depressive symptoms and cardiovascular events (5).

Selective serotonin reuptake inhibitors (SSRIs) are a group of agents characterized by preventing the reuptake of serotonin in synaptic clefts. This leads to an increase in brain serotonin activity, which is their common mechanism of action. These agents are considered selective because they have very little activity in blocking the reuptake of norepinephrine or other neurotransmitters. SSRIs are currently the most widely used antidepressants (6, 7). SSRIs are considered as first-line pharmacotherapy for most patients with depression due to their efficacy and better overall tolerability compared to other antidepressants (8). While initially approved for depression treatment, the U.S. the Food and Drug Administration (FDA) has approved SSRIs also for various other conditions (8). Clinically, the off-label prescription of SSRIs is increasing due to their demonstrated efficacy in many other therapeutic applications. Off-label use of SSRIs may include fibromyalgia, premature ejaculation, and neurocardiogenic syncope (9).

Sertraline serves as a medication aimed at the management and treatment of a range of mental health disorders, including major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder. This medication belongs to the class of SSRIs, selective serotonin reuptake inhibitors (SSRIs), specifically designed to modulate serotonin levels in the brain. Operating as an antidepressant within the SSRIs category, sertraline functions primarily by impeding the reuptake of serotonin at presynaptic sites. Consequently, this interference with serotonin reuptake fosters an accumulation of serotonin in the neural synapses. Given serotonin's pivotal role in regulating mood, personality, and wakefulness within the central nervous system, the obstruction of its reuptake proves advantageous in conditions such as major depression. While sertraline's impact on norepinephrine and dopamine uptake is minimal, research has shown that it exhibits greater dopaminergic activity compared to other SSRI drugs. Sertraline's mechanism of action makes it highly effective when used to treat various psychiatric conditions (10).

Nitric Oxide (NO)-Mediated Vasodilation

The vasodilation process mediated by Nitric Oxide (NO) was initially demonstrated by Furchgott and Zawadzki (11), showcasing how the endothelium counteracts acetylcholine-induced vasoconstriction in vascular smooth muscle by releasing NO. Numerous experimental and clinical studies have further verified the release of NO from all arterial endothelial cells, and to a lesser extent from venous endothelial cells. Several pathological conditions lead to endothelial dysfunction primarily by a reduction in endothelium-dependent vasodilation. In cases where endothelial dysfunction progresses to the extent of impeding NO release, vasoconstriction is induced by agonists directly activating smooth muscle receptors, instead of triggering endothelium-dependent vasodilation. Contraction of smooth muscle cells is prompted by an elevation of intracellular free Ca^{2+} levels. When the endothelium is intact, this latter effect is balanced by the strong vascular relaxing effect of NO. This phenomenon holds true for various agonists, including acetylcholine, bradykinin, serotonin, adenosine, ADP, ATP, histamine, and thrombin. Notably, even angiotensin II stimulates the release of NO from the macrovascular endothelium, which can modulate the vasoconstrictive effect of angiotensin II on smooth muscle cells. However, this favorable effect can be counteracted by the simultaneous production of peroxynitrite (ONOO-) within the vascular wall, which can contribute to diverse pathological processes (12, 13).

It is believed that nitric oxide (NO) has the potential to induce vasodilation either through the direct relaxation of

vascular smooth muscle or indirectly lowering blood pressure by acting on the rostral brainstem to reduce central sympathetic output, leading to decreased norepinephrine release from sympathetic nerve terminals (14). Various abnormalities in endothelial vascular tone regulation have been demonstrated in genetic and experimental hypertension models. Individuals with essential hypertension exhibit reduced endothelium-dependent relaxation. In these patients, the response of forearm blood flow to NG-monomethyl-L-arginine also diminishes, hinting at a potential contribution of impaired nitric oxide production to their hypertension. Notably, the abnormality in endothelial function in patients with essential hypertension is not limited to single surface receptor-type agonists and cannot be corrected by increasing the substrate availability for nitric oxide synthase (15). Vanhoutte (16) proposed that the production of an endothelium-derived contracting factor by endothelial cells reduces endothelium-dependent dilator responses. Indeed, several researchers have reported elevated plasma endothelin concentrations in human hypertension. Along with the imbalance between endothelium-dependent relaxation and contraction, this abnormal endothelial function may contribute to abnormal vascular responses with increased peripheral vascular resistance, which is a central hemodynamic abnormality in hypertension (15, 17).

For more than 40 years, tricyclic antidepressants (TCAs) have been extensively used in depression treatment. However, they have also revealed serious cardiovascular side effects that could potentially limit their therapeutic value. The most common side effect of TCAs is orthostatic hypotension, which may result from impaired vasoconstriction and reduced myocardial contractility. This side effect has been observed at therapeutic doses necessary for psychiatric treatment, making it potentially dangerous when administered to elderly patients or those with pre-existing heart disease. Selective serotonin reuptake inhibitors SSRIs have become the most commonly used drugs in depression treatment due to their significantly fewer side effects compared to TCAs. However, no extensive animal studies regarding the side effects of SSRIs have been conducted. Until recently, most studies on the cardiovascular side effects of antidepressant treatment were clinical reports, and the majority of research focused on TCAs. Additionally, a few reports have suggested that they have a blocking effect on calcium entry and inhibit vasoconstriction dependent on depolarization. Selective Serotonin Reuptake Inhibitor SSRI group of antidepressant drugs is commonly used in patients with cardiovascular disorders. However, their specific effects on blood vessels have not been investigated in an experimental study. Our study aims to elucidate whether sertraline, an SSRI drug, affects the contraction of the endothelium-damaged aorta in an animal study.

MATERIALS AND METHOD

Approval for the study was granted by the Local Ethics Committee for Animal Experiments at the Experimental Medicine Application and Research Center, under decision number 035- 2021, and all procedures in the study were conducted in accordance with the ethics committee protocol. For the research, adult male Wistar Albino rats (weighing between 250-300 grams) were utilized. Two experimental groups were formed with 12 animals in each group, and their distribution was randomized. Throughout the experiment, the animals had ad libitum access to food and water and were kept under controlled conditions with a constant temperature (21 ± 2ºC) and a 12-hour dark/12-hour light cycle (lights on at 07.00) periods. The aorta extraction procedure was performed on all animals in the experimental groups between 09:00-10:00 in the morning. The groups were as follows:
- Group 1: Intact endothelium group (consisting of 12 animals)
- Group 2: Damaged endothelium group (consisting of 12 animals).

The animals were subjected to cervical dislocation under anesthesia with ketamine/xylazine (80mg/kg-20mg/kg). After cervical dislocation, the descending thoracic aorta was rapidly isolated and placed in Krebs solution. Following the removal of any residual tissue and blood, the aorta were sectioned into rings measuring 3-4 mm. The rings were placed on hooks in a transverse plane within isolated organ baths containing Krebs solution, thermoregulated at 37°C, and continuously gassed (95% O_2 and 5% CO_2) and the tension was adjusted to 2 grams. Changes in isometric tension of the aorta rings were recorded using a four-channel force transducer. After the tissues were hung, they were washed at 15-minute intervals for one hour to allow the effects of anesthetic agents to diminish. Phenylephrine (PE 10-6 M) was administered to the isolated organ bath chambers, and contractions were recorded in both groups. Subsequently, sertraline (SE 50 mg) was administered in increasing doses (10^{-9}-10^{-4} M) to group 1. In group 2, endothelial damage was induced in aorta by scratching the endothelium with a needle (18). After verifying endothelial damage by administering 10^{-6} M of Acetylcholine (Ach), the damaged strips were washed as well for one hour to reduce the effect of anesthetic agents, and it was followed by the second dose of PE administration; then, SE was administered in increasing doses (10^{-9}-10^{-4} M) to the group 2, and contractions were recorded.

Recordings of the contractions were documented in terms of both frequency and tension, utilizing the isolated organ bath system. Statistical analysis was conducted using the Friedman and Kruskal-Wallis tests, facilitating an assessment of the contraction or relaxation responses observed in the aortic segments following the administrations.

RESULTS

A total of 24 experimental animals were included in our study, distributed across group 1 (n=12) and group 2 (n=12). The initial contraction baseline in the aorta-intact group registered an average of 1376 tension-mg. Following the administration of a 10^{-6} M dose of phenylephrine, this baseline contraction surged to an average of 2588 tension-mg. Subsequent to this, sertraline administration was performed in increasing doses. When sertraline was administered at a dose of 10^{-9} M, a tension of 2281 tension-mg was recorded. At the dose of 10^{-8} M, the

tension decreased to 1926 tension-mg. A further decrease to 1848 tension-mg was noted at the 10^{-7} M dose. At the dose of 10^{-6} M, the recorded tension subsided to 1778 tension-mg. Concluding the series, the tension levels reached 1744 tension-mg at 10^{-5} M and descended to 1675 tension-mg at 10^{-4} M. Remarkably, it was observed that the difference between these obtained data was statistically significant (p=0.001) (Table 1, Figure 1).

Table 1. Dose-dependent contraction force of the intact aorta

Doses (tension-mg)	Contraction force	P-value
Self contraction	1376	p= 0.001*
PE 10-6	2588	
SE 10-9	2281	
SE 10-8	1926	
SE 10-7	1848	
SE 10-6	1778	
SE 10-5	1744	
SE 10-4	1675	

* The Friedman test was used.
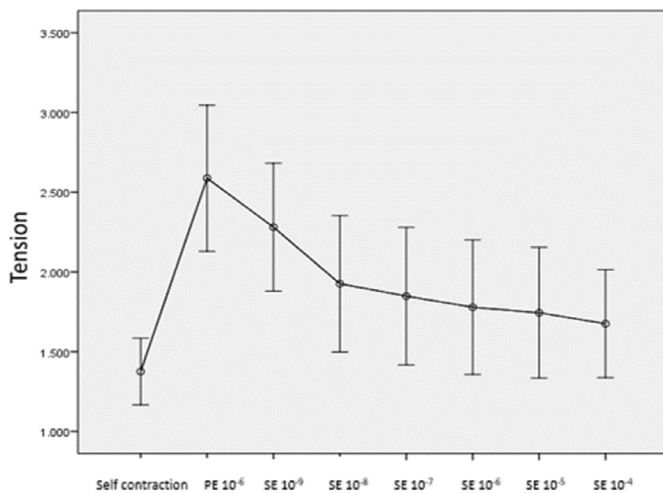
Figure 1. Drug dose-dependent contraction forces of the intact aorta

Statistically significant differences emerged in the contraction forces of the intact aorta, as affirmed by the Friedman test. To discern the specific groups accountable for these substantial disparities, pairwise comparisons were meticulously executed using the Mann-Whitney U test.

Compared against the SE 10^{-9}, SE 10-8, SE 10^{-7}, and PE 10^{-6} doses, the basal value of the intact aorta exhibited a higher vasorelaxation (p values respectively: p=0.004, p=0.000, p=0.000, p=0.000). The SE 10^{-4} dose displayed a significant increase in vasorelaxation in comparison to the SE 10^{-9}, SE 10^{-8}, and PE 10^{-6} doses (p values respectively: p=0.001, p=0.000, p=0.000). Furthermore, the SE 10^{-5} dose exhibited a significant increase in vasorelaxation when compared to the SE 10^{-9}, SE 10^{-8}, and PE 10^{-6} doses (p values respectively: p=0.050, p=0.002, p=0.000). Likewise, the SE 10-6 dose demonstrated a noteworthy increase in vasorelaxation compared to the SE 10^{-9} and PE 10^{-6} doses (p values respectively: p=0.050, p=0.001) (Table 2).

The basal contraction of the damaged aorta was recorded at an average of 1489 tension-mg. Following the administration of phenylephrine at a dose of 10^{-6} M, this contraction increased to an average of 2697 tension-mg. When ACh was administered at a dose of 10^{-6} M, an average of 2604 tension-mg was recorded. The tension labeled as "basal contraction-2" was 1384 tension-mg. Then, a second dose of phenylephrine was administered at a dose of 10^{-6} M. The tension obtained after the second dose of phenylephrine was recorded as 2816 tension-mg. Afterward, increasing doses of sertraline were administered. When sertraline was administered at a dose of 10^{-9} M, the tension was 2648 tension-mg. 10^{-8} M sertraline administration yielded a tension of 2626 tension-mg. At a dose of 10^{-7} M sertraline, the tension was found to be 2635 tension-mg. 10^{-6} M sertraline administration lowered the tension to 2571 tension-mg. At a dose of 10^{-5} M, the tension was recorded to be 2542 tension-mg, and finally, the 10^{-4} M dose, demonstrated a tension of 2422 tension-mg. It was observed that the difference between these obtained data was statistically significant (p=0.000) (Table 3, Figure 2).

Significant differences were found in the contraction forces of the damaged aorta according to the Friedman test. In order to determine which groups were the cause of this significant difference, pairwise comparisons were conducted using the ***Mann-Whitney U test.***

There was no significant difference between the first and second self contractions of the damaged aorta (p>0.05).

Table 2. Comparison of pairwise results for the intact aorta (P-significance levels)

	Self contraction	PE 10^{-6}	SE 10^{-9}	SE 10^{-8}	SE 10^{-7}	SE 10^{-6}	SE 10^{-5}
PE 10^{-6}	0.000						
SE 10^{-9}	0.000						
SE 10^{-8}	0.000						
SE 10^{-7}	0.004						
SE 10^{-6}		0.001	0.050				
SE 10^{-5}		0.000	0.002	0.050			
SE 10^{-4}		0.000	0.000	0.001			

Table 3. Dose-dependent contraction force of the damaged aorta

Doses	Contraction force (tension-mg)	P-value
Self contraction	1489	p= 0.000*
PE 10^{-6}	2697	
Ach 10^{-6}	2604	
Self contraction-2	1384	
PE 10^{-6} (2. dose)	2816	
SE 10^{-9}	2648	
SE 10^{-8}	2626	
SE 10^{-7}	2635	
SE 10^{-6}	2571	
SE 10^{-5}	2542	
SE 10^{-4}	2422	

* The Friedman test was used
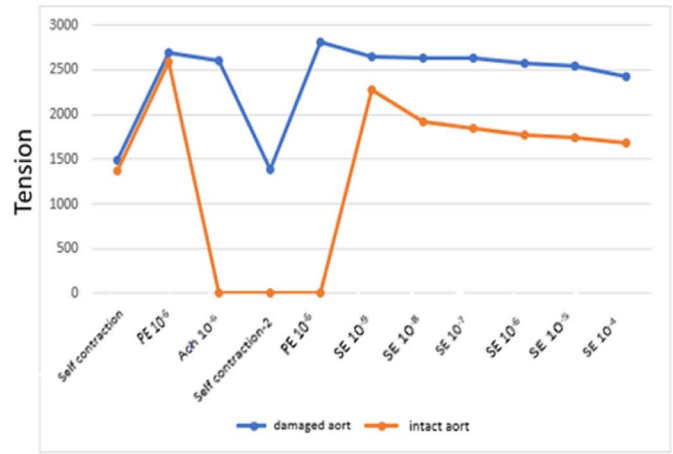
Figure 3. Dose-dependent contraction patterns in both groups (intact and damaged aorta)
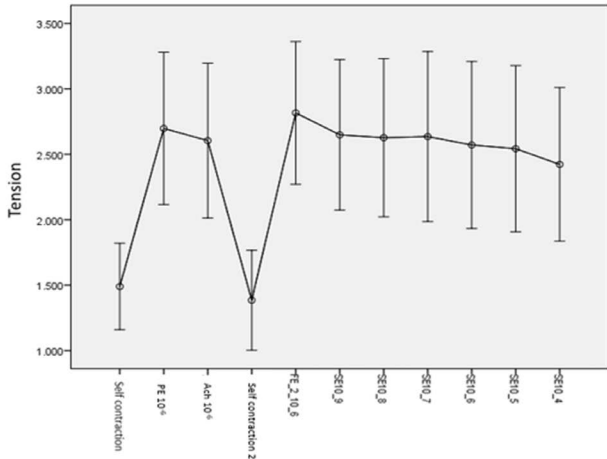
Figure 2. Dose-dependent contraction forces of the damaged aorta

The basal value of the damaged aorta showed a significant increase in vasorelaxation when compared to the SE 10^{-9}, SE 10^{-8}, SE 10^{-7}, SE 10^{-6}, PE 10^{-6}, and second PE 10^{-6} doses (p values respectively: p=0.004, p=0.002, p=0.000, p=0.031, p=0.000, p=0.000). Furthermore, second self contraction of the damaged aorta showed a significant increase in vasorelaxation when compared to the SE 10^{-9}, SE 10^{-8}, SE 10^{-7}, SE 10^{-6}, PE 10^{-6}, and second PE 10^{-6} doses (p values respectively: p=0.003, p=0.002, p=0.002, p=0.025, p=0.000, p=0.000). Additionally, the SE 10^{-4} dose also showed a significant increase in vasorelaxation when compared to the PE 10^{-6} and second PE 10^{-6} doses (p values respectively: p=0.002, p=0.003) (Table 4). The dose-dependent contraction responses obtained from the intact and damaged aorta are presented in Figure 3.

Table 4. Comparison of pairwise results for the damaged aorta (P-significance levels)

	Self contraction	PE 10^{-6}	Ach 10^{-6}	Self contraction-2	PE 10^{-6} (2. dose)	SE 10^{-9}	SE 10^{-8}	SE 10^{-7}	SE 10^{-6}	SE 10^{-5}
PE 10^{-6}	0.000									
Ach 10^{-6}										
Self contraction-2		0.000								
PE 10^{-6} (2. dose)	0.000			0.000						
SE 10^{-9}	0.004			0.003						
SE 10^{-8}	0.002			0.002						
SE 10^{-7}	0.002			0.002						
SE 10^{-6}	0.031			0.025						
SE 10^{-5}										
SE 10^{-4}		0.002			0.003					

DISCUSSION

Sertraline is an SSRI class drug used to manage and treat major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder. Sertraline is an antidepressant that primarily exerts inhibitory effects on presynaptic serotonin reuptake. This inhibition of serotonin reuptake leads to an accumulation of serotonin. Serotonin plays a role in regulating mood, personality, and wakefulness in the central nervous system, thus making the blockade of serotonin reuptake beneficial for disorders like major depression. Sertraline also has minimal effects on norepinephrine and dopamine reuptake, and research has shown that it exhibits greater dopaminergic activity compared to other drugs in the same SSRI class (19, 20).

Coronary artery disease (CAD) and depression have started to become a significant financial burden in recent years. Moreover, both diseases often coexist in the same individuals. Therefore, there is an increasing emphasis on antidepressant interventions in patients with CAD. Since their introduction to the market in 1987, the use of Selective Serotonin Reuptake Inhibitors (SSRIs) has significantly increased. SSRIs are increasingly prescribed to CAD patients, including those who underwent coronary artery bypass surgery (CABG) (21). However, our knowledge regarding the cardiovascular effects of SSRIs is mainly based on animal studies conducted in various vascular beds. Additionally, SSRIs have shown conflicting results with both vasodilator and vasoconstrictor responses (22). Unfortunately, the vasoactive effects of these drugs on different arteries are not always directly comparable.

Antidepressants have been found to reduce the risk of developing chronic heart disease when used in the treatment of depression and have positive effects on patients who already have this condition. It is known that the increase in total cholesterol levels leading to dyslipidemia also contributes to the increased prevalence of cardiovascular diseases. These findings were derived from studies conducted on depressive monkeys (22). The results showed an increase in heart rate as a consequence of impaired autonomic functions and an elevation in cortisol levels. In the 2000s, depression treatment associated with coronary diseases often involved the use of SSRIs for this particular reason. Moreover, it has been discovered that the use of tricyclic antidepressants is associated with the destabilization of diastolic and systolic blood pressure, as well as the development of hypertension.

The current evidence demonstrates that sertraline has a mitigating effect on atherosclerosis. Sertraline has been shown to reduce the expression of the proinflammatory cytokine interferon-gamma (IFN-γ) in blood stimulated with lipopolysaccharide (LPS) and phytohemagglutinin while increasing the expression of the anti-inflammatory and anti-atherogenic cytokine interleukin-10 (IL-10) (23, 24). Similarly, in human aortic endothelial cells (HAECs) stimulated with TNF-alpha, sertraline reduced the expression of VCAM-1 and ICAM-1 and inhibited the adhesion of HAEC to U937 monocytes. It has been proposed that sertraline stabilizes NF-κB by binding

to cell surface receptor molecules dependent on intracellular calcium influx, inducing constitutive nitric oxide synthase (cNOS) expression and NO production (25). The vascular effects of sertraline may also be mediated by endothelium-independent mechanisms through the inhibition of calcium influx into smooth muscle cells (26).

The effects of other SSRIs, such as fluoxetine, on the aorta have also been investigated in some studies. In one study, the vasorelaxant effects of fluoxetine on thoracic aortic rings of endothelium-damaged and endothelium-intact rats were examined. The cumulative increase in fluoxetine dose was shown to induce dose-dependent vasorelaxation significantly in both endothelium-intact and endothelium-damaged groups. The dilation effect of fluoxetine has been observed to occur independently from endothelium-derived dilator factors such as nitric oxide, as no significant difference was observed in the relaxation response averages between the groups (27).

Seabrook and Nolan reported a rightward shift in the 5-HT dose-response curve in rat mesenteric arteries caused by fluoxetine. A recent report by Ungvari et al. explains the finding that fluoxetine causes dilation in rat cerebral arteries. In some studies, sertraline has been found to induce concentration-dependent relaxation in pre-contracted mesenteric artery rings. Cohen and Wiley conducted a study indicating that fluoxetine exhibits vasodilatory effects in rat aorta pre-contracted with norepinephrine and 5-HT. In the study conducted by Melle (28), the effect of sertraline on the internal mammary artery was investigated. In this relevant study, it was determined that sertraline preserved the endothelium of both the human internal mammary artery and rat aorta and induced vasorelaxation. In our study, the vasorelaxant effect of sertraline was experimentally investigated in rat aorta. Two randomly assigned rat groups, one with intact endothelium and the other with damaged endothelium were prepared in our study. Phenylephrine (PE 10^{-6} M) was administered to the isolated organ bath chambers, and contractions were recorded in both groups. Then, sertraline (SE 50 mg) was administered in increasing doses (10^{-9}-10^{-4} M) to group 1. Subsequently, in Group 2, the same procedure was followed, but with the addition of acetylcholine (Ach) at a dose of 10^{-6} M, and contractions were recorded. The obtained results were recorded and compared. The basal contraction of the intact aorta was recorded as an average of 1376 tension-mg. After the application of phenylephrine at a dose of 10^{-6} M, this contraction increased to an average of 2588 tension-mg. Subsequently, sertraline was administered in cumulative doses. When sertraline was introduced at a dosage of 10^{-9} M, a resultant tension of 2281 tension-mg was observed. This value decreased to 1926 tension-mg at the 10^{-8} M dose, followed by a further reduction to 1848 tension-mg at the 10^{-7} M dose. Subsequently, at the 10^{-6} M dose, the recorded tension decreased to 1778 tension-mg. Continuing this pattern, the tension decreased to 1744 tension-mg at the 10^{-5} M dose, and finally, reached 1675 tension-mg at the 10^{-4} M dose. The difference between these obtained data was found to be statistically significant (p=0.000). In our study, it was determined that sertraline exhibited a vasorelaxant

effect in increasing doses, and this was found to be statistically significant. Similarly, a study was conducted on the damaged aorta. After damaging the aorta, sertraline was administered at cumulative doses following the protocol described in detail above. According to the results, there was no significant difference between the first and second self contractions of the damaged aorta (p>0.05). The basal value of the damaged aorta compared to SE 10^{-9}, SE 10^{-8}, SE 10^{-7}, SE 10^{-6}, PE 10^{-6}, and PE-2 10^{-6} doses, it was observed that vasorelaxation was significantly higher (p-values respectively: p=0.004, p=0.002, p=0.000, p=0.031, p=0.000, p=0.000). When comparing the second self-contraction of the damaged aorta with SE 10^{-9}, SE 10^{-8}, SE 10^{-7}, SE 10^{-6}, PE 10^{-6}, and PE-2 10^{-6} doses, a similar trend emerged and vasorelaxation was found to be significantly increased (Respectively, p-values; p=0.003, p=0.002, p=0.002, p=0.025, p=0.000, p=0.000). Moreover, the SE 10^{-4} dose exhibited a significant increase in vasorelaxation compared to PE 10^{-6} and PE-2 10^{-6} doses (p-values respectively: p=0.002, p=0.003). The vasorelaxant effect of the sertraline drug was observed in both the damaged aorta and the intact aorta. It was found that the vasorelaxant effect was less pronounced in the damaged aorta compared to the intact aorta, and this decrease was determined to be due to a reduction in NO release.

The mechanism responsible for the vasodilator responses of SSRIs has not been fully elucidated yet. Research conducted by Ungvari et al. using fluoxetine suggests that this SSRI interacts with L-type calcium channels to prevent Ca^{2+} influx. This reduction in Ca^{2+} influx by sertraline may decrease smooth muscle contraction induced by high extracellular K+, which promotes extracellular Ca^{2+} entry (29). Additionally, sertraline has also been found to reduce contractions following PE and 5-HT, which rely on (IP3-mediated) calcium mobilization/release from intracellular stores. Thus, if inhibition of calcium influx through L-type calcium channels were the primary mechanism, sertraline would not be expected to reduce receptor-mediated contractions as observed. Therefore, it is possible that the dilator effects of sertraline, similar to findings with fluoxetine, may arise from interactions with intracellular calcium signaling pathways in addition to the blockade of calcium influx through L-type calcium channels (30).

One of the limiting factors of our study is the possible contractile-relaxant mechanism of sertraline or other SSRIs at the cellular level, which we could not investigate due to our limited resources. Further detailed studies with sertraline and other SSRI drugs will help to elucidate the underlying mechanisms more clearly.

CONCLUSION

It was observed that sertraline inhibited smooth muscle contraction induced by PE in isolated rat aorta in this study. Acetylcholine administration in the endothelium-damaged aortic tissue resulted in slower inhibition of PE-induced smooth muscle contractions. Endothelial damage led to a decrease in NO release in the aorta treated with PE, causing a reduction in the NO-mediated vasodilation effect. It is suggested that sertraline inhibits PE-induced contractions through the NO mechanism. Sertraline, the most widely used antidepressant drug with a lower side effect profile, showed a significant vasorelaxative effect in isolated rat thoracic aorta. It is therefore conceivable that sertraline increases coronary and peripheral blood flow in vivo, which may contribute to its previously described beneficial effects in depression-related cardiovascular diseases. Although this study constitutes a step forward for science, new and advanced studies are also needed to better understand the effects of sertraline on the cardiovascular system.

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