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EDİTÖRE MEKTUP LETTER TO EDITOR

ENDOTRAKEAL ENTÜBASYON TARIHINE KISA BAKIŞ
Brief Overview of the History of Endotracheal Intubation

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ABSTRACT

Maintaining the patient's ventilation and oxygenation can be achieved with a simple maneuver such as repositioning the patient's head, or it can be achieved with a technique that is so complex that it requires opening a surgical airway for the patient. Endotracheal intubation is a medical procedure in which a tube is inserted into the trachea through the mouth or nose. It can be applied to ensure oxygenation in cases where oxygenation cannot be achieved, to ensure airway safety or during surgical procedures.

Keywords: *Intubation, History, Respiratory Therapy, Emergency services*

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Sayın editör,

Doku oksijenlenmesini sağlamak için öncelikle oksijenden zengin oda havasının alveollere kadar ulaşması ve burada sistemik dolaşıma katılması ventilasyonun temel taşıdır. Havayolunda tıkanıklık olması veya hastanın mevcut kliniği nedeniyle hava yolu açıklığını sağlayamayacağı durumlarda hava yolu açıklığını sağlamak ve hava yolu güvenliğini oluşturmak hayati öneme sahiptir (1). Bu amaçla baş geri çene ileri şeklinde hastaya pozisyon verilmesi gibi noninvazif yöntemler yanı sıra hava yoluna uygulanacak değişik enstürmanlar şeklinde invazif yönterler de vardır. Endotrakeal entübasyon bu invazif yöntemler içinden en sık uygulanılanıdır (2). Endotrakeal entübasyon, ağız veya burun yoluyla trakeaya bir tüpün yerleştirildiği tıbbi bir prosedürdür. Oksijenlenmenin sağlanamadığı durumlarda oksijenlenmeyi sağlamak için, hava yolu güvenliğini sağlamak için veya cerrahi işlemler sırasında uygulanabilir (3).

İlk elektif endotrakeal entübasyon Macewen tarafından 1878 yılında bildirildi. Orak kavite tümörü olan hastada hipofarinksi tıkayarak, trakeayı kan ve diğer salgıların sızıntısından korudu. Daha sonra Rosenberg ve Kuhn, entübasyon sırasında öksürük refleksini bastırmak için lokal anestezik olarak kokain verilmesini önerdiler (4). Bu gelişmelerden kısa süre sonra, O'Dwyer, pediatrik popülasyonda difterinin neden olduğu psödö membrana çözüm arayışına girdi. Enfeksiyon kaynaklı bu mekanik hava yolu tıkanıklığına karşı yine mekanik bir koruma yöntemi geliştirdi. O'Dwyer, tarafından geliştirilen temelde bir metal boru sistemiydi. Bu sistemde trakeayı veya vokal kortları görüntüleyebilecek bir ayna sistemi söz konusu değildi (4).

Magill (1888-1986), trakeal entübasyonun avantajlarını fark etti bunları raporladı. Ayrıca onun çabalarıyla anestezi bağımsız bir uzmanlık alanı haline geldi (5). 1913 yılında ilk anestezik laringoskop Jackson tarafından icat edildi ve Magill, Miller ve Macintosh tarafından modifiye edildi. Bu gelişmelerin ardından patlak veren Birinci Dünya Savaşı sırasında endotrakeal entübasyon yaygın olarak kullanılmıştır. 1942'de kürar, genel anestezi sırasında karın duvarı gevşemesi için bir kas gevşetici olarak tanımlandı ve kullanımı endotrakeal entübasyon, büyük batın ameliyatları ve diğer ameliyatlarda rutin hale geldi (6).

Batı tıbbındaki bu gelişmelere rağmen İbni Sina (980-1037) dispnede ilk orotrakeal entübasyonu tanımlamıştır. Batı dünyasında Avicenna olarak bilinen İbni Sina'nın yine batı dünyasında Canon olarak bilinen 14 ciltlik eseri yıllarca dünya genelinde temel tıp kitabı olarak

.

okutulmuştur. Arapça yazılmış ve 1025 yılında tamamlanmış bu eserde hava yolunun korunması ve ventilasyonun devamlılığı vurgulanmıştır. İbni sina solunum sıkıntısı stridor ve boğulmanın tedavilerini anlattığı bölümde (El-Kanun fi't-Tıb Cilt 3 Bölüm 9) "Etrafına pamuk dolanmış kamış veya kamış benzeri bir boru ile hava yolunu temizlemek veya dilate etmekte zarar yoktur. Boğulma devam ederse ve tedaviler başarısız olursa, trakeayı kesmek faydalı olacaktır. Baş geriye uzatılır ve cilt insizyondan önce kanca ile kıvrılır ve gerilir. Trakea görüldükten sonra kıkırdak doku kesilmesinden sakınılarak iki trakeal halka arasından insizyon yapılır. Cildin kesik kenarları içe katlanarak alttaki dokuya zarar vermeden dikilir." şeklinde endotrakeal entübasyonu tanımlamıştır (6).

Ülkemizde ilk sistemik anestezi örneği 1948 yılında kapalı sistemle azot protoksit anestezisi uygulanmasıdır (6). Azot protoksit anestezisi uygulayacak cihazın ülkemize getirildiği dönemde ülkemizde bu alanda tecrübeli kimse bulunmadığından; bu dönemde İstanbul üniversitesinde cerrahi ihtisasına yeni başlamış olan Dr. Sadi Sun bu konuda görevlendirilmiştir. Azot protoksit anestezisi için gerekli entotrakeal entübasyon Sadi Sun ve Burhanettin Toker tarafından 1949 yılında uygulanmıştır (7). Bu işlem ülkemizde raporlanan ilk endotrakeal entübasyon idi. Bu gelişmelerin ardından ilk anestezi uzmanı unvanı Cemalettin Öner'e ve Sadi Sun'a verilmiştir.

Sonuç olarak; endotrakeal entübasyon uygulaması yıllar içinde uygulama alanları ve amaçları değişiklik göstermiş olsa da elimizde ilk tarifleri olan İbni Sina'nın tarifinden çok da farklı olmamak üzere günümüz tıbbında en sık uygulanan girişimsel işlemlerden biridir.

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EDİTÖRE MEKTUP LETTER TO EDITOR

EDİTÖRE MEKTUP
Letter To The Editor

Ozlem Dulger, MD[1]

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Related publication:Menendi M , Serin AN , Özkan N.A Rare Cause Of Abdominal Pain: Vagınal Foreıgn Body. IJOHSON. 2023; 3(2):60-4.

ABSTRACT

Vaginal foreign bodies are more commonly observed in children according to the literature, however, they can also occur in adults due to multiple reasons.

Vaginal insertion of foreign objects is commonly done for therapeutic, contraceptive, abortive, and sexual stimulation purposes in adults. They can be implanted for medical causes and sexual pleasure, or by someone else during a sexual assault.

Several diagnostic tools can be used to identify foreign objects in the vagina. They can be detected with anamnesis, although they can also be identified through gynecological examination or imaging methods when the anamnesis is inadequate.

Keywords: *diagnosis , ultrasound, vaginal foreign body, X-ray*

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Dear Editor,

We have thoroughly read the article titled "A rare cause of abdominal pain: vaginal foreign body" authored by Menendi et al., which was published in the third issue of your journal in 2023 (1). We express our gratitude to the authors and editorial board for the publication that presents the diagnosis (pelvic X-ray) and management of a rarely observed vaginal foreign body. Additionally, we would like to discuss alternative techniques for diagnosing vaginal foreign bodies, including ultrasound, doppler ultrasound, and computed tomography.

Doppler ultrasound findings can be distinctive for diagnosing the presence of a foreign body in the vagina. In a case with symptoms of vaginal bleeding and foul-smelling discharge, the ultrasound examination indicated signs of vaginal distension caused by a mixture of heterogeneous- hematic substances, as well as thickening of the vaginal wall (3). During the Doppler examination, a notable observation of increased blood flow was detected in the upper two-thirds of the vaginal wall. This result was first taken as an indication of localized inflammation, which could indicate the presence of a foreign object.In the same case toilet paper in the same case was removed with vaginoscopy.

Doppler ultrasonography is a first and supplementary approach.

In an another retrospective review 181 patients were evaluated and the role of combined transperineal and transabdominal ultrasonography was investigated . X-ray imaging revealed abdominal findings in just 43 out of the 181 cases, accounting for 23.7% of the total. According to the study, using a combination of transperineal and transabdominal ultrasonography could be beneficial for identifying foreign objects, particularly when the foreign object is greater than 5 mm in size(4).

Consequently, ultrasonography may be the most appropriate approach for the initial assessment of suspected vaginal foreign bodies because of its noninvasive nature, lack of radiation exposure, and cost-effectiveness.

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DERLEME REVIEW

CARDIAC EFFECTS OF AGING; A REVIEW

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ABSTRACT

This review examines the alterations in the cardiovascular system that occur during aging. It analyzes relevant scientific articles and research findings, focusing on the important disorders that may occur in the heart structure and function as we age. The review discusses the consequences of aging-related changes on the cardiovascular system and the investigation of their function in the emergence of cardiovascular disease. The main conclusions drawn indicate that even if aging's phenotypes are clearly identified, the health of the heart is greatly impacted by the recently identified molecular mechanisms of cardiac aging and its implications for heart disease. In addition to presenting some of the most recent developments in the creation of therapies to prevent or reverse cardiac aging, this review will give an overview of the phenotypic changes associated with cardiac aging and the molecular mechanisms behind these changes. It acknowledges current limitations due to the limited scope and variability of existing studies and highlights the need for more comprehensive, long-term studies to further investigate healthy heart aging. In summary, the review underlines the significant benefits of addressing the adverse effects of aging on heart health in improving cardiovascular health and potentially reducing the risk of cardiovascular disease.

***Keywords**: Aging, Heart Aging, Cardiovascular System Health, Healthy heart aging*

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Background

This review focuses on the changes that occur in the cardiovascular system mechanisms with aging. In addition to examining the impact of age-related alterations to cardiovascular health; the benefits of studies aimed at eliminating age-associated detrimental alterations to the cardiovascular system and the potential of reducing the risk of developing cardiovascular system problems in later life were also examined.

Studies carried out to reveal the secrets of healthy aging are becoming increasingly important in order to enhance the old age population's standard of living, which is increasing day by day around the world. This review aims to provide an effective research area to improve living standards and reduce the risk of cardiovascular disease in people who are aging or who have the effects of aging on their heart mechanisms for different reasons, and to combine information with a molecular level perspective on the changes that aging causes on the heart.

Objectives

This review aims to provide an effective research area to improve living standards and reduce the risk of cardiovascular disease in people who are aging or who have the effects of aging on their heart mechanisms due to different reason, and to combine information with a molecular level perspective on the structural and functional changes that aging causes on the heart. It is expected that the information provided by the compilation will provide a projection for the studies planned to be conducted on the subject in the future. A structured search strategy was adopted to collect studies on cardiac aging.

Keywords Selection

A comprehensive set of keywords were carefully selected for the research. Key words consisted of the terms ‘mitophagy’, 'aging', 'heart', 'cardiovascular health', 'cardiovascular disorders', 'aging heart', 'health', 'failing heart', 'inflammation', 'mitochondrial dysfunction' and ‘heart failure’. Our search strategy involved using Boolean operators (AND, OR) and strategic combinations of keywords.

Database Exploration

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A comprehensive search was conducted through the large databases PubMed and Google Scholar. Only publications written in English were included in the searches.

Inclusion and Exclusion Criteria

The studies that will be covered in the review had to be within the following scope: 1. To examine how aging affects the heart. 2. To examine the effects of aging-related molecular alterations in the heart on the cardiovascular system. 3. To examine the mechanism and possible causes of cardiovascular diseases that may be affected by heart aging. 4. Must be published between January 2000 and March 2024. Studies were excluded if: 1. Studies that do not focus on changes in the cardiovascular system resulting from molecular changes in the heart due to aging. 2. Studies not published in peer-reviewed journals. 3. Publications published outside of the English language.

INTRODUCTION

Aging is a complicated, multifactorial process marked by a decrease in the function of cells, tissues, and organs as well as an increased vulnerability to severe and chronic illnesses, associated with numerous disorders that contribute significantly to morbidity worldwide (1, 2). One of the greatest achievements of human endeavor is the extension of life through adaptations to medical care, nutrition and sanitation. The resulting upward demographic change in human age offers a wide area of research for medical science on how to ensure healthy aging of people (1). Undoubtedly, with increasing age, the likelihood of developing heart failure increases. Important reasons explaining the increase in the incidence of heart failure include processes involving increased exposure to harmful factors including ischemic injury, metabolic stress, or high blood pressure. Due to the heart's limited ability for endogenous repair or regeneration, the total amount of prior injury is reflected in cardiac function at any given time. Therefore, it stands to reason that elderly individuals are more susceptible to heart failure due to a larger decline in their cardiac reserves. (3). Even without obvious damage, the heart exhibits functional and structural alterations as we age; this contributes to elderly individuals' heightened risk of heart failure (4).

Commonly, normal aging is associated with a general increase in left atrial enlargement and cardiac fibrosis, stiffening and thickening walls of the left ventricular, in particular the interventricular septum (5). There is subclinical diastolic and systolic dysfunction in the aging heart, even when

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resting heart function is not appreciably compromised. (6). As we age, changes occur at the structural, metabolic and molecular levels, such as telomere shortening, secreted factors related with aging, accumulation of somatic mutations, epigenetic alterations and alterations in non-coding Ribonucleic acid (RNA) that control the expression of genes. Many processes, such as changes in molecular mechanisms due to current influences and inflammation, mechanical stiffening and diastolic dysfunction, mitochondrial dysfunction and increased imbalance between loss and formation of cardiomyocytes driven by these changes, contribute to heart dysfunction (3). But the steady decline in cardiac reserves is the most prominent functional alteration seen in the aging heart. The most prevalent type of heart failure in elderly people, "Heart Failure With Preserved Ejection Fraction," has this crucial pathophysiological characteristic (7).

There are connections between cardiac aging and metabolic disorders such as substrate metabolism, lipid storage and insulin resistance, cellular and molecular networks, cellular interaction and epigenetic modification, mitochondrial dysfunction, mitophagy and impaired oxidative phosphorylation. In addition to increasing inflammation, oxidative stress, cell death, and Deoxyribonucleic acid (DNA) damage, all of these result in decreased Adenosine triphosphate (ATP) generation, systolic phenotype, signaling, and electron transport. Finally, various pathological conditions, such as cardiac hypertrophy caused by myocyte growth, cardiac fibrosis mediated by cell proliferation and endothelial-mesenchymal transition, hemodynamic disorder, deposition-cardiac lipotoxicity caused by lipid accumulation insufficient energy-mediated myocyte systolic dysfunction, contribute to the aging of the heart and heart failure (8).

While newborn mammals can renew myocardial tissue after an injury, research on humans and mice has shown that adult cardiomyocytes can renew at a regenerate of 0.5-2% annually (9). This indicates that the adult heart has some endogenous regenerative potential, though restricted. However, this regeneration decreases with age, suggesting a diminished capacity to offset the loss of cardiomyocytes (10). This reduction in regeneration potential may have detrimental effects, because experimentally caused loss of cardiomyocytes, even at very low levels, causes cardiomyopathy and death (11). As people age, their left ventricular mass index and left atrial size both rise noticeably. In a study, while diastolic function decreased with age, systolic function decreased moderately from young adult group to the oldest one. In addition, myocardial performance index

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is among the results reported to consistently deteriorate with age in systolic and diastolic functions (12).

Cardiac Aging and Lipid Metabolism

Dyslipidemia, characterized by high cholesterol, hypertriglyceridemia and high low-density lipoproteins, has the potential to trigger thrombosis and increase cardiovascular risk (13). Increased dysregulation of heart function with aging is linked to decreased oxidation of fatty acids. An accumulation of lipid-laden cells and free fatty acids in cardiac tissues, which is consistent with pathological cardiac hypertrophy, is an indication of this syndrome. (14). Conversely, major aging situations enhance the transport of fatty acids to cardiomyocytes. The excess of intracellular lipids results from an imbalance between the uptake and utilization of fatty acids. This leads to the formation of toxic lipid species and ultimately lipotoxicity during cardiac aging (15). A lipid molecule called ceramide causes mitochondria dysfunction in cardiomyocytes and a decrease in cardiolipin levels. Both of these accelerate aging (16). It has been reported that in type 2 diabetic mice, elevated catabolism of ceramide reduces cardiac lipotoxicity, corroborating the detrimental effects of ceramide on the heart. (17).

Increased cardiac fatty acid translocase CD36 promotes fatty acid transport and maintenance of improved cardiac lipid content during aging (18). Lipid accumulation decreases in the heart cells of aged mice depleted of CD36. Moreover, ATP formation and cardiac dysfunction also increase. (19). In contrast, fatty acid absorption and increased heart lipid content throughout aging are encouraged by high-fat diets and CD36 overexpression (20). Additionally, Suppression of peroxisome proliferator-activated receptor-γ coactivators (PGC1s) and peroxisome proliferator-activated receptor (PPAR)-α signaling occurs in cardiac dysfunction brought on by aging (21), whereas aging increases activation of PPAR-γ. (22). All of these disrupt fatty acid mitochondrial flux and result in downregulating oxidative enzymes in cardiomyocytes (23).

Ketone bodies, consisting of beta-hydroxybutyrate, acetoacetate and acetone produced by fatty acid oxidation, acts as the body's main source of energy in physiological homeostasis when on a ketogenic diet and fasting (24). Studies have shown that enzymes related to the oxidation of ketone bodies and intermediates produced by their metabolism are elevated in heart failure patients as well as experimental models. (25). Given that aging is associated with reduced use of glucose and oxidation of fatty acids, ketone bodies may be a key substrate that reduces heart dysfunction

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brought on by aging and acts as a compensating fuel. Increased flow of ketone bodies enhances the elderly heart's cardiac dysfunction. (26). In this way, aging causes cardiac hypertrophy as the heart makes up for a lack of contractile function. It not only provides energy but also metabolizes β-hydroxybutyrate, an antagonist of histone deacetylase, which promotes proliferation of cells and reduces inflammation (27). Therefore, it's possible that β-hydroxybutyrate inhibits inflammation associated with aging. Therefore, it can be said that the ketogenic diet seems advantageous for age-related cardiovascular problems. During cardiac aging, to enhance metabolism of energy and improve metabolic efficiency of heart, substantial amounts of ketones are required. More ATP is produced during beta-hydroxybutyrate catabolism than during fatty acid palmitate catabolism (28). Cardiac succinyl-CoA-3-oxoacid coenzyme A (CoA) transferase (SCOT), a mitochondrial enzyme in charge of liver independent metabolism of ketone bodies, provides significantly increased activity in aged animals (29). Absence of SCOT in mice increases sensitivity to ketosis and decreases plasma glucose and lactate levels (30). Additionally, ketone bodies are known to have metabolic effects that have an antioxidant effect via increasing the ratio of glutathione, both oxidized and reduced, so neutralizing oxygen radicals and directly reducing oxidative stress (31). Additionally, increasing ketone bodies benefit mitochondrial reconstruction by inducing the clearance of damaged mitochondria via the Parkin-mediated mitophagy pathway during cardiac aging (32). Despite the fact that ketone bodies inhibit the clearance of mitochondria, the crosstalk between fatty acid oxidation and mitophagy is especially important when it comes to cardiac aging. Research has demonstrated that a ketogenic diet can lower midlife mortality, enhance memory, and maintain a similar cardiac profile in aged mice to that of young mice. Moreover, the ketone diet inhibits longevity-related signaling of the insulin and mechanistic Target of Rapamycin (mTOR) pathway. In particular, it activates PPAR-α, a key player that controls the transcription of genes involved in mitochondrial homeostasis and ketogenesis (33). Unlike only the short-term effects of the ketone diet, its long-term effects on on cardiomyopathy related to ageing are not entirely clear. Furthermore, it is unknown how ketone bodies affect immune, endothelial and cardiac fibroblast cells.

Acetyl-CoA, the final metabolite of fatty acid oxidation and glycolysis, is a crucial cofactor in the regulation of metabolism. It feeds the Krebs cycle and produces ketone bodies. Furthermore, it has

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been reported that changes in acetyl-CoA concentration play a role in changes in histone modification and thus regulate gene expression. (34). acetyl-CoA synthetase 2 (ACSS2) and ATP-citrate lyase (ALY) are both in charge of acetyl-CoA production (35). When ACLY is insufficient, citrate-mediated nuclear acetyl-CoA production is reduced. This, in turn, inhibits p300's acetyl-transferase activity and increases autophagy, which fends off the effects of aging (36). Furthermore, nuclear acetyl-CoA synthesis is triggered by the translocation of the pyruvate dehydrogenase complex through the mitochondria into the nucleus, which is necessary for histone modification and epigenetic control (37). Additionally, diazepam binding inhibitor, or acyl-CoA binding protein, is a regulating component of autophagy and decreases cardiac fibrosis, lending credence to the hypothesis that acyl-CoA binding protein likely promotes cardioprotection in cardiac aging (38). Senescence-inducing autophagy is inhibited by cytoplasmic ACSS2 and induces adenosine monophosphate-activated protein-mediated ACSS2 nuclear translocation, which is more effective in aging outcomes than cytoplasmic ACSS2. In particular, the transcriptional capability of histone acetyltransferase (HAT), including Cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB)-binding protein (CBP) and p300/CBP-related factor, was enhanced by nuclear ACSS2 accumulation; during cardiac aging, they act as enhancers to promote the transcription of genes that are cardioprotective and to simplify in lysosomal biogenesis and autophagy (39, 40). The altered psition of ACSS2 caused reversal of senescence, demonstrating the variety of roles that acetyl-CoA plays in the regulation of heart aging. In line with acetyl-CoA, acetate has been proposed to be the substrate that ACSS2 uses to reverse the senescence phenotype in stem cells (35). Therefore, during cardiac aging, acetyl-CoA functions as a secondary messenger and a metabolic product at the same time, regulating metabolic homeostasis. However, it is still unknown how histone modification affects heart lifespan and aging. Studies have confirmed other metabolites such as malonylation, lactylation, crotonylation and glutarylation, and related posttranslational modifications in cardiac metabolism (41-44). Therefore, studies are needed that highlight the way that metabolite-related changes influence transcription and autophagy regulation, two major processes that contribute to organismal aging.

Cardiac Aging and Glucose Metabolism

Besides aging directly inhibiting fatty acid oxidation, raised insulin inhibits the action of key rate-limiting enzymes in cardiomyocytes, which helps to inactivate fatty acid oxidation (45). To make

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matters worse, lipid buildup within cells also results in post-translational changes to a number of components that control the generation of insulin. As a result, resistance of insulin accelerates and cell aging accelerates even more (46).

In contrast to the adult heart, myocardial lipid catabolism is proportionately reduced in the aged heart. In the aged heart, anaerobic glycolysis gradually replaces glucose oxidation as the primary energy source; pathophysiological alterations such heart enlargement and compromised contractile function are consistent with this (47). Additionally, insulin resistance linked to aging involves dysregulated cellular insulin activity and compromised mitochondrial structure, even in the absence of obesity (48). In particular, because glucose transporters (GLUTs) lose some of their capacity to carry glucose as we age, glucose in circulation increases dramatically, thereby leading to elevations in preprandial blood glucose levels and insulin (49). Emerging evidence suggests that cellular aging is accelerated when cells are cultured in hyperglycemia or high insulin environments. (50). Age-related insulin resistance and glucose intolerance are consistently linked to poor cardiac function as people age and can cause diabetes, cardiovascular disease, and stroke (51).

With insulin resistance and impaired glucose flux, a commensurate reduction in fatty acid oxidation and lipid accumulation occurs. As with heart failure brought on by myocardial ischemia, glycolysis is unlikely to make make up for reduced glucose oxidation and fatty acid use in the process of supplying energy. Therefore, decreased fatty acid consumption and anaerobic glycolysis work together to produce a permanent energy deficit and aberrant cardiac contractility. Additionally, the increased pentose phosphate pathway prevents glucose use in the aged heart (52). Contemporaneously, stimulation of the pentose phosphate pathway can lead to decreased fatty acid oxidation and higher cumulation of lipofuscin in cardiomyocytes, which could cause cardio-lipotoxicity (53). The exact process underlying this is still unknown, though. Consequently, pyruvate to malate via carboxylation without producing acetyl-CoA may partially explain the increased glycolytic flux. Also referred to as the anaplerotic process and partially neutralizes compromised oxidation of pyruvate, although Krebs cycle produces less energy in the mitochondria. Anaplerotic reactions appear to partially make up for deficient fuel intake and keeps pyruvate from building up in the heart.

Cardiac Aging and Inflammation

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Research suggests that despite the lipid-lowering properties of monounsaturated fatty acids, their ability to induce the release of pro-inflammatory elements within the senescence-associated secretory phenotype (SASP) from lipid metabolites is substantially heightened in the aged heart (54), in addition, exogenous lipids have been shown to build up and combine with triacylglycerols to create a large number of lipid droplets in the aging heart (55). Lipid metabolism has also been shown to influence T cell activation in cardiac aging concurrently with glucose metabolism (56). There are reports that atherosclerosis can be suppressed by macrophage fatty acid oxidation (57), however, it's unclear exactly how macrophage lipid metabolism contributes to heart aging.

One of the products produced from fatty acids is oxylipins. Pro-inflammatory prostaglandin E2, prostaglandin synthetase 2, thromboxanes and leukotrienes are among those that increase in cellular aging, while anti-inflammatory lipoxin A4 and resolvin are among those that decrease (58-60). Moreover, increased cytokines resulting from lipid metabolism promote proliferation of cardiac fibroblasts, thus leading to diastolic dysfunction and wall stiffness in the elderly heart.

The development of myocardial ischemia reperfusion injury is influenced by the inflammatory response, which can be controlled in a timely and efficient manner to aid in the healing of damaged heart tissue (61). Furthermore, the inflammatory pathway is central to the pathophysiological network of atrial fibrillation, contributing to atrial fibrosis and heterogeneous conduction, increasing susceptibility to atrial fibrillation (62). These findings demonstrate the important roles that lipid metabolism and inflammation play in heart aging.

Cardiac Aging and Autophagic Mechanisms

Autophagy is a critical mechanism for preserving tissue homeostasis in the aging heart because it is essential for the catabolism of long-lived proteins and organelles (63). When aging occurs, autophagy decreases in the heart (64). Seemingly paradoxically, although autophagy can be stimulated by reactive oxygen species (ROS) and misfolded proteins; however, misfolded proteins, malfunctioning mitochondria, and increased oxidative stress are frequently found in aging hearts, which can lead to autophagy suppression. This paradox could be explained, in part, by the possibility that prolonged autophagic activation brought on by increased oxidative stress and protein misfolding could eventually wear down the autophagic mechanism and ultimately lead to suppression of autophagy (65). The reduction of stress-induced adaptations is another characteristic of aging, which could be partially attributed to autophagy inhibition. Specifically, to increase the

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protective effect of ischemia preregulation, autophagy must be activated (66), this suggests that reduction of autophagy may be a factor in older individuals' increased sensitivity to myocardial ischemia.

Cardiac Aging and Mitochondrial Dysfunction

As a matter of fact, regenerative capacity declines with age and may be correlated with a rise in cell death. This could be linked to the buildup of senescent cells and an age-related reduction in mitochondrial function. In addition to being the heart's main source of ATP, mitochondria also play a critical role in controlling cardiomyocyte survival. One of the main characteristics of cardiac aging is mitochondrial dysfunction, which is the intersection of numerous important aging-related pathways. A key element leading to heart failure appears to be the general loss in mitochondrial function that occurs with cardiac age, this leads to an increase in the production of ROS. It has been demonstrated that as people age, their heart's production of mitochondrial ROS increases noticeably (67). Additionally, there is significant evidence that abnormal ROS production by mitochondria is linked to age-related mitochondrial dysfunction and cardiomyopathy (68).

Cardiac mitochondria are divided into two groups: subsarcolemmal mitochondria (SSM) and interfibrillar mitochondria (IFM). These two groups have distinct functions. In particular, age-related cardiac dysfunction is linked to declining IFM, while SSM remains constant with age. Defective IFM causes cardiac aging. Age-related declines in the inner mitochondrial membrane for each unit mitochondrial volume are observed in aging rats (69). Moreover, impairment of IFM regeneration and reduced IFM clearance resulted in the build-up of aberrant IFM carrying high amounts of ROS in monocytes, all of which are factors that accelerate oxidative stress and the characteristics of aging (70). With impaired IFM in the heart, aging compromises mitochondrial integrity; this disruption may be the first morphological alteration prior to cardiac hypertrophy and fibrosis. Current research on mitochondrial dysfunction in aged hearts supports the aging theory of oxidative stress, which proposes that Excessive synthesis of ROS in the mitochondria causes oxidative stress that damages mtDNA and redox-sensitive mitochondrial proteins, which in turn causes mitochondrial dysfunction and increases ROS production. It is suggested that this oxidative damage cycle that is self-repeating limits lifespan and healthspan by leading to a decline in cellular and organ functionality. Using mitochondria-specific overexpression of the antioxidant enzyme catalase in mitochondrial-targeted catalase transgenic (MCAT) mice, the direct contribution of mitochondrial oxidative

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damage to cardiac aging has been shown. Longer lifespans and characteristics of shortened cardiac aging, such as decreased cardiac hypertrophy, improved diastolic function, and improved myocardial performance, have been identified in mCAT mice. These enhancements are correlated at the molecular level with a decrease in the incidence of oxidative damage to mitochondrial proteins, mtDNA mutations, and deletions (71). This scenario is further supported by analyses carried out in mice with homozygous mutations of mitochondrial polymerase (Polg $^{m/m}$), which demonstrate considerable increases in mtDNA mutations and deletions with aging (72, 73). Polg $^{m/m}$ mice had shorter lives and in middle age developed cardiomyopathy (72, 74). It's interesting to note that mCAT partly rescues Polg $^{m/m}$ mice's cardiomyopathy and mitochondrial damage, providing more evidence that mitochondrial ROS contribute to cardiac aging (74).

Increasing evidence suggests that heart aging is characterized by the absence of mitophagy, which results in oxidized and damaged lipofuscin. This produces oxygen radicals and exacerbates mitochondrial damage in older hearts. Regarding molecular metabolism, defective mitochondria are labeled by phosphatase and tensin homolog deleted on chromosome 10 (PTEN)-induced kinase 1-Parkin-mitofusin2 (PINK1-Mfn2), and autophagosomes are attracted to target mitochondria in a way that is dependent on the LC3 receptor (75). The aberrant buildup of mitochondria in cardiomyocytes caused by Parkin ablation in aged mice highlights the significance of Parkin-mediated mitophagy during cardiac aging (76). It's interesting to note that whereas forced expression of Parkin in the heart enhanced mitochondrial health and reduced the aging process in the heart, Parkin-deleted animals displayed increased senescence capability and accumulation of aberrant mitochondria in the aged heart (77). Particularly, cardiac fibrosis is the outcome of chronic Parkin overexpression or higher Parkin expression (78), nonetheless, the mechanism is still unknown. In particular, recent discoveries suggest that throughout aging, mitochondrial autophagy results in a Parkin-independent way (79), however it's still unknown exactly what mechanism behind this behavior.

Cardiac Aging and Oxidative Stress

Another factor in metabolic restructuring is the ratio of nicotinamide adenine dinucleotide (NADH)/NAD$^{(+)}$, which is n essential factor in intracellular signaling, oxidative stress, and electron transport. It is known that NADH/NAD$^{(+)}$ ratios are increased in human hearts fails and experimental model of pathological hypertrophy (80). Based on experimental models, it is possible

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that $NAD^{(+)}$ functions partially via the mitochondrial $NAD^{(+)}$-dependent deacetylases Sirtuin (Sirt) 3 and 4, which control the transition pore of mitochondrial permeability and survival of cells, two crucial factors in the survival and functionality of cardiomyocytes. (81). In addition to their involvement in autophagy, sirtuins directly control cardiac aging's metabolic and structural reconfiguration. In the hearth, Sirt1 stimulates forkhead box class O proteins (FoxO) 1 deacetylation-dependent transcriptional activation of Rab7, thereby promoting autophagosome formation and its fusion with the lysosome (82). Additionally, an age-related decrease in $NAD^{(+)}$ causes lysosomal dysfunction and Sirt suppression, which further impairs formation of autophagy-lysosome and further increases the buildup of dysfunctional mitochondria (83). Research indicates that mtDNA mutation occurs more quickly with age, and this stops autophagy-induced defective mitochondrial breakdown via cGAS-STING and mTOR signaling activation (84, 85). Further research is needed to determine how cardiac aging affects these processes. While the correlation between autophagy and aging has been shown in cardiomyocytes, the impact of autophagy on macrophages, fibroblasts, and endothelial cells remains incompletely understood.

An early warning indicator for a number of abnormal cardiac phenotypes is increased ROS emission. ROS release primarily occurs in mitochondria, particularly in the quinol oxidation site in complex III (Qo center); here increased ROS production occurs before functional change. Mitochondria-Endoplasmic reticulum (ER) interaction regions are also strongly linked to the mitochondria's complex III Qo region, which produces ROS. Through this region, ER stress can lead to an increase in ROS and trigger mitochondrial ROS-induced ROS release (86). With regard to potential mechanisms, during heart aging, redox centers that directly react to Oxygen (O_2) to produce ROS are reduced when respirasomes are reduced. Furthermore, electron transport chain (ETC) complex activity and content both dramatically decline with cardiac aging, which directly encourages ROS assembly. Furthermore, more ROS formation in aged hearts is a result of faulty complex III in IFM rather than SSM. In these cellular compartments, Oxidative stress markers are upregulated with aging, consistent with enhanced ROS assembly in the IFM (87). Living cardiomyocytes in the aged heart depend on the synergy between oxidative metabolism of metabolites and mitochondrial synthesis of oxidants. As an example, nuclear factor-erythroid 2-related factor 2 (NRF2) is a redox-sensitive factor that mediates the removal of ROS; in older people, NRF2 is shown to be downregulated (88). Some preclinical research has indicated a connection between ROS and

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cardiac aging. Loss of mitochondrial superoxide dismutase (SOD) 2, a scavenger of ROS, produces to aging and the progress of senescence (89). In aged mice, SOD3 mutation results in constant inflammation mediated by ROS and degenerative diseases (90). Additionally, Jun N-terminal kinase is activated by mitochondrial ROS, which leads chromatin fragments to be released from cytoplasm and increase in SAPS (91). Numerous investigations have proposed potential protective advantages of a limited combination of ROS and classic ischemia preconditioning (92). Nevertheless, since aging results in an increased ROS content, the idea of ischemia preconditioning protection is not relevant to elderly individuals. Overall, Whether ROS contribute to the increased aging-related mitochondrial aging is an open-ended question. In particular, more research is needed on the complicated connection between ROS and cardiac aging, as ROS are critical molecules for a number of cardio-pathological processes, including immune response, differentiation, cardiomyocyte regeneration, and fibroblast proliferation.

By inducing autophagy, suppression of mTOR by rapamycin, in addition to ROS production, has been shown to reduce the adverse effects of cardiac aging and increase lifespan (93). According to a preclinical study, chronic mTOR suppression increased the lifespan of immunodeficient mice by slightly changing their intestinal metagenomes, certain metagenomic impacts were linked to immunological results (94). Sadly, the exact process is yet unknown, and further research is needed to determine how the mTOR inhibitor affects the immune system and how long life is extended. As expected, an appropriate amount of exercise may laten cardiac aging by increasing autophagy, and activating B-cell lymphoma (Bcl)-2 phosphorylation and its separation from Beclin1 (95). In elderly mice, alginate oligosaccharide effectively inhibits cardiac aging by enhancing mitochondrial biogenesis and maintaining mitochondrial integrity (96). Similar to this, by specifically targeting cardiolipin, the mitochondrially targeted peptide elamipretide dramatically reduces mitochondrial ROS and protein oxidation in aging hearts (97). Senolytic medications, which target and eradicate aged cells, have enormous promise for delaying the aging process; they are all found in natural products and are small molecule synthesizers. Similarly, the application of these techniques in cardiac aging is not well-supported by clinical research.

Cardiac Aging and Growth Signals

One of the mechanisms playing a role in the pathogenesis of cardiac aging is growth signaling. Increased lifespans and a significant slowing down of the aging process are linked to decreased

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levels of growth hormone (GH) and insulin-like growth factor (IGF) and enhanced insulin sensitivity (98). Insulin resistance may be regulated by GFs, insulin receptor substrate-1, and insulin receptors. These factors may also play a role in the metabolic syndrome. Regarding cardiac aging, IGF-1 and GF1-R interaction speeds up myocardial disease in mammalian heart longevity and aging. Forced myocardial IGF receptor expression in Drosophila consistently promoted cardiac aging (99). IGF-1R deficiency in cardiomyocytes blocks the development of aging-related cardiomyopathy. Some researchs have demonstrated that age-related diastolic dysfunction decreases via the endogenous IGF-IR pathway (100). In mice overexpressing IGF-1, Protection of cardiac SERCA expression and activity ameliorated irregular diastolic and systolic activity of aging hearts and a delay in cardiac aging (101). In contrast, another research found that pharmacologically targeting the cardiac IGF-1 pathway may offer a novel approach to maintaining and extending the life of the heart (102). These findings highlight the regulatory role of IGF-1/IGF-1R along the aging process, which makes it challenging to differentiate between the systemic and cardiac effects of IGF-1Research on regulated suppression of IGF-1R in cardiomyocytes and plasma IGF-1 lack have been conducted in an attempt to answer this mystery (100); high blood IGF-1 levels indicate the positive effects of forced expression of IGF-1 in cardiac tissues, and IGF-1 promotes the recovery of ischemic heart function (103). Thus, the effects of systemic and cardiac IGF-1 on cardiac aging are different.

Cardiac Aging and Glucose Transport

GLUT-1, the most abundant glucose transporter in the heart, controls basal cardiac glucose flow and is located in the sarcolemma, which is predominant in cardiomyocytes at rest. However, GLUT-4, the primary variant that accounts for approximately 70% of all GLUTs, localizes to a specific section within cells and migrates to the plasma membrane in response to insulin action and cardiomyocyte contraction. It is important that GLUT-4 may be degraded during aging, decreasing cardiomyocytes' intake and use of glucose (104). Advanced glucose end products (AGE) have also been suggested to be related to cardiomyopathy, particularly in the hearts of elderly people with diabetes (105). The buildup of AGEs in the myocardial interstitium causes the extracellular matrix proteins to crosslink excessively, which stiffens the heart muscle and causes diastolic dysfunction (106). Additionally, AGE specifically interacts with the AGE receptor to activate

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Nuclear factor kappa B (NF-κB) translocation, which increases p21 or p16 expression and stimulates ROS overproduction in the myocardium (107, 108). However, it is not fully understood how circular AGE is taken up by and removed from cardiomyocytes. Therefore, to completely understand cyclic AGE transport and AGE in individuals with aged hearts, more investigation is required.

Cross-talk between cardiac fibroblasts and cardiomyocytes, as well as cardiomyocytes, suppresses the expression of the lactate transporter and the activity of glucose metabolism enzymes, probably as a result of the fibroblast growth factor 21-adiponectin pathway when heart failure is induced by aging (109). More to the point, immunological activation in non-cardiomyocytes is associated to impaired glucose metabolism in the aged heart. High insulin levels, in particular, during aging encourage T cell activation, followed by an increase in glycolytic and insulin receptors, two factors necessary for adaptive immunity. Briefly, the polyclonal activation of CD4 and CD8 cells and the consequent multiple secretory ro-inflammatory cytokines such as interferon (IFN)-γ, Tumor Necrosis Factor (TNF), and interleukin (IL)-17 are facilitated by insulin receptor overexpression (110). Significantly, elevated insulin levels also prevent regulatory T cells from antagonize inflammation, which is a factor in heart aging (111). These findings imply that local inflammation in heart aging may be significantly triggered by the T cell-mediated immune response. Similarly, although myeloid-derived macrophages play a major role in causing chronic inflammation in the aging heart, it is currently unknown how hyperglycemia impacts cardiac macrophages in the aging process. A number of research have demonstrated that endothelial cells undergo cellular senescence as a result of hyperglycemia, due in part to decreased expression of arginase-1 and decreased synthesis of nitric oxide (112), a product crucial for vascular growth and angiogenesis. Additionally, increased glucose levels cause telomere shortening, which causes cardiac fibroblasts to senesce. (113); this is a condition that may be caused by SASP of different cell types as a result of isolated cardiac fibroblasts' hyposensitivity to hyperglycemia (114). Thus, more research is required to determine how glucose affects the aging process of different cell types.

Cardiac Aging and Telomere Shortening

The length of telomeres (115), which are repeats of DNA that act as the defensive coverings that encase chromosomal ends, is perhaps the best-known cellular marker of aging (116). Repetitive replication or other forms of cellular stress can cause telomere attrition, which can lead to cellular

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senescence, a situation in which cells long term stop growing, experience a reduction in function, and develop a pro-inflammatory phenotype (117). Human myocardial telomere length decreases by 20 base pairs per year (118). Telomeres get shorter during cell division and aging or in in return for stressors like oxidative stress and inflammation. The barelin complex is destabilized by critically short telomeres, thus disrupting the structure of the telomeric DNA, resulting in DNA damage, cell cycle arrest, cellular senescence, and cell death (119). When heart tissues from patients with end-stage heart failure were compared to those from age- and sex-matched, normal or hypertrophic obstructive cardiomyopathy individuals with no pump failing, the latter revealed shorter telomeres and less Telomeric repeat-binding factor (TRF) 2, associated with increased cardiac apoptosis. (120). Animal studies consistently indicate that telomere shortening plays a key role in heart aging and disease (116). Due to its short telomeres at being born, Mus musculus castaneus (the species of wild mouse) has an early cardiac aging characteristic. (121). Likewise, it has been demonstrated that crossing across several generations of Telomerase RNA component (TERC)-deficient mice will cause crucial telomere shortening, which will result in heart failure and myocardial remodeling that resembles the effects of aging (122), on the other hand, in cardiomyocytes derived from animals lacking TERC, severely reduced telomeres marked by γH2AX, a DNA double-strand break indicator, cause p21-dependent cardiomyocyte cell cycle arrest, which aligns with the characteristics of aging and heart disease, in line with an aging profile and an unhealthy heart (123). Delaying the process of telomere shortening could save the heart from pathological stress. TRF2 is decreased in mice with partial aortic stenosis due to biomechanical stress. Chk2 (the DNA damage response, protein) activation cardiomyocyte apoptosis and telomere length decrease are also results of biomechanical. Overexpressing telomerase reverse transcriptase or telomeric repeat binding factor 2, which are unique to the heart, attenuates these alterations (120). Cardiomyocyte apoptosis was also reduced by telomerase overexpression specific to the heart either in serum-free insulin-free stimulation in vitro or during cardiac ischemia reperfusion in vivo (124). Due to the activation of mitochondrial dysfunction, telomere shortening can have a partial cardiac effect. Increased cardiac aging in the third-generation TERC $^{-/-}$ telomerase-deficient prematurely old model of mice is linked to p53-mediated suppression of PGC-1α, which results in mitochondrial dysfunction. Moreover, in TERC mice, overexpressing PGC-1α specifically in the heart causes extended healthspan, latens the first signs of cardiac symptoms related to age, and partially heals heart function (125). Overall results from human studies and animal models indicate that telomere length in

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cardiac cells has a critical role in failure of the heart, aging of the heart, and the functioning of mitochondria. All of these findings point to the possibility that the aging effects on the heart are phenotyped by increased telomere shortening.

Cardiac Aging and Diastolic Dysfunction

Peccant active relaxation of cardiomyocytes is one of the causes behind age-related diastolic dysfunction. Calcium ions separate out of the actin-myosin complex during relaxation and are either transported to the sarcoplasmic reticulum or eliminated from the cardiomyocyte. Ca^{2+} cycling disruption, increased stiffness of the myofilament, and reduced Ca^{2+} sensitivity of the myofilament proteins, and disrupt cardiomyocyte relaxation may result from modifications to the characteristics of actin or myosin (126). Na^{+}/Ca^{2+} exchanger levels increased in response to a decrease in SERCA2 expression and action in elderly mice hearts (71, 127). Studies indicate that the aging heart preserves sarcoplasmic reticulum loading, intracellular Ca^{2+} transients, and contractions of older cardiomyocytes by compensating with an increase in L-type Ca^{2+} currents and a prolonging of action potential duration (128, 129). Post-translational revision of SERCA2, including age-associated oxidation and nitration, have also been demonstrated (130), yet it's unclear how they contribute to cardiac aging.

One of the most significant characteristics of the aging heart is altererd Ca^{2+} homeostasis because it plays a role in the coupling of cardiac excitation and contraction. While aging in progress, With the growth of cardiac myocytes, the current density of the L-type Ca^{2+} channel increases dramatically as well, leaving the L-type Ca^{2+} channel current density unaltered, this causes current density of the L-type Ca^{2+} channel to remain unchanged (131). Action potential duration increases when L-type Ca^{2+} channel inactivation gets slower, and compared to adult control cells, aged cardiac cells exhibit an increase in net Ca^{2+} flow during each action potential. (132). While messenger RNA (mRNA) or protein levels of the sarcoplasmic Ca^{2+} release channel (ryanodine receptor) do not change significantly with progressing age, the abundance of mRNA and the aging-related decreases in the sarcoplasmic reticulum Ca^{2+} pump's intensity with aging and are related to a reduced rate of sarcoplasmic Ca^{2+} retention in the aging heart (133). Age-related modifications to the Ca^{2+} cycle lead to an increase in Ca^{2+} inflow, slowing of sarcoplasmic reticulum sequestration, and prolongation of Ca^{2+} transit and contraction time (134). These changes that extend electromechanical systole can be explicated as a modification, since they increase the aged cells' capability to

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carry force after stimulation (129). This helps maintain function of heart in the aged heartBut in times of stress and aging of the heart, they also raise the risk of Ca^{2+} overload and Ca^{2+}-associated arrhythmias. While aging-related reduction in β-adrenergic receptor responsiveness is a contributing factor to decreased contractile reserve, these receptors can be seen as partially adaptive, they protect from calcium overload under stress. (135).

Cardiac excitation-contraction coupling requires a massive volume of cellular energy; myosin ATPase, ion exchange ATPase, and SERCA are the main users of energy (136). It should be noted that energy consumption and Ca^{2+} transport rates are related to post-translational modifications. As an example, the rate of Ca^{2+} transport and contractility of the heart are increased by both the phosphorylation of SERCA and RyR2 and the deacetylation of SERCA (137-139). Hearts are rich in metabolic components that support mitochondrial oxidative phosphorylation in order to meet the need for energy. Nevertheless, there are noticeable changes in the aging rat heart, namely, some components (Cav1.2, Cav1.3, HCN4 ve RYR2) decrease while the densities and proteins of others (NCX and SERCA) increase (140). Additionally, in the aging heart, ROS-induced SERCA oxidation at Cys674 causes SERCA deactivation and impaired myocyte relaxation (141). The relationship between impaired metabolism, calcium homeostasis, and myocyte systolic phenotype during cardiac aging is not entirely understood, despite the fact that the relationship between Ca^{2+} and this phenomenon has been established.

Currently, potential approaches to target the structural, functional, and molecular mechanisms at play in cardiac aging needs to be specified and further studies is needed to transform this knowledge into workable and efficient approaches.

CONCULUSION

Evidence obtained from the literature and current review information indicate that aging has an impact on the deterioration of the structural, functional and molecular mechanisms of the heart and circulatory system. It can be said that the changes that occur due to aging have an important role, especially in changing cardiovascular health, and that aging affects many mechanisms that affect cardiovascular health. At this point, the application of the 'heterochronic parabiosis' model in medicine, which is an experimental approach to investigate the role of circulatory factors in aging phenotypes and aims to develop a common circulatory system in animals of different chron-

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ological ages, comes to the agenda. With the introduction of the model into medical practice, improvements have been observed in neuromuscular and cardiac phenotypes that vary depending on age (142-144). 13 proteins were identified that were differentially expressed in plasma samples from mice; of these, growth differentiation factor-11 (GDF11) levels in circulating, a TGFβ superfamily member, have been found to be considerably lower in older mice. It has been proposed that enhancing GDF11 circulating levels in aged mice promotes neurogenesis, regeneration of skeletal muscle, regression of cardiac hypertrophy, and improves general fitness. This suggests that a systemic functional decrease in GDF11 levels occurs due to aging.

It is obvious that there are significant negative changes in cardiovascular health with age. However, more comprehensive and detailed research on inflammation, mitochondrial dysfunction and mitophagy is needed in order to protect the health of the cardiovascular system, which is gradually deteriorating due to aging, and to maintain healthy aging. Future studies on heterochronic parabiosis and at the molecular level need to focus on the deterioration of heart mechanisms with aging and cardiac aging.

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ARAŞTIRMA MAKALESİ RESEARCH ARTICLE

THE RELATIONSHIP BETWEEN LUNG CHANGES IN COMPUTED TOMOGRAPHY AND C-REACTIVE PROTEIN IN PATIENTS WITH SARS-COV-2 INFECTION

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ABSTRACT

Aim: *To investigate the relationship between chest computed tomography and C-reactive protein value in hospitalized SARS-CoV-2 infected patients.* ***Material and methods****: This study was carried out Chart-Review retrospective study in the emergency department of a training hospital. Adult patients presented emergency department from January 1, 2021, through February 1, 2021, with symptoms of SARS-CoV-2 infection and confirmed with rt-PCR were included in study. The groups were evaluated as mild, moderate and severe involvement according to the computed tomography-based weighted rating scale according to the British Society of Thoracic Imaging consensus statement. The relationship between computed tomography severity findings and C-reactive protein level was evaluated with the Spearman correlation test.* ***Results****: A total of 99 SARS-CoV-2 infected patients were included in the study. The median value of C-reactive protein value was 73 mg/L (25th and 75th percentiles: 42.5-138). Computed tomography weight scoring were listed as mild, moderate, and severe involvement. The frequencies of these involvements were mild 37 (38%), moderate 26 (26%) and severe 36 (36%). C-reactive protein values and chest computed tomography uptake levels were evaluated linearly. A statistically significant correlation was found (rho: 0.559, p: <0.001 Spearman's test).* ***Conclusion and suggestions****: In conclusion, according to the results of his study, there is a positive correlation between computed tomography findings and C-reactive protein levels in SARS-CoV-2 infected patients.*

Keywords*: Coronavirus, SARS-CoV-2, COVID-19, C-reactive protein, Tomography.*

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INTRODUCTION

The novel coronavirus disease 2019 was identified in December 2019 with the case in Wuhan. The mortality of the disease varies between 0.4% and 7% (1). The symptoms of the disease are very extensive. The most common symptoms are cough, shortness of breath, weakness, joint and muscle pains, loss of smell and taste. The first case was described with severe respiratory failure(1,2).

The burden the disease placed on the healthcare system was enormous, and researchers studied scoring systems (such as Rapid Acute Physiology Score and Rapid Emergency Medicine Score), biomarkers, and computed tomography (CT) findings to determine priority in patients (3–5). Bio markers associated with mortality were found to be low lymphocyte count, high D-Dimer, high C-reactive protein (CRP), high lactate dehydrogenase enzyme and high interleukin-6 (2). Chest CT was the most used imaging method since the early part of the pandemic that access to rt-PCR testing was limited. These laboratory and CT findings were used for the decision to isolate patients and to decide on hospitalization and admission to the intensive care unit. CT has become the clinician's choice as it is a rapid and effective diagnostic imaging method (5). Although specific findings for SARS-CoV-2 have been defined on CT, it is not sufficient to make a specific diagnosis in every patient (6). Patients with chest CT findings should be supported with inflammation markers such as CRP. In this study, we aimed to investigate the relationship between chest CT findings and CRP value in hospitalized SARS-CoV-2 infected patients.

2. Materials and Method

2.1. Type of Research

This study was designed a Chart-Review retrospective study and evaluated data collected from January 1, 2021, through February 1, 2021, in the emergency department of Ümraniye Training and Research Hospital.

2.2. Research Universe and Sample

The hospital where the study was conducted was a 750-bed training hospital. Adult patients presented symptoms of SARS-CoV-2 infection and confirmed with rt-PCR were included in study.

Only patients aged over 18 years were included in the study. Those with missing data were excluded.

2.3. Data Collection and Tools

Data of patients were collected from computer-based patient information system of hospital. Documented patient data included demographic data, comorbidities, laboratory parameters, and CT findings. Comorbidities were noted as, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, coronary artery disease, chronic renal failure, congestive heart failure, and malignancy. Laboratory parameters were noted as, white blood cell count, neutrophil count, lymphocyte count, platelet count, hemoglobin, hematocrit, mean corpuscular volume, neutrophil-to-lymphocyte ratio, and C-reactive protein.

The groups were evaluated as mild, moderate, and severe involvement according to the CT-based weighted rating scale according to the British Society of Thoracic Imaging (BSTI) consensus statement (6). CT findings that (predominant pattern) bilateral, basal, ground glass opacity (GGO), crazy paving, peripheral consolidation, reverse halo, and perilobular pattern were considered as mild. CT findings that non-peripheral GGO, complex, unilateral were considered moderate. CT findings that lobar pneumonia, cavitation, tree-in-bud, centrilobular nodules, lymphadenopathy, effusions were considered severe**.**

2.4. Ethical Aspects of the Research

Ethics committee approval was obtained from the local ethics committee with the date March 2022 and number 71. The study was conducted following the principles of the Declaration of Helsinki. Since the data were collected retrospectively and did not contain personal information, consent was not obtained from the patients or relatives within the knowledge of the ethics committee.

2.5. Statistical Analysis

Open-source software (Jamovi, Sidney, Australia, https://www.jamovi.org, v. 1.6.21) was used for the statistical analyses of the data. The normality of distribution of continuous variables was tested by Kolmogorov-Smirnov test. Continuous data were expressed as median ± (interquartile range (IQR)), Categorical data were presented as percentages and numbers. The differences between the

groups were compared using the nonparametric kruskal-wallis test. Dwass-Steel-Critchlow-Fligner test was used to compare significant groups. The pairs of correlations were analyzed by the Spearman test. A p-value of <0.05 was considered statistically significant.

3. Results

The data of 148 hospitalized patients were evaluated for the study. Forty-nine of them were excluded from the study because of incomplete data. A total of 99 patients were included in the study. The flowchart of the study is shown in Figure 1. The median age of the patient was 59 (25th-75th percentile, 48-72) years and 51 (51.5%) of the patients were female. The median value of CRP value was 73 mg/L (42.5-138). Baseline characteristics of the enrolled patients presented in table 1.

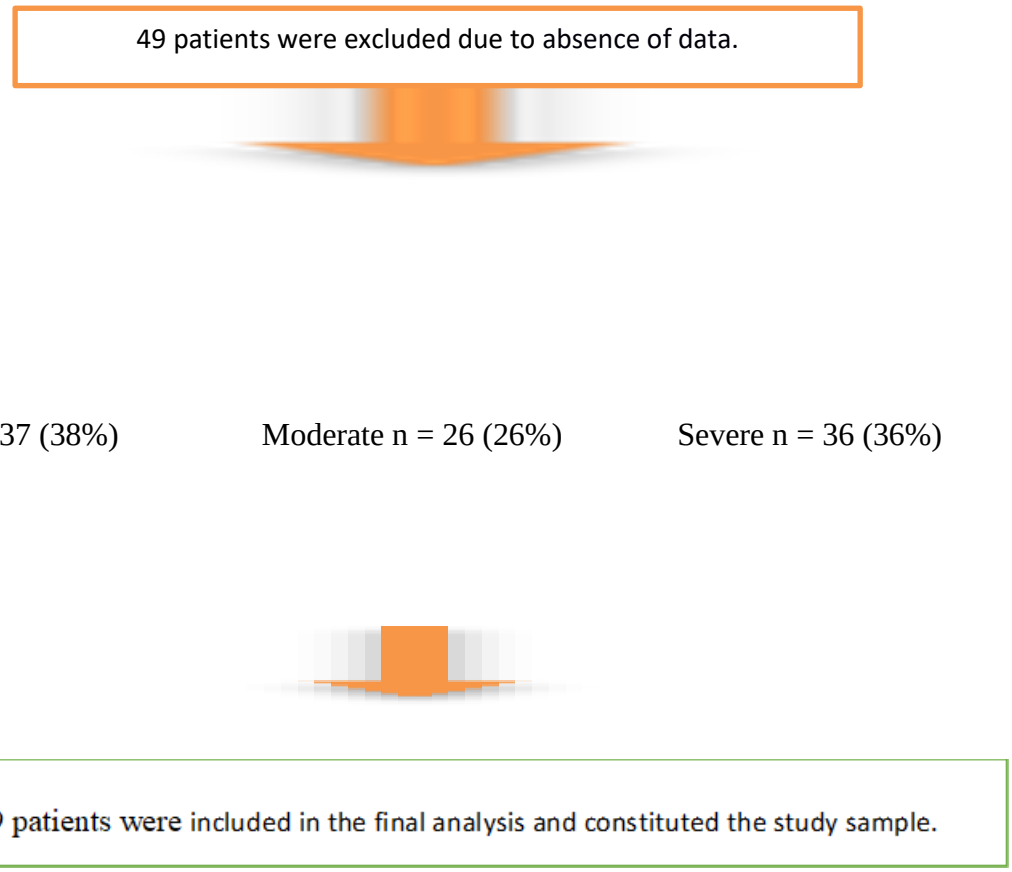

Figure 1. Flowchart of the study

Table 1. Baseline Characteristics of the Enrolled Patients

Variables	n = 99
Age, years (25^{th}-75^{th} percentile)	59 (48-72)
Sex *(%)*	
Male	48 (48.5%)
Female	51 (51.5%)

Comorbidities (%)	
Chronic obstructive pulmonary disease	6 (6.1%)
Hypertension	43 (43.4%)
Diabetes mellitus	24 (24.2%)
Coronary artery disease	5 (5.1%)
Chronic renal failure	5 (5.1%)
Congestive heart failure	7 (7.1%)
Malignancy	1 (0.8%)
Initial vital parameters (25^{th}-75^{th} percentile)	
Systolic blood pressure (mmHg)	126 (113-143)
Diastolic blood pressure (mmHg)	76 (70-80)
Pulse rate (/min)	91 (79-101)
Body temperature (∘C)	36.5 (36.4-37)
Respiratory rate (/min)	20 (18-45)
Oxygen saturation (%)	90 (86.5-93)
Mean arterial pressure (mmHg)	92 (86-99)
Initial laboratory parameters (25^{th}-75^{th} percentile)	
White blood cell count (/μL)	7.49 (5.52-9.23)
Neutrophil count (/μL)	4.68 (3.25-7.58)
Lymphocyte count (/μL)	0.92 (0.63-1.94)
Platelet count (/μL)	225 (176-274)
Hemoglobin (g/dl)	12.2 (11.2-14.1)
Hematocrit (%)	39.9 (35.4-42.8)
Mean corpuscular volume (fL)	84.5(81.6-88.5)

Neutrophil-to-lymphocyte ratio	3.9 (6.17-172)
C-reactive protein (mg/L)	73 (42.5-138)
Blood urea nitrogen (mg/dl)	30 (24-43.5)

According to BSTI-CT weight scoring; were listed as mild, moderate, and severe involvement. The highest CRP level were in severe group (131.5 mg/L (84.75-164)). The lowest Sp02 level were in severe group (87.5 % (82-90.25)). The median age was not different between the groups (mild 57 (46.75-74.5), moderate 59.5 (51.25-64.75), severe 60.5 (50.75-72) p=0.749). The need for oxygen support was highest in the severe group (4lt/min (2-5)). Pulse rate, systolic blood pressure. Diastolic blood pressure, respiratory rate, blood urea nitrogen, and lactate levels were no different between the groups. Baseline characteristics of the groups mild, moderate and severe presented in Table 2.

Table 2. Baseline Characteristics of the Mild, Moderate, and Severe Groups

	Mild	Moderate	Severe	P*
	n = 37 (38%)	n = 26 (26%)	n = 36 (36%)	
Age	57 (46.75- 74.5)	59.5 (51.25- 64.75)	60.5 (50.75-72)	0.749
Pulse Rate (/min)	91.5 (76 -104.25)	92 (83-98)	90 (83.75-100.5)	0.947
Sp02 (%)	92.5 (88.75- 96)	90.5 (88.25-93)	87.5 (82-90.25)	< .001
Systolic Blood Pressure (mm/hg)	124 (111- 135.5)	126.5 (112.5-144.75)	125.5(117.75- 44.25)	0.480
Diastolic Blood Pressure (mm/hg)	74.5 (68.75-80)	78 (75-81.75)	77(69.25-80.59	0.215
O2/Lt	2 (0-4)	2(2-2.75)	4 (2-5)	0.003
Respiratory Rate (/min)	20 (17.5-24.25)	19.5 (18-22)	22.5 (20-25)	0.130
Blood Urea Nitrogen (mg/dl)	30 (19-50.5)	29.5 (25.25-41.5)	30(23.75-45.25)	0.846
C-Reactive Protein (mg/dl)	39 (21.5-66.5)	86 (57-124.5)	131.5(84.75-164)	< .001
Lactate (mg/dl)	1.4 (0.98-1.87)	1.6 (1.25-2.05)	1.6(1.15-2)	0.789

*Kruskal-Wallis test The frequencies of these involvements were mild 37 (38%), moderate 26 (26%) and severe 36 (36%). Multiple comparisons between significant groups are shown in table 3. CRP values and BSTI-CT weight scores correlation matrix was evaluated figure 2. A statistically significant correlation was found (rho: 0.559, p: <0.001 Spearman's test).

Table 3. Multiple comparisons between significant groups

BSTI-CT weight scores	$Sp0_2$	O_2/lt	C-Reactive Protein
Mild-Moderate	0.517	0.985	0.003
Mild-Severe	< .001	0.009	< .001
Moderate-Severe	0.031	0.009	0.053

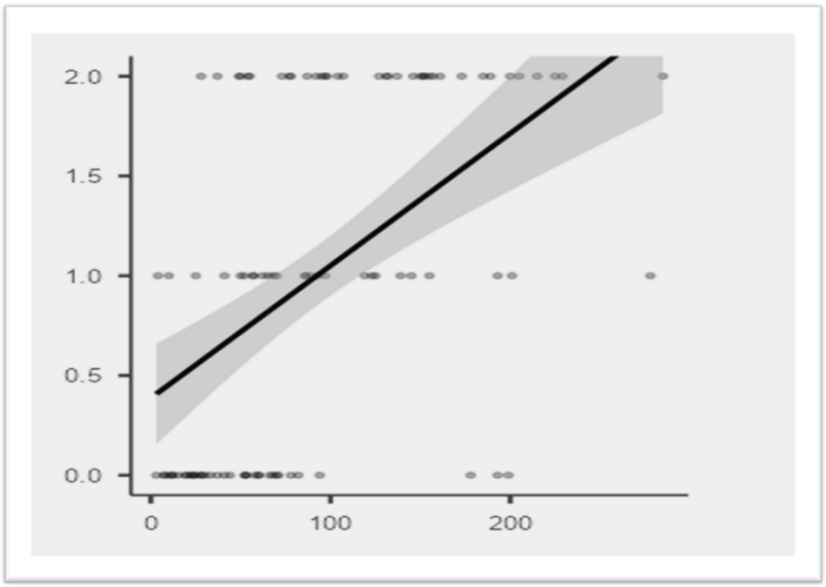

Figure 2. C-reactive protein and British Society of Thoracic Imaging Computed Tomography weight scores correlation graph.

DISCUSSION

In the present observational study with a retrospective design, the relationship between CT findings according to the British Society of Thoracic Imaging (BSTI) consensus statement and CRP was investigated. According to the results of our study, there was a positive and fair correlation between CRP and CT lung involvement.

Hematological, biochemical, and coagulation-related tests and acute phase reactants show pathological changes in patients infected with SARS-CoV-2 (7). These changes can be observed in one or more parameters. Hematological changes include lymphopenia, leukocytosis, leukopenia, and mild thrombocytopenia (8). Increases in the levels of positive acute phase reactants can be observed during infections. In many studies in the literature, elevated CRP levels were also observed in SARS-CoV-2 infection (7–10). In the study of Guan et al. with more than 1000 patients, in study of Xu et al. with 90 patients, increase in CRP was reported in early period of pandemic (9,10). More recent studies, study of Yousaf et al., and study of Özdemir and Algin, emphasized the relationship between poor outcome and high CRP (2,7). In our study, the CRP level was found to be high in 98 % of the patients and 77 % were over 50 mg/L. Based on these results, although the virulence of SARS-CoV-2 has changed with the mutations it has undergone, the importance of CRP in the management of the disease has not changed.

The most specific of the pulmonary infiltrates associated with SARS-CoV-2 infection are GGOs. Rates ranging from 60-98% and 25-53%, respectively, have been reported for the sensitivity and specificity of CT in the diagnosis of SARS-CoV-2 infection. CT findings may vary from patient to patient or according to the stage of the disease (11–13). Pan et al. reported that a large proportion of small subpleural GGOs were seen in the early phase of the disease, followed by the development of a cobblestone landscape and consolidation for up to two weeks (14). SARS-CoV-2 related pneumonia typically presents with diffuse or subzone-distributed GGO in the peripheral and posterior lung areas, it has been shown in many studies that GGO is alone or with consolidation (15). Apart from GGO, different findings have been described in the imaging of SARS-CoV-2 infected patients. A review evaluates 11 studies, reported variable rates for CT findings: 34-98% GGO, 2-64% consolidation, 41-64% consolidation and GGO, 5-71% cobblestone view, 14-80% air bronchogram, 1-33% bronchiectasis, 9-29% peribranchial thickening, 20% -28 subpleural lines, 59-82% vascular enlargement, 18-64% halo sign, 2-5% inverted halo sign, 0-32% nodules, 0-14% pleural effusion, 0-32% pleural thickening, 5%- 6 pericardial effusions, 0-8% lymphadenopathy (16).

There are studies in the literature evaluating the relationship between laboratory parameters and CT findings (17–19). Similar to the current study, Beydoğan et al. investigated the relationship

between CRP and CT findings(18). The methodologies of their study differed from the current study in that they used the Radiological Society of North America recommended criteria to assess the severity of CT findings (14,18). Tan et al. conducted research with a similar purpose. In the study of tan et al. evaluated lung lobes with CT severity criteria. Using these criteria, they demonstrated the relationship between CRP and CT severity (19). Similar results were validated in the current study using the BSTI consensus statement for CT severity.

In our study, patients in the severe group had higher CRP levels. This result will be useful for clinicians to predict whether there is lung involvement in SARS-CoV-2 patients. Likewise, high oxygen support requirement and low Sp02 levels are also associated with lung involvement of patients. These parameters can give clinicians an idea about lung involvement in cases where thorax computed tomography cannot be performed.

There are several limitations of our study. First, the retrospective design of the study is an important limitation. Secondly, its limited sample is another limitation. Third, SARS-CoV-2 subtypes could not be documented in our study.

In conclusion, according to the results of his study, there is a correlation between chest CT findings and CRP levels in SARS-CoV-2 infected patients. We think that CRP levels can be used to predict lung involvement in cases where CT imaging cannot be performed, and CRP levels can support clinical decision making.

5. Acknowledgement.

None.

6. Author's Contributions

Planning the study, reviewing the literature, methodology, analysis and editing, writing: XXXX.

7. Conflict of Interest

There is not a conflict of interest.

8. Financial Disclosure

There is not a financial support

9. Ethical Approve and Informed Consent

Ethical approval was obtained (XXX University of health sciences AAA Training and Research Hospital Clinical Research Ethics Committee 10/03/2022/71).

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ARAŞTIRMA MAKALESİ RESEARCH ARTICLE

CİDDİ COVİD-19 HASTALARINDA İNFLAMATUAR İNDEKSLERİN PROGNOZ İLE İLİŞKİSİ
RELATIONSHIP OF INFLAMMATORY INDICES WITH PROGNOSIS IN SEVERE COVID-19 PATIENTS

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ABSTRACT

Defined as inflammation indices; It is possible to obtain ratios such as systemic inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI) from CBC parameters, which is an easy and inexpensive test that is frequently used in clinical practice. Additionally, these indices can be helpful in monitoring response to treatment and predicting prognosis, especially in patients with severe COVID-19 in intensive care unit (ICU).A total of 788 patients who were hospitalized with a confirmed diagnosis of severe COVID-19 in the emergency department of a university hospital between 01/06/2019 and 01/06/2022 and who met the inclusion criteria, respectively, were analyzed retrospectively.While age, WBC, neutrophil, monocyte, SII, SIRI, AISI and MV support requirement were significantly higher in deceased patients compared to survivors, lymphocyte, albumin and PNI levels were found to be lower ($p<0.05$). However, no significant difference was detected between the groups in terms of gender, PLT and hospital stay. However, no significant difference was detected between the groups in terms of gender, PLT and hospital stay. In recent studies, it has been mentioned that SII can reflect the intensity of inflammation in COVID-19 and predict the severity of the disease with high accuracy.

SII is a good independent marker for the need for invasive mechanical ventilation and mortality and is also strongly associated with respiratory failure severity and systemic inflammation and can be used as a biomarker for disease severity and progression, triage and outcome.

Key Words: *SII, SIRI, AISI, PNI, mortality*

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GİRİŞ

Koronavirüs hastalığı (COVID-19), bugüne kadar dünya çapında salgına ve çok sayıda ölüme neden olmuştur. COVID-19'a bağlı gelişen acute respiratory distress syndrome (ARDS), multi organ disfonksiyonu (MODS) ve ölümün, artmış inflamatuar yanıt ile ilişkili olduğu bilinmektedir.Bu yüzden, inflamatuar parametreler COVID-19 hastalarında prognozu tahmin etmek için kullanılabilirler (1). Araştırmalar, hematolojik parametrelerin COVID-19'un triyajında ve yönetiminde önemli olduğunu göstermiştir. Beyaz kan sayımı (WBC), nötrofil, lenfosit, trombosit sayısı (PLT) gibi parametrelerden oluşan tam kan sayımı (CBC) bileşenleri veya bu değerlerin birbirlerine oranlarısistemik inflamasyonun erken belirteçleri olarak kullanılabilirler (2,3).

İnflamasyon indeksleri olarak tanımlanan;systemic inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI) gibi oranların klinik pratikte sıkça kullanılan, kolay ve ucuz bir test olan CBC parametrelerinden elde edilmesi mümkündür.Ayrıca bu indeksler, özellikle yoğun bakımdaki (ICU) ciddi COVID-19'lu hastalardatedaviye yanıtın izlenmesi ve prognozun tahmini açısından yardımcı olabilirler (1,4).

Kötü beslenme ve immun disfonksiyonu, COVID-19'un neden olduğu enfeksiyon için risk faktörleri olarak kabul edilir. Yapılan çalışmalarda, hastaların bağışıklık-beslenme durumunu yansıtan Prognostik Beslenme İndeksi (PNI)'nın, enflamatuar hastalıklar, kardiyovasküler hastalıkve COVID-19 olan hastalarda ciddiyet ve mortalitenin bir göstergesi olduğu belirtilmiştir (5, 6, 7).

Son yıllarda SII, SIRI, AISI ve PNI gibi inflamatuar indekslerinCOVID-19 dayararlı prediktörler olduğu gösterildiğinden (8,9).Çalışmamızda bu indekslerin ciddi COVID-19'da hastalığın şiddet ve prognozunu tahmin etmedeki etkisi araştırıldı.

2. MATERYALVE METOD

Çalışma Dizaynı

01/06/2019 ve 01/06/2022 tarihleri arasında bir üniversite hastanesinin acil servisinde ciddi COVID-19 tanısı onaylanarak hastaneye yatırılan ve dahil olma kriterlerini sağlayan sırasıyla toplam 788hasta retrospektif olarak analiz edildi.18 yaşından büyük, kadın veya erkek, real-

time reverse transcriptase polymerase-chain reaction (RT-PCR) sonucu pozitif olanve severe/critical COVID-19 tanısı güncel rehberlere göre kesinleştirilen hastalar sırasıyla çalışmaya dahil edildi**(10).** Kanserler, gebeler, travmalar, özgeçmişinde kronik akciğer, kalp, böbrek ve karaciğer rahatsızlığı olanlar, hematolojik ve romatalojik hastalığa sahip hastalar, immunsupresif olanlar, 18 yaşından küçükler, kronik alkol veya madde bağımlılığı olanlar, bakteriyal pnömoni/sepsis tanısı alanlar ve elektronik kayıt sisteminden bilgilerine ulaşılamayan hastalar çalışma dışı bırakıldı. SII = [(trombosit sayısı × nötrofil sayısı)/lenfosit sayısı], SIRI = [(Nötrofil sayısı × Monosit sayısı) / Lenfosit sayısı], AISI= [(nötrofil x platelet x monosit/lenfosit sayısı)] ve PNI = [(10 ×serum albümini [g/dL]) + (0,005 × lenfosit/μL)] formülleri ile hesaplandı(7, 9)Başta SII, SIRI, AISI ve PNI düzeyleriolmak üzere diğer tüm parametreler hasta grupları (hayatta kalanlar ve kalmayanlar, MV desteği alanlar ve almayanlar) arasında istatistiksel olarak karşılaştırıldı. Çalışma Necmettin Erbakan Üniversitesi Tıp Fakültesi Yerel Etik Kurulu tarafından 06/01/2023 tarih ve 2023/4134(12574) sayı ile onaylanmıştır. Bu hastaların yaş, cinsiyet, özgeçmiş, acil servise başvuru anındaki rutin kan analizinden elde edilen lökosit (WBC), platelet (PLT), nötrofil, lenfosit, monosit ve albümin değerleri, PCR sonucu, toraks spiral computed tomography (CT) raporu, hastane yatış süresi, mekanik ventilasyon (MV) (noninvazif/ invazif/ high-flow nasal cannula oxygen) ihtiyacı olup olmaması ve sonuçlarına (taburcu/ hastane içi mortalite) hastane kayıt sistemi ve hasta epikrizlerinden geriye doğru ulaşıldı. RT-PCR testi için Coronex COVID-19 QPCR (DS BIO and NANO Tech. Ltd., Ankara, Turkey) kiti kullanıldı.Complete blood count (CBC); Mindray auto hematology analyzer BC-6800 cihazı kullanılarak ölçüldü (Shenzhen, China). Albumin; Mindray chemistry analyzer BS-2000M cihazı kullanılarak elde edildi.

3. BULGULAR

Hayatta kalan ve kalmayan hasta gruplarının demografik, klinik ve laboratuvar bulguları Tablo 1 de gösterildi.

Tablo 1. Hasta gruplarının demografik ve laboratuvar bulgularının karşılaştırılması

		Hayattta kalanlar *(n=438)*	**Hayatta kalmayanlar** *(n=350)*	**P value**
Parametre	**Birim**			
		+	+	
Yaş	*yıl*	66,71 ± 15,66	72,2 ± 13,23	**<0,001**
Cinsiyet				
Erkek		226 (%53,8)	194 (%46,2)	0,284
Kadın		212 (%57,6)	156 (%42,4)	
WBC	$10^3/mL$	8,4 (6,2 – 11,21)	12 (8,16 – 16)	**<0,001**
Nötrofil	$10^3/mL$	6,95 (4,71 – 9,23)	10,9 (6,9 – 15)	**<0,001**
Monosit		0,5 (0,25 – 0,77)	0,6 (0,3 – 1)	**0,002**
Lenfosit	$10^3/mL$	0,8 (0,5 – 1,14)	0,6 (0,3 – 0,8)	**<0,001**
Platelet		205 (153 – 275)	195 (145 – 261)	0,011
Albumin		38,25 (34,2 – 45)	26 (25 – 28,7)	**<0,001**
SII		1796,41 (933,75 – 3410,427)	3598,2 (2057,97 – 6673,33)	**<0,001**
SIRI		3,6 (1,59 – 8,21)	10,78 (4,13 – 26,13)	**<0,001**
AISI		736,5 (312 – 1950)	1969,6 (703,5 – 5175)	**<0,001**
PNI		382,51 (342 – 450,01)	260 (248 – 287)	**<0,001**
MV ihtiyacı				
Var		109 (%25,6)	316 (%74,4)	**<0,001**
Yok		329 (%90,6)	34 (%9,4)	
Hastane kalış süresi	*Gün*	11 (8 – 18)	10 (6 – 17)	0,052

Buna göre, hayatta kalanlara kıyasla ölen hastalarda yaş, WBC, nötrofil, monosit, SII, SIRI, AISI ve MV destek ihtiyacı anlamlı olarak daha yüksek iken, lenfosit, albümin ve PNI düzeyleri daha düşük bulundu ($p<0.05$). Fakat gruplar arasında cinsiyet, PLT ve hastane yatış süresi açısından anlamlı fark tespit edilmedi.

Laboratuvar parametrelerinin MV destek ihtiyacı olan ve olmayan hastalarla kıyaslaması Tablo 2 de gösterildi.

Tablo 2. Mekanik Ventilasyon ihtiyacı ile parametrelerin karşılaştırılması

Parametreler	MV alan hastalar (n=427)	MV almayan hastalar (n=363)	p değeri
WBC	11,5 (7,79 – 15,4)	8 (6,13 – 11)	<0,001
Nötrofil	9,7 (6,61 – 14)	6,6 (4,7 – 9,08)	<0,001
Monosit	0,6 (0,3 – 1)	0,5 (0,27 – 0,77)	<0,001
Lenfosit	0,6 (0,4 – 0,8)	0,8 (0,5 – 1,16)	<0,001
Platelet	200 (149,75 – 272)	200 (152,25 – 266,75)	0,367
Albumin	27,3 (25 – 32,4)	38 (34 – 45)	<0,001
SII	3401,14 (1915,6 – 6348,33)	1727,14 (922,5 – 3210)	<0,001
SIRI	9,2 (3,67 – 23,2)	3,44 (1,56 – 7,8)	<0,001
AISI	1717,5 (617,6 – 4837,83)	688 (286,95 – 1737)	<0,001
PNI	273 (250 – 324)	380,02 (340 – 450,01)	<0,001

MV ihtiyacı olmayanlara kıyasla, MV destek alan hastalarda WBC, nötrofil, monosit, SII, SIRI ve AISI anlamlı olarak daha yüksek iken, lenfosit, albümin ve PNI düzeyleri daha düşük idi ($p<0.001$).

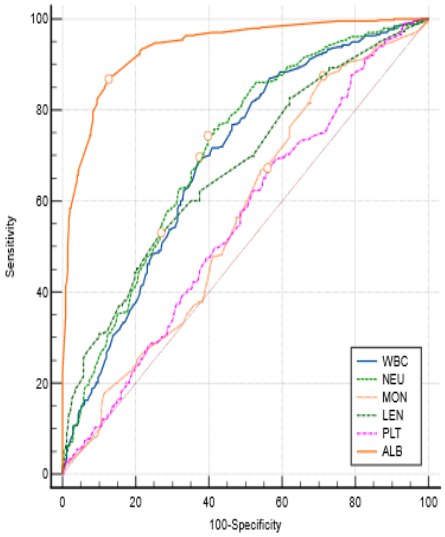
Parametrelerin mortalite tahminindeki ROC analizi grafiği Şekil 1'de ve ROC analizi sonuçları da Tablo 3 de gösterildi.

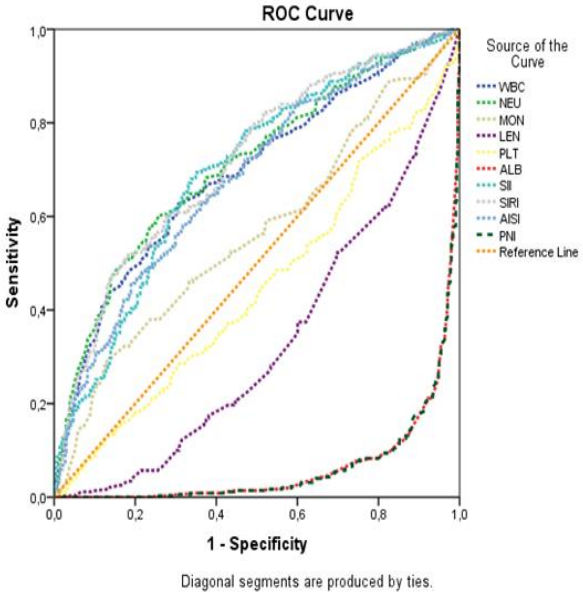
Tablo 3. Mortalite tahminindeparametrelerin ROC analizi

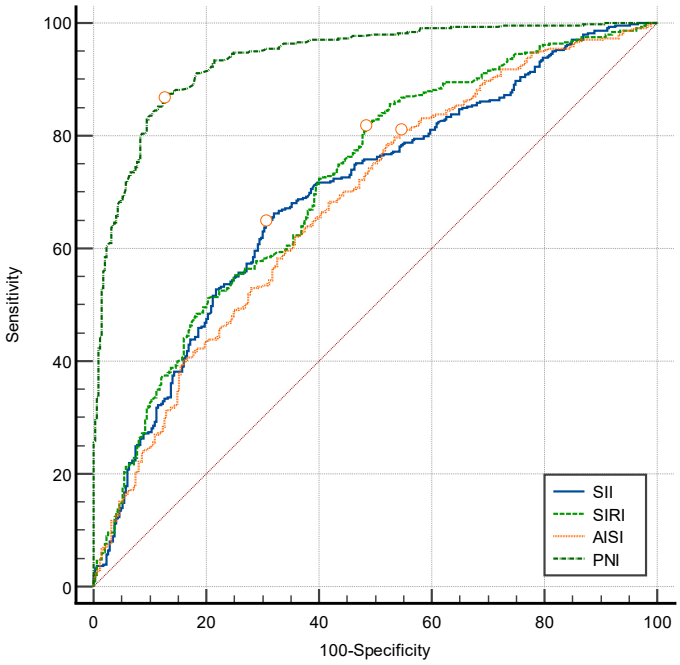
	AUC (%95 CI)	Cut-off*	p	Sensitivite (%)	Spesifite (%)
WBC	0,692	≤10	<0,001	69,63	62,57
Nötrofil	0,709	≤9	<0,001	74,2	60,29
Monosit	0,565	≤0,93	0,002	87,44	28,86
Lenfosit	0,672	>0,76	<0,001	52,97	73,14

Platelet	0,553	>174	0,011	67,12	44
Albumin	0,936	>30,9	<0,001	86,76	87,43
SII	0,697	≤2475	<0,001	64,84	69,43
SIRI	0,716	≤10,27	<0,001	81,74	51,71
AISI	0,680	≤2368,8	<0,001	81,05	45,43
PNI	0,937	>309	<0,001	86,76	87,43

Buna göre; PNI, albümin, SIRI, SII ve AISI düzeylerinin mortalite tahmininde yüksek AUC değerleri gösterdikleri tespit edildi (sırasıyla 0.937, 0.936, 0.716, 0.697, 0.680, hepsi için p<0.001).







Şekil 1. ROC sonuçlarının Analiz Göstergesi

TARTIŞMA

Kontrolsüz ve ciddi inflamatuar cevap, COVID-19'un patofizyolojisinde hayati bir rol oynar. Yüksek morbidite ve mortalitesinden dolayı, bu hastalığınerken tanısını, şiddetini ve ölüm riskini tahmin edebilecekucuz, yaygın ve kolay ölçülebilir daha basit göstergelerin belirlemesi gerekmektedir(11).Günümüzde biyokimyasal ve hematolojik parametrelerin, COVID-19 da dahil olmak üzere birçok çalışmada sistemik inflamasyon ve enfeksiyon belirteçleri olarak sıkça kullanıldığı görülmektedir (1,2,3,12). WBC, nötrofil, lenfosit ve monositler, sistemik inflamatuar yanıtta doğrudan yer alırken, PLTise hemostazın ana mediatörleridir. Nötrofiller, venöz sistemden göç ederek bağışıklık sistemini aktive eden WBC popülasyonunun önemli bir bileşenidir. Viral enfeksiyon tarafından tetiklenen immun bağışıklık yanıt, esas olarak lenfositlere dayanır. Şiddetli COVID-19 enfeksiyonun seyri sırasında çoğunlukla, bozulmuş bir lenfosit yanıtı ile birlikte lenfositopeni ve monositoz gözlemlenmiştir(12).İlaveten, PLT ve nötrofiller enfeksiyon, inflamasyon ve tromboz sırasında etkileşime girerek birbirlerinin fonksiyonlarını regule ederler(11).COVID-19 enfeksiyonuna genellikle trombositopeni eşlik eder ki bu durum, bozulmuş hemostaz nedeniyle önemlidir.(12)

COVID-19 nedeniyle ICU da yatan hastalardan oluşan bir çalışmada, nötrofil, lenfosit ve PLT düzeyleri hayatta kalan ve ölen gruplar arasında anlamlı farklılık gösterdi.Bu çalışmada, ROC analizine göre lenfosit ve PLT istatistiksel olarak önemli bulundu ($p < 0.05$).(1)

Asaduzzaman MD ve ark. çalışmasında daciddi hastalarda, WBC ve nötrofil sayısı anlamlı olarak daha yüksekken ($p<0.001$), lenfosit ve PLT sayısı daha düşük bulunmuştur (sırasıyla $p= 0.006$,$p = 0.449$). Bu nedenle yazarlar, riskli hastaların triyajı sırasında bu belirteçlerin kullanılması gerektiğini önermiştir(11).

Bizim çalışmamızda da, hayatta kalmayan hasta grubunda WBC, nötrofil ve monosit anlamlı olarak yüksek iken, lenfosit ve PLT ise düşük bulundu. Logistik regresyon analizine göre sadece nötrofil ve lenfosit, MV ihtiyacını tahmin edebilen prediktörlerdi. Ayrıca ROC analizine göre mortalite tahmininde WBC, nötrofil, monosit, lenfosit ve PLT düzeyleri düşük sensitivitelerine rağmen istatistiksel olarak anlamlılık gösterdi.

Sistemik inflamasyonu değerlendirmek için önerilen indekslerden biri olanSII,PLT ve nötrofil sayısının lenfosit sayısına bölünmesiyle hesaplanır.Bu üç hematolojik parametreye monosit sayısının da eklenmesi ile elde edilen AISI da yeni keşfedilen inflamatuar indeksler arasındadır(8)

İnflamasyonun şiddetini tahmin etmede tek bir CBC parametresi yeterli olamayabilir. Bu yüzden nötrofil, monosit ve lenfosite dayalı bileşik bir indeks olan SIRI'nın, inflamasyon şiddetinitahmin yeteneği daha yüksek olabilir.(13)

Özer ve arkadaşlarının covid 19 hastalarında yoğun bakım yatışını etkileyen faktörleri araştırdığı çalışmasında nlr düzeyini yüksek tespit etmiştir.(14)

Küçükceran ve arkadaşlarının acil servise başvuran covid 19 lu hastalrın mortalitesinin tespiti için yaptıkları çalışmada ortalama albümin değerinin hayatta kalmayan grupta hasyatta kalan gruba göre anlamlı düşük çıkmış olup, bizim çalışmamızda da albumin düşüklüğü mortalite üzerine etkili bulundu. (15)

Konağın bağışıklığı ve inflamatuar durumu arasındaki dengeyi yansıtan SII'nın, sepsiste ve farklı kanser türlerinde prognoz ile ilişkili olduğu gösterilmiştir (16)

Literatürde,çeşitli enfeksiyon ve inflamatuar hastalıklarda SIRI ve mortalite arasında yakın ilişki olduğunu gösteren çalışmalar mevcuttur(13, 17, 18)

Son yıllarda yapılan çalışmalarda SII'nın, COVID-19'daki inflamasyonun yoğunluğunu yansıtıphastalığın şiddetini yüksek doğrulukla tahmin edebileceğinden bahsedilmiştir(19, 20)

SII invaziv mekanik ventilasyon ihtiyacı ve mortalite için iyi bir bağımsız belirteçtir ve ayrıca solunum yetmezliği şiddeti ve sistemik inflamasyonla güçlü bir şekilde ilişkilidir ve hastalığın şiddeti ve ilerlemesi , triaj ve sonuç için bir biyobelirteç olarak kullanılabilir.(20)

SONUÇ

Hayatta kalanlara kıyasla ölen hastalarda yaş, WBC, nötrofil, monosit, SII, SIRI, AISI ve MV destek ihtiyacı anlamlı olarak daha yüksek iken, lenfosit, albümin ve PNI düzeyleri daha düşük bulundu. Bu da SII, SIRI, AISI mortaliteyi ve MV ihtiyacını belirlemede önemli birer belirteç olduğunu ortaya koymuştur.

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VAKA TAKDİMİ CASE REPORT

CAN THE CHEST PAIN THAT REFERS TO THE EMERGENCY DEPARTMENT BE WELLENS SYNDROME?

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ABSTRACT

Wellens syndrome is a cardiac disease that is highly specific for critical, proximal stenosis of the left anterior descending (LAD) coronary artery, and is generally divided into 2 groups,specially the change of deep inverted T waves or biphasic T waves in leads V2-V3.Alternatively,it is known as anterior, descending T wave syndrome.Patients with Wellens syndrome often show symptoms consistent with acute coronary syndrome.Typical complaints include chest pain described as squeezing or pressure-like, often occurring with physical activity and relieved by rest.Our aim in this case report was to draw attention to ECG changes due to Wellens syndrome without ST elevation or depression,especially in patients presenting to the emergency department. A 58-year-old female patient presents with chest pain that has been going on for 3-4 days and has been increasing for the last 3 hours (pressure-like pain radiating to the front of the chest.There is no known additional disease in her medical history other than hypertension.She applied to the emergency room again for bronchitis and chest pain 3 days ago and was prescribed LRTI. He leaves the emergency room with his vital signs:Temperature: 36.6, Pulse: 103,TA: 110 / 80 spO2: 99,left count: 22.According to the FM,his Neurological examination is normal, he is conscious, oriented and cooperative, GCS is 15, SS is normal,Abdominal examination was normal and urological examination was normal.WBC: 8.788 K/ul NEU: 3.67 K/ul in the blood taken.Creatinine 0.69 mg / dL urea: 85 mg / dL CRP: 1.77 mg / L Troponin: < 10. ECG of the patient.Biphasic T waves were seen in his chest and he was consulted to cardiology and admitted to the coronary intensive care unit with the preliminary diagnosis of Wellen syndrome. As a result,Wellens syndrome is a condition that develops before coronary occlusion.If this condition is not recognized early and treated appropriately,the disease will progress to a massive acute anterior wall myocardial infarction,resulting in mortality. For this reason,ECG findings should be evaluated, especially in patients with predisposing risk factors who present to the emergency department for reasons other than chest pain.Early recognition of the Wellens pattern is important in reducing mortality and morbidity.

Key words: *Chest Paın , Emergency Department , Wellens Syndrome*

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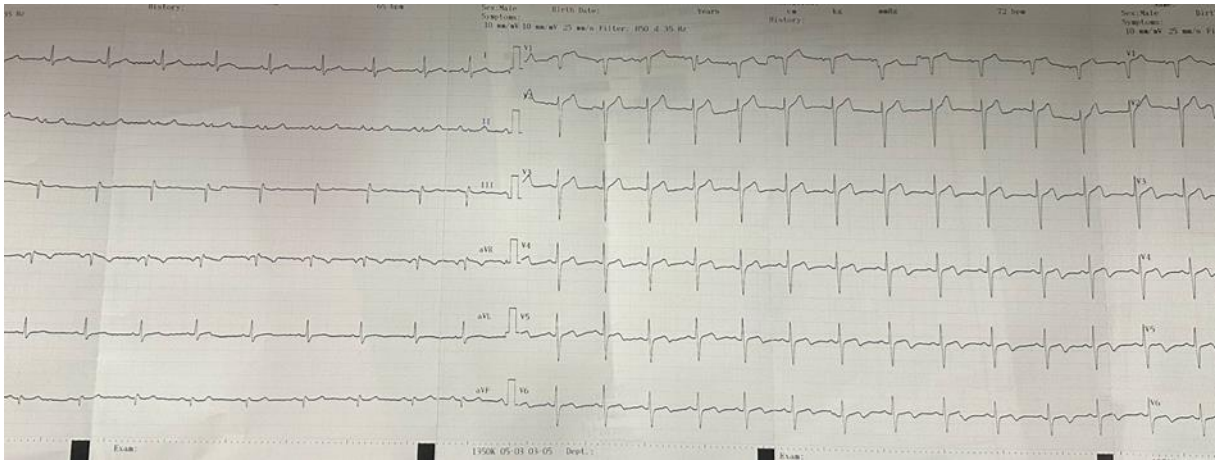
INTRODUCTION

Wellens syndrome is a cardiac disease that is highly specific for critical, proximal stenosis of the left anterior descending (LAD) coronary artery, and is generally divided into 2 groups, especially the change of deep inverted T waves or biphasic T waves in leads V2-V3. Alternatively, it is known as anterior, descending T wave syndrome (1). The ECG pattern of Wellens syndrome is relatively common in patients exhibiting symptoms consistent with unstable angina. Patients with Wellens syndrome often show symptoms consistent with acute coronary syndrome. Typical complaints include chest pain described as squeezing or pressure-like, often occurring with physical activity and relieved by rest. Pain may radiate to the neck, jaw or shoulder. Patients are usually pain-free when they present to the emergency department. Dr. In studies by Wellens and colleagues, an ECG pattern was present in 14% to 18% of patients admitted for unstable angina(1).

Our aim in this case report was to draw attention to ECG changes due to Wellens syndrome without ST elevation or depression, especially in patients presenting to the emergency department.

CASE PRESENTATION

A 58-year-old female patient presents with chest pain that has been going on for 3-4 days and has been increasing for the last 3 hours (pressure-like pain radiating to the front of the chest. There is no known additional disease in her medical history other than hypertension. She applied to the emergency room again for bronchitis and chest pain 3 days ago and was prescribed LRTI. He leaves the emergency room with his vital signs: Temperature: 36.6, Pulse: 103, TA: 110 / 80 spO2: 99, left count: 22. According to the FM, his neurological examination is normal, he is conscious, oriented and cooperative, GCS is 15, SS is normal, of normal. Abdominal examination was normal and urological examination was normal. WBC: 8.788 K/ul NEU: 3.67 K/ul in the blood taken. Creatinine 0.69 mg / dL urea: 85 mg / dL CRP: 1.77 mg / L Troponin: < 10. ECG of the patient. Biphasic T waves were seen in his chest and he was consulted to cardiology and admitted to the coronary intensive care unit with the preliminary diagnosis of Wellen syndrome.



Picture 1. Electrocardiography image of the patient

DISCUSSION

Dr. Although De Zwaan, Wellens and colleagues first described the syndrome in the early 1980s, they stated that 75% of patients with these ECG findings developed an acute, anterior wall, myocardial infarction within weeks if they were planned to be treated with medical treatment alone (2). When patients with Wellens syndrome present to the emergency department, they are painless and cardiac enzymes are usually normal or slightly elevated (3). These patients generally have symptoms consistent with acute coronary syndrome; typical complaints include chest pain described as tightness or pressure-like, often occurring with physical activity and relieved by rest. Pain may radiate to the neck, jaw or shoulder. Patients are usually pain-free when they present to the emergency department. Dr. In studies by Wellens and colleagues, the ECG pattern was present in 14% to 18% of patients admitted for unstable angina. When the patient experiences chest pain, the ST segment and T wave pattern may turn into hyperacute upright T waves, biphasic T may become vague and the T wave pattern may appear to be normalizing, or it may even turn into ST segment elevations (1). In our case, there was no symptom of absence of chest pain, especially as described in Wellens syndrome. The patient's troponin and cardiac enzyme panels were normal. The patient's typical pain led us to obtain an ECG. In the patient's first ECG, there was a tendency for biphasic

T recovery. In particular, the typical description of angina and the tendency for the ECG pattern to improve normally supported the studies.

As a result, Wellens syndrome is a condition that develops before coronary occlusion. If this condition is not recognized early and treated appropriately, the disease will progress to a massive acute anterior wall myocardial infarction, resulting in mortality. For this reason, ECG findings should be evaluated, especially in patients with predisposing risk factors who present to the emergency department for reasons other than chest pain. Early recognition of the Wellens pattern is important in reducing mortality and morbidity.

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VAKA TAKDİMİ CASE REPORT

SPONTANEOUS BİLATERAL QUADRİCEPS TENDON RUPTURE; PRESENTATİON OF A CASE DİAGNOSED WİTH CHRONİC RENAL FAİLURE

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ABSTRACT

Spontaneous Quadriceps Tendon Rupture has been rarely reported in the literature. Although it is generally seen unilaterally in traumatic situations, some metabolic conditions increase the possibility of bilateral and non-traumatic occurrence. In our case, the patient with chronic renal failure and long-term prednol treatment had bilateral non-traumatic quadriceps tendon rupture. In bilateral ruptures, caution should be exercised in the differential diagnosis due to the symmetry of physical findings. USG will be more sensitive in diagnosis than plain radiography. The treatment is surgery.

Key words: Quadriceps Tendon Rupture, Bilateral, Spontaneous

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INTRODUCTION

Although quadriceps rupture is generally seen in traumatic situations, it can also be seen non-traumatically in rare metabolic disorders. Bilateral rupture is seen very rarely in the literature (1). In bilateral ruptures reported in the literature; Conditions such as metabolic disorders, systemic diseases and chronic renal failure occur (2). Our case was a 59-year-old routine dialysis patient with chronic kidney disease. Bilateral quadriceps rupture was detected in the patient who presented with sudden onset of severe non-traumatic knee pain.

CASE REPORT

A 59-year-old female patient applied to our emergency department with complaints of limited extension and pain in her knees. There was no history of trauma. His medical history included chronic renal failure, hypertension and diabetes mellitus. She was undergoing hemodialysis three times a week.

The patient's arterial blood pressure: 160/80 mmHg, pulse: 95 beats/min, oxygen saturation: 95% and temperature 36℃. On physical examination, there was widespread hematoma and loss of extension in the bilateral knees. In the anamnesis taken from the patient, we found that he received continuous prednol treatment for a period (for 8 months). Apart from this, no other obvious pathology was detected in the anamnesis and physical examination.

There was bilateral quadriceps rupture in the ultrasonography (USG) performed at the external center to which the patient first applied. Although the patient had no signs of trauma, a direct radiograph was taken in the emergency room due to severe joint pain. No acute bone pathology was seen on direct radiography (Figure 1).

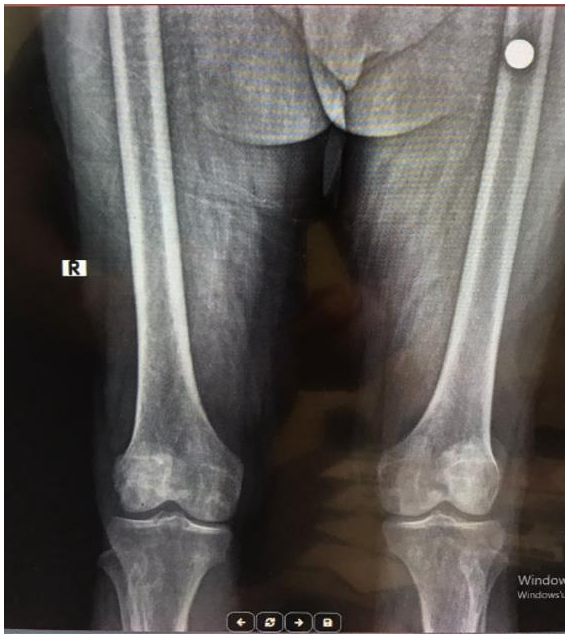

Figure 1. Xray image of the patient who presented with bilateral knee pain and did not have any acute bone pathology

In laboratory values: WBC: 7.39 K/ul, Creatinine: 4.05 mg/dl, CRP: 16 mg/L. Other parameters and coagulation values were within normal range. Orthopedics and traumatology consultation was requested for the patient. The patient, who had bilateral quadriceps tendon rupture, was deemed appropriate to be admitted to the orthopedic service for the operation. The tendons were repaired in the patient who underwent surgical intervention (Figure 2).

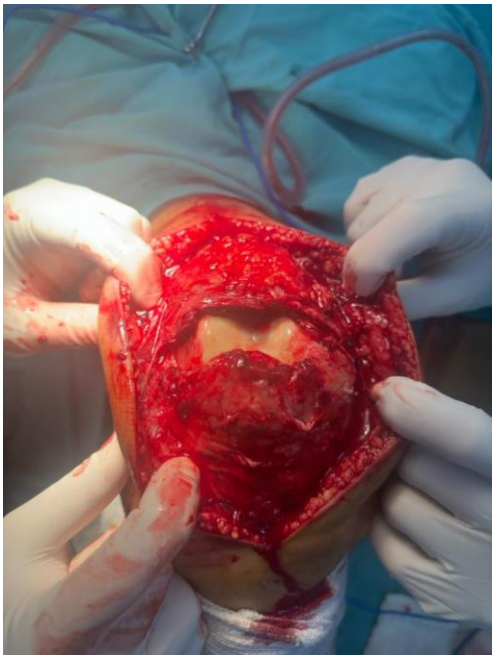

Figure 2: Quadriceps tendon rupture seen during surgery

The patient, who did not develop any complications during post-operative follow-up, was discharged.

DISCUSSION

Our article is about a case of bilateral tendon rupture who complained of pain and swelling in the knees. In this case, we aimed to emphasize that there may be a serious underlying condition in patients with a history of chronic disease who present with non-specific symptoms such as knee pain, and how important physical examination and anamnesis are. It has been observed in the literature that approximately 30% of cases of bilateral quadriceps rupture occur in patients with underlying medical predispositions (3).

For spontaneous tendon rupture; There are risk factors such as corticosteroid use, anabolic steroids, fluoroquinolones, diabetes, chronic renal failure, and previous tendon rupture (4). Symmetry of physical findings, especially in bilateral ruptures; Care should be taken in the diagnosis as it can be confused with cerebrovascular accident, rheumatoid arthritis, disc prolapse, neuropathy and even a psychiatric disorder (5). In our case, the possible risk factor was that he was a chronic kidney disease patient undergoing routine dialysis, as stated in the literature.

It is suggested that the most likely cause of tendon ruptures in patients receiving hemodialysis is uncontrolled hyperparathyroidism, hypertension, resulting in spontaneous bone fractures and tendon sensitivity. In addition, this may also be caused by weakening of the tendon as a result of the replacement of collagen with elastin during chronic metabolic acidosis that develops due to chronic renal failure (2). In our case, we did not detect any laboratory findings of obvious hyperparthyroidism. There was no sign of pathological bone fracture in the radiographs taken. But our patient had signs of hypertension.

Bilateral quadriceps rupture has been reported in the literature in athletes consuming anabolic agents. Additionally, corticosteroid injections and fluoroquinolone use have been associated with an increased risk of tendon rupture (6,7). We think that our patient's long-term steroid treatment may have revealed his current condition.

In case of symptoms such as pain and swelling in the joints, it is recommended to first take a direct graph. In case of suspicion of tendon rupture, USG and Magnetic resonance imaging (MRI) are recommended. MRI is a diagnostic tool recommended for very sensitive and definitive diagnosis (8,9). We used USG, one of the methods recommended in the literature, for the diagnosis of our patient.

CONCLUSION

In all cases, the emergency department has large collections in the diagnosis of quadriceps rupture, with non-traumatic bilateral knee pain and limitation of extension separated by anamnesis and detailed history collection. USG will be more sensitive than plain radiography in showing tendon rupture. USG can diagnose partial or complete tendon ruptures and is performed cheaply, easily

and reliably. It should not be forgotten that the treatment method, especially in cases of complete ruptures, is surgery.

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