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SRIWIJAYA JOURNAL OF MEDICINE

The Importance of Exercise in Mitigating Age-Related Cardiac Apoptosis

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Abstract

Aging causes a progressive decline in heart function. Loss of cardiomyocytes through programmed cell death or apoptosis is a critical factor contributing to this age-related damage. As we age, the heart undergoes structural changes, such as loss of cardiomyocytes, cardiomyocyte hypertrophy, and increased connective tissue with changes in heart geometry. It is widely known that mitochondria are vital sites of apoptosis. Mitochondrial-mediated apoptotic pathways are important regulators of apoptosis with aging. Mitochondrial dysfunction and oxidative stress also contribute to the cardiac remodeling and apoptosis associated with the aging process. On the other hand, exercise can improve heart function and reduce the risk of heart disease. Recent studies suggest that aging increases apoptotic signaling in the left ventricle. However, chronic exercise reduces this mitochondrial-mediated apoptotic signaling pathway in the aging heart. This review will describe the impacts of aging and exercise on cardiac apoptosis, highlighting the importance of exercise in reducing age-related cardiac apoptosis.

Keywords: Apoptosis, Cardiomyocytes, Exercise, Reactive Oxygen Species

1. Introduction

Aging is a process which can gradually reduce heart capacity, including stroke volume, cardiac output, blood flow, and oxygen consumption. This also leads to increased inflammation and oxidative stress. Cardiomyocyte loss due to aging is caused by two different mechanisms: necrosis, which is happening by accident cell death, and apoptosis, which is programmed cell death. Necrosis occurs due to cell injury, often due to infection or inflammatory disease, and is characterized by cell swelling and cell rupture.[1] Apoptosis, on the other hand, is programmed cell death without inflammation, indicated by cell shrinkage, cell clumping, and cell nucleus condensation. Although apoptosis is an important process for cell elimination in regulating cell development, growth, and repair, excessive apoptosis can result in dysfunction and disease.[2] In the left ventricle of the rat heart, aging was reported to cause a significant increase in the level of apoptosis, while the rate of necrosis remained constant.[3] In post-mitotic tissues such as the cardiomyocytes, progressive apoptosis due to aging is a severe problem, as lost myocytes are not replaced.[1] Mechanisms related to age-related cardiac apoptosis need more research to prevent the disease.

A reduced number of cardiomyocytes directly causes impaired heart contractility, cardiomyopathy, heart disease, and heart failure.[2] Apoptosis, or programmed cell death, occurs in several heart conditions such as ischemia-reperfusion, myocardial infarction, and heart failure.[1] Reactive oxygen species (ROS) induce apoptosis mainly by modulating the mitochondrial-mediated apoptotic pathway.[1,4] High levels of oxidative stress can make mitochondrial membrane homeostasis unstable and induce the formation of permeable pores in the mitochondrial membrane, which release pro-apoptotic factors. Regular and correct aerobic physical exercise can increase the capacity of antioxidant defenses, which can

ward off the negative effects of radical Reactive Oxygen Species (ROS), thereby preventing damage caused by free radicals to normal cells.[1,5–7]

Endurance physical training can increase the protein Manganese superoxide dismutase (MnSOD), which is an endogenous antioxidant, and decrease caspase-3 activity and apoptosis index.[4] Although not a cause-and-effect relationship, this observation shows that attenuation of apoptosis in heart muscle cells after physical exercise is related to increased antioxidant capacity in the muscle and modulates the level of oxidative stress resulting from physical exercise. Exercising for 12 weeks at a speed of 20 m/minute for 55 minutes in rats can reduce left ventricular apoptosis induced by aging.[8]

2. Apoptosis

The term "apoptosis" was first introduced by Kerr in 1972, meaning "falling off" to describe the physical changes that occur in dying cells.[9] Apoptosis, also known as "programmed cell death", is a process where a single cell dies in a planned manner. It is characterized by specific morphological, biochemical, and molecular events, initiated by physiological or pathological stimuli without causing an inflammatory reaction.[10]

Apoptosis is a programmed cell death that aims to maintain cell homeostasis and development.[11] This process involves a highly coordinated and active sequence of events that requires energy and is initiated by the cells themselves. The process is carried out by the activation of caspases, which act as the effector molecules of apoptosis. The activation of caspases is triggered by various signals, such as DNA damage, oxidative stress, or the presence of cellular toxins. Once activated, caspases initiate a complex cascade that leads to the dismantling of the cell, including the breakdown of proteins, fragmentation of DNA, and bodies apoptotic formation. These apoptotic bodies are then recognized and engulfed by phagocytic cells, preventing the release of cellular content and the potential damage to surrounding tissues. Overall, apoptosis is a crucial process that maintaining the integrity of tissues and prevents the accumulation of damaged or abnormal cells.[9–11]

Apoptosis is a fascinating biological process that enables organisms to remove unwanted or potentially harmful cells. It is a highly intricate process that occurs during the development and aging of multicellular organisms. In normal circumstances, apoptosis serves as a mechanism that helps to regulate cell populations. It acts as a defense mechanism during an immune response or when cells are damaged by disease or harmful substances. Apoptosis is an important process of regulation of cell number, proliferation and cell elimination. It is also responsible for removing excessive reactive lymphocyte cells, deleting cells during epithelial cell proliferation, and inducing cell death in viral infections and tumor development. Moreover, apoptosis occurs in pathological conditions where it is responsible for cell death due to external damage caused by radiation, cytotoxic anti-cancer drugs, viral infections, pathological atrophy in the organ parenchyma after obstruction of the ducts, and cell death in tumors. Dysregulation of this cell death process has a role in the pathogenesis of diseases. The apoptosis index expresses the number of cells that undergo death due to apoptosis.[9,11,12]

3. Apoptosis Mechanism

Apoptosis is a complex process that involves a molecular cascade that requires energy. It can occur through two main pathways, which are triggered by various factors, both internal and external.[9] The intrinsic pathway, also referred to as the

mitochondria-mediated pathway, is triggered by internal factors, while the extrinsic pathway, also referred to as the death receptor pathway, is triggered by external factors.[9] These two pathways are interconnected, and the constituents in one pathway can impact the other.[9]

In addition to the two pathways, there is one additional pathway involving cytotoxic T cells called the perforin/Granzyme pathway.[9] This pathway has the capacity to induce apoptosis via either granzyme-A or granzyme-B. The extrinsic, intrinsic, and granzyme-B pathways ultimately converge to form the execution pathway.[9] The execution pathway begins with the activation of caspase-3. Caspase activation will cause the activation of the DNA fragmentation process, degradation of the cytoskeleton and nuclear proteins, protein cross-linking, formation of apoptotic bodies, activation of ligand expression for phagocytic cell receptors. The process ends with phagocytosis. In addition, granzyme A can trigger cell death without involving the caspase pathway, rather through single-strand DNA damage.[9]

Apoptosis is initiated by an extrinsic signaling pathway that involves the binding of death signal proteins, present outside the cell, to specific death receptors on the cell surface.[13] The tumor necrosis factor (TNF) receptor, has a cysteine-rich extracellular domain and a cytoplasmic domain, known as the “death domain”, which transmits death signals from the cell surface to intracellular signaling pathways. Examples of extracellular death signals include TNF-α and Fas-Ligand (Fas-L), and the most common death receptors include FasR, TNFR1, DR3, DR4, and DR5. The following table displays the proteins involved in the extrinsic pathway.[9]

The extrinsic pathway of apoptosis is a process that involves how cells die. There are two ways that this happens - through the Fas/FasL and TNF-α/TNFR1. When the receptor and its ligand bind, they form a complex. This complex then recruits adapter proteins to help it work. For the FasL/FasR pathway, the adapter protein is called FADD, and for the TNF/TNFR pathway, it is called TRADD. The adapter protein connects with pro-caspase-8, which then forms the death inducing signaling complex (DISC). This complex causes pro-caspase-8 to be activated, and this leads to cell death. However, a protein called c-FLIP can stop the process from happening. c-FLIP binds to FADD and caspase-8, and this makes them unable to work correctly.[9,14]

The intrinsic pathway is responsible for initiating apoptosis, which is triggered by various non-receptor-mediated stimuli that generate intracellular signals related to mitochondria. The Bcl-2 protein family regulates this pathway, which can act as either pro-apoptotic or anti-apoptotic proteins. The intrinsic pathway is activated by either negative or positive signals. Negative signals occur due to the absence of certain hormones, cytokines, or growth factors, while positive signals occur due to radiation, toxins, hypoxia, hyperthermia, viral infections, or free radicals.[9]

The intrinsic pathway stimulus leads to changes in the mitochondrial membrane pores, causing the release of two groups of pro-apoptotic proteins into the cytosol. The first group stimulates caspase - dependent mitochondrial pathways, while the second promotes apoptosis.

Bax is a pro-apoptotic protein that penetrates the mitochondrial membrane, releasing cytochrome-c, which binds with Apaf-1 to form the apoptosome complex. This complex initiates a sequence of caspase activities that lead to the phagocytosis of the cell.[9]

The activity of proapoptotic Bcl-2 family members, such as Bax, is controlled in a latent form. The presence of a lethal signal

causes Bax to undergo a conformational change, leading to the release of cytochrome-c. Similarly, Bid proteins move to the mitochondria and cause the release of cytochrome-c. This cellular mechanism regulates the activity of the Bcl-2 gene family and controls apoptosis.[9,15,16]

4. Reactive Oxygen Species (ROS) Are A Significant Trigger For Apoptosis

There are various factors that can cause cardiomyocyte apoptosis. Some of these factors include mechanical factors like excessive stretching, increased calcium concentrations in the cytosol, and/or increased concentrations of neurohormones such as angiotensin II and norepinephrine, as well as increased cytokines such as TNFα. Apart from these, other factors that can trigger cardiomyocyte apoptosis include the formation of free oxygen radicals (reactive oxygen species) and exposure to hypoxia.[1,2] Several changes occur intracellularly and extracellularly during ischemia and/or reperfusion, such as excess nitric oxide (NO) which is a free radical involved in the induction of apoptosis.[17–19]

Reactive oxygen species (ROS) and mitochondria play a crucial and well-established role in inducing apoptosis, which is the process of programmed cell death, in both physiological and pathological conditions. It is a well-known fact that mitochondria not only serve as the source but also as the target of ROS. The release of cytochrome-c from mitochondria, which triggers caspase activation, is mainly mediated by ROS either directly or indirectly, which has been extensively studied and documented.[1]

Receptors from the Tumor necrosis factor (TNF) or nerve growth factor (NGF) families have various functions, ranging from growth receptors to cell death receptors. A subset of this family has been extensively studied and demonstrated to induce apoptosis through several systems and is therefore called death receptors. The TNF/NGF receptor has a death domain in the cytoplasm that is critical for inducing cell death through a caspase-dependent mechanism. However, ROS generation is equally important in inducing apoptosis, and the antioxidant N-acetylcysteine has been shown to block TNF in several systems, indicating a functional role of ROS during this process. ROS can induce TNF, which has an established role in apoptosis. Besides, ROS can activate the Fas receptor, which also belongs to the TNF/NGF receptor family, causing apoptotic signal transduction. Antioxidants have been shown to inhibit the Fas receptor, which is based on extensive evidence.[1,2]

ROS can cause oxidation of mitochondrial pores, which disrupts the mitochondria membrane potential, leading to the release of cytochrome-c. Interestingly, mitochondria themselves can release ROS through mechanisms that are not yet fully understood. These ROS can directly or indirectly increase mitochondrial pores. This shows that mitochondria are both targets and sources of ROS, which has been extensively researched and documented. Nitric oxide (NO) has been shown to induce apoptosis in various cell systems such as epithelial cells, mesangial cells, and endothelial cells.[20,21] The mechanism of NO-induced apoptosis is not entirely known. Some researchers observed an increase in Fas receptor expression, while others suggested that changes in mitochondrial permeability due to increased ROS were the mechanism. However, the fact that NO, which can trigger apoptosis, is inhibited by Bcl-2 shows that mitochondria are indeed the main target of NO, which is a well-established and widely accepted fact.[22]

5. Exercise Protection Against Cardiac Apoptosis

Physical exercise has several benefits for our health. It can depress the risk of cell damage, oxidative stress, and inflammation. However, it's important to avoid overtraining. Additionally, physical exercise can increase cardiovascular capacity and reduce the risk factors associated with cardiovascular disease in both young and elderly adults.[2,15]

Moreover, physical exercise can also help in reducing apoptosis (programmed cell death) by increasing the production of stress-sensitive proteins such as nuclear factor kappa B (NF-kB), insulin-like growth factor (IGF-1), and heat shock proteins (HSP90 and HSP70).[2,4]

The aging process is accompanied by a deterioration of heart function and increased oxidative stress, which might induce cellular death caused by mitochondrial dysfunction. Studies conducted on rats have revealed that aging renders the heart more susceptible to DNA fragmentation or apoptosis.[1,2]

Nonetheless, extended periods of exercise have been shown to reduce apoptosis in the aging heart, suggesting a positive effect of exercise on heart health. It is noteworthy that while apoptosis increases with age, the heart-to-body weight ratio between young and old sedentary rats remains constant. This is due to a significant loss of cardiac myocytes and reactive hypertrophy of the remaining cells characterizing aging in humans and animals. Hence, the loss of cardiomyocyte does'nt necessarily correspond to a reduction in mass. Furthermore, the connective tissue in the heart increases with age, making the heart walls stiffer and thicker, thereby reducing its elasticity. Nonetheless, hypertrophied cardiac myocytes often exhibit poor contractile function due to increased left ventricle wall thickness. Further research is needed to elucidate in more detail the impact of exercise on the protective mechanisms of aging cardiomyocytes. Previous studies showed the effect of exercise training in increasing Mn isoform superoxide dismutase (MnSOD), NF-kB, extracellular receptor kinase (ERK), IGF-1/Akt pathway, and Heat shock proteins (HSPs) in the heart, which may function as upstream regulators. potential of age-induced apoptosis in the aging heart (see Figure 1).[2,4,23]

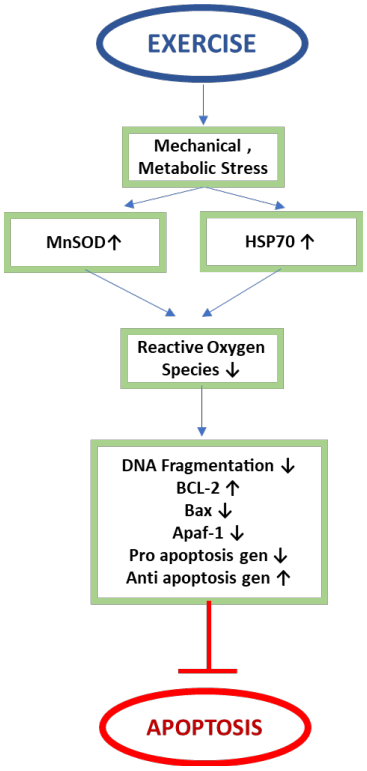

Figure 1. Role Of Physical Exercise In Inhibiting Apoptosis *(adapted from Kwak,2013)*[2]

According to a study conducted by Siu et al (2004), regular moderate-intensity physical exercise can impact the apoptosis process in young rat cardiomyocytes.[4] This study showed a positive correlation between the HSP70 and the Bcl-2 levels protein/mRNA. Conversely, there was an opposite correlation observed between the levels of HSP70 and Bax mRNA. In addition, the study also indicated that MnSOD protein

showed a positive correlation with Bcl-2 transcription and HSP70 protein, while there was a negative correlation observed with the apoptosis index and caspase-3 activity. These findings suggest that HSP70 and MnSOD may play a significant role in regulating the homeostasis of apoptotic factors in cardiomyocytes.[4,15]

Physical exercise has been found to have a positive impact on the apoptosis process. In particular, moderate-intensity physical exercise can reduce DNA fragmentation, increase protein and transcription levels of Bcl-2, and lower Apaf protein levels in cardiomyocytes of mice. These changes are not observed in mice that do not undergo physical exercise. Mitochondrial pathway (intrinsic pathway) is affected by reactive oxygen species, which can disrupt the stability of mitochondrial membrane homeostasis, leading to the formation of permeable mitochondrial pores and releasing pro-apoptotic factors such as cytochrome-c.[4]

Bcl-2 family proteins play a crucial role in modulating the formation of permeable pores in the mitochondrial membrane, thereby regulating apoptosis through the intrinsic pathway. In a research study involving mice who underwent eight weeks of endurance physical training, the Bcl-2 protein, which is an anti-apoptotic gene product, increased, while the Bax protein, which is a pro-apoptotic gene product, decreased.[4,15]

The study also found that exercise can increase the levels of important endogenous antioxidants such as Cu/Zn-SOD, catalase, glutathione peroxidase, glutathione reductase, and MnSOD. In particular, the antioxidant MnSOD increased in mice who underwent endurance physical training for eight weeks compared to the control group. The study also showed that MnSOD was negatively correlated with the apoptotic levels and caspase-3 activity and positively correlated with the transcriptional activity of Bcl-2 and HSP-70. Thus, reduced apoptosis in cardiomyocytes is potentially related to increased antioxidant capacity and modulation of oxidative stress levels caused by physical exercise.[2,8]

Physical exercise has been found to reduce apoptosis, or programmed cell death, through a variety of mechanisms. One such mechanism is by increasing the expression of endogenous antioxidants and the HSP70 protein.[24] Additionally, physical exercise can alter the expression of several proteins involved in apoptosis, such as pro-apoptotic proteins like Bax, caspase, and Apaf-1, and anti-apoptotic proteins like Bcl-2. By increasing the expression of anti-apoptotic proteins and decreasing pro-apoptotic proteins, physical exercise can help prevent cell death. Furthermore, physical exercise can also reduce the expression of death ligands like Fas-L and TNF-α, as well as death receptors such as the TNF receptor, further inhibiting apoptosis. HSP70 has also been shown to inhibit the activity of Bax, AIF, Apaf-1, and death receptors like the TNF receptor and Fas receptor.[2,4,15]

6. Conclusion

In summary, the aging process induced upregulation of mitochondrial-mediated apoptotic signaling cascades, encompassing heightened expression of pro-apoptotic effector proteins including Bax, an increased Bax/Bcl-2 expression ratio, as well as amplified caspase-9 and cleaved caspase-3 activity, culminating in intensified apoptotic events. However, chronic endurance exercise training attenuated these amplifications in apoptotic signaling and apoptosis, indicating that such physical conditioning confers anti-apoptotic defensive effects upon cardiac tissue. Nevertheless, additional investigation remains imperative to elucidate the precise

cellular and molecular pathways through which endurance training mitigates aging-associated apoptosis in cardiac myocytes.

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The Importance Of Exercise In Mitigating Age-Related Cardiac Apoptosis

By Mustika Anggiane Putri

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The Importance Of Exercise In Mitigating Age-Related Cardiac Apoptosis

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Abstrak

Abstract

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2. Apoptosis

The term "apoptosis" was first introduced by Kerr in 1972, meaning "falling off" to describe the physical changes that occur in dying cells.[9] Apoptosis, also known as "programmed cell death", is a process where a single cell dies in a planned manner. It is characterized by specific morphological, biochemical, and molecular events, initiated by physiological or pathological stimuli without causing an inflammatory reaction.[10]

Apoptosis is a programmed cell death that aims to maintain cell homeostasis and development.[11] This process involves a highly coordinated and active sequence of events that requires energy and is initiated by the cells themselves. The process is carried out by the activation of caspases, which act as the effector molecules of apoptosis. The activation of caspases is triggered by various signals, such as DNA damage, oxidative stress, or the presence of cellular toxins. Once activated, caspases initiate a complex cascade that leads to the dismantling of the cell, including the breakdown of proteins, fragmentation of DNA, and bodies apoptotic formation. These apoptotic bodies are then recognized and engulfed by phagocytic cells, preventing the release of cellular content and the potential damage to surrounding tissues. Overall, apoptosis is a crucial process that maintaining the integrity of tissues and prevents the accumulation of damaged or abnormal cells.[9–11]

Apoptosis is a fascinating biological process that enables organisms to remove unwanted or potentially harmful cells. It is a highly intricate process that occurs during the development and aging of multicellular organisms. In normal circumstances, apoptosis serves as a mechanism that helps to regulate cell populations. It acts as a defense mechanism during an immune response or when cells are damaged by disease or harmful substances. Apoptosis is an important process of regulation of cell number, proliferation and cell elimination. It is also responsible for removing excessive reactive lymphocyte cells, deleting cells during epithelial cell proliferation, and inducing cell death in viral infections and tumor development. Moreover, apoptosis occurs in pathological conditions where it is responsible for cell death due to external damage caused by radiation, cytotoxic anti-cancer drugs, viral infections, pathological atrophy in the organ parenchyma after obstruction of the

ducts, and cell death in tumors. Dysregulation of this cell death process has a role in the pathogenesis of diseases. The apoptosis index expresses the number of cells that undergo death due to apoptosis.[9,11,12]

3. Apoptosis Mechanism

Apoptosis is a complex process that involves a molecular cascade that requires energy. It can occur through two main pathways, which are triggered by various factors, both internal and external.[9] The intrinsic pathway, also referred to as the mitochondria-mediated pathway, is triggered by internal factors, while the extrinsic pathway, also referred to as the death receptor pathway, is triggered by external factors.[9] These two pathways are interconnected, and the constituents in one pathway can impact the other.[9]

In addition to the two pathways, there is one additional pathway involving cytotoxic T cells called the perforin/Granzyme pathway.[9] This pathway has the capacity to induce apoptosis via either granzyme-A or granzyme-B. The extrinsic, intrinsic, and granzyme-B pathways ultimately converge to form the execution pathway.[9] The execution pathway begins with the activation of caspase-3. Caspase activation will cause the activation of the DNA fragmentation process, degradation of the cytoskeleton and nuclear proteins, protein cross-linking, formation of apoptotic bodies, activation of ligand expression for phagocytic cell receptors. The process ends with phagocytosis. In addition, granzyme A can trigger cell death without involving the caspase pathway, rather through single-strand DNA damage.[9]

Apoptosis is initiated by an extrinsic signaling pathway that involves the binding of death signal proteins, present outside the cell, to specific death receptors on the cell surface.[13] The tumor necrosis factor (TNF) receptor, has a cysteine-rich extracellular domain and a cytoplasmic domain, known as the "death domain", which transmits death signals from the cell surface to intracellular signaling pathways. Examples of extracellular death signals include TNF-α and Fas-Ligand (Fas-L), and the most common death receptors include FasR, TNFR1, DR3, DR4, and DR5. The following table displays the proteins involved in the extrinsic pathway.[9]

The extrinsic pathway of apoptosis is a process that involves how cells die. There are two ways that this happens - through the Fas/FasL and TNF-α/TNFR1. When the receptor and its ligand bind, they form a complex. This complex then recruits adapter proteins to help it work. For the FasL/FasR pathway, the adapter protein is called FADD, and for the TNF/TNFR pathway, it is called TRADD. The adapter protein connects with pro-caspase-8, which then forms the death inducing signaling complex (DISC). This complex causes pro-caspase-8 to be activated, and this leads to cell death. However, a protein called c-FLIP can stop the process from happening. c-FLIP binds to FADD and caspase-8, and this makes them unable to work correctly.[9,14]

The intrinsic pathway is responsible for initiating apoptosis, which is triggered by various non-receptor-mediated stimuli that generate intracellular signals related to mitochondria. The Bcl-2 protein family regulates this pathway, which can act as either pro-apoptotic or anti-apoptotic proteins. The intrinsic pathway is activated by either negative or positive signals. Negative signals occur due to the absence of certain hormones, cytokines, or growth factors, while positive signals occur due to radiation, toxins, hypoxia, hyperthermia, viral infections, or free radicals.[9]

The intrinsic pathway stimulus leads to changes in the mitochondrial membrane pores, causing the release of two groups of pro-apoptotic proteins into the cytosol. The first group stimulates caspase - dependent mitochondrial pathways, while the second promotes apoptosis.

Bax is a pro-apoptotic protein that penetrates the mitochondrial membrane, releasing cytochrome-c, which binds with Apaf-1 to form the apoptosome complex. This complex initiates a sequence of caspase activities that lead to the phagocytosis of the cell.[8]

The activity of proapoptotic Bcl-2 family members, such as Bax, is controlled in a latent form. The presence of a lethal signal causes Bax to undergo a conformational change, leading to the release of cytochrome-c. Similarly, Bid proteins move to the mitochondria and cause the release of cytochrome-c. This cellular mechanism regulates the activity of the Bcl-2 gene family and controls apoptosis.[9,15,16]

4. Reactive Oxygen Species (ROS) Are A Significant Trigger For Apoptosis

There are various factors that can cause cardiomyocyte apoptosis. Some of these factors include mechanical factors like excessive stretching, increased calcium concentrations in the cytosol, and/or increased concentrations of neurohormones such as angiotensin II and norepinephrine, as well as increased cytokines such as TNFα. Apart from these, other factors that can trigger cardiomyocyte apoptosis include the formation of free oxygen radicals (reactive oxygen species) and exposure to hypoxia.[1,2] Several changes occur intracellularly and extracellularly during ischemia and/or reperfusion, such as excess nitric oxide (NO) which is a free radical involved in the induction of apoptosis.[17–19]

Reactive oxygen species (ROS) and mitochondria play a crucial and well-established role in inducing apoptosis, which is the process of programmed cell death, in both physiological and pathological conditions. It is a well-known fact that mitochondria not only serve as the source but also as the target of ROS. The release of cytochrome-c from mitochondria, which triggers caspase activation, is mainly mediated by ROS either directly or indirectly, which has been extensively studied and documented.[1]

Receptors from the Tumor necrosis factor (TNF) or nerve growth factor (NGF) families have various functions, ranging from growth receptors to cell death receptors. A subset of this family has been extensively studied and demonstrated to induce apoptosis through several systems and is therefore called death receptors. The TNF/NGF receptor has a death domain in the cytoplasm that is critical for inducing cell death through a caspase-dependent mechanism. However, ROS generation is equally important in inducing apoptosis, and the antioxidant N-acetylcysteine has been shown to block TNF in several systems, indicating a functional role of ROS during this process. ROS can induce TNF, which has an established role in apoptosis. Besides, ROS can activate the Fas receptor, which also belongs to the TNF/NGF receptor family, causing apoptotic signal transduction. Antioxidants have been shown to inhibit the Fas receptor, which is based on extensive evidence.[1,2]

ROS can cause oxidation of mitochondrial pores, which disrupts the mitochondria membrane potential, leading to the release of cytochrome-c. Interestingly, mitochondria themselves can release ROS through mechanisms that

are not yet fully understood. These ROS can directly or indirectly increase mitochondrial pores. This shows that mitochondria are both targets and sources of ROS, which has been extensively researched and documented. Nitric oxide (NO) has been shown to induce apoptosis in various cell systems such as epithelial cells, mesangial cells, and endothelial cells.[20,21] The mechanism of NO-induced apoptosis is not entirely known. Some researchers observed an increase in Fas receptor expression, while others suggested that changes in mitochondrial permeability due to increased ROS were the mechanism. However, the fact that NO, which can trigger apoptosis, is inhibited by Bcl-2 shows that mitochondria are indeed the main target of NO, which is a well-established and widely accepted fact.[22]

5. Exercise Protection Against Cardiac Apoptosis

Physical exercise has several benefits for our health. It can depress the risk of cell damage, oxidative stress, and inflammation. However, it's important to avoid overtraining. Additionally, physical exercise can increase cardiovascular capacity and reduce the risk factors associated with cardiovascular disease in both young and elderly adults.[2,15]

Moreover, physical exercise can also help in reducing apoptosis (programmed cell death) by increasing the production of stress-sensitive proteins such as nuclear factor kappa B (NF-kB), insulin-like growth factor (IGF-1), and heat shock proteins (HSP90 and HSP70).[2,4]

The aging process is accompanied by a deterioration of heart function and increased oxidative stress, which might induce cellular death caused by mitochondrial dysfunction. Studies conducted on rats have revealed that aging renders the heart more susceptible to DNA fragmentation or apoptosis.[1,2]

Nonetheless, extended periods of exercise have been shown to reduce apoptosis in the aging heart, suggesting a positive effect of exercise on heart health. It is noteworthy that while apoptosis increases with age, the heart-to-body weight ratio between young and old sedentary rats remains constant. This is due to a significant loss of cardiac myocytes and reactive hypertrophy of the remaining cells characterizing aging in humans and animals. Hence, the loss of cardiomyocyte does'nt necessarily correspond to a reduction in mass. Furthermore, the connective tissue in the heart increases with age, making the heart walls stiffer and thicker, thereby reducing its elasticity. Nonetheless, hypertrophied cardiac myocytes often exhibit poor contractile function due to increased left ventricle wall thickness. Further research is needed to elucidate in more detail the impact of exercise on the protective mechanisms of aging cardiomyocytes. Previous studies showed the effect of exercise training in increasing Mn isoform superoxide dismutase (MnSOD), NF-kB, extracellular receptor kinase (ERK), IGF-1/Akt pathway, and Heat shock proteins (HSPs) in the heart, which may function as upstream regulators. potential of age-induced apoptosis in the aging heart (see Figure 1).[2,4,23]

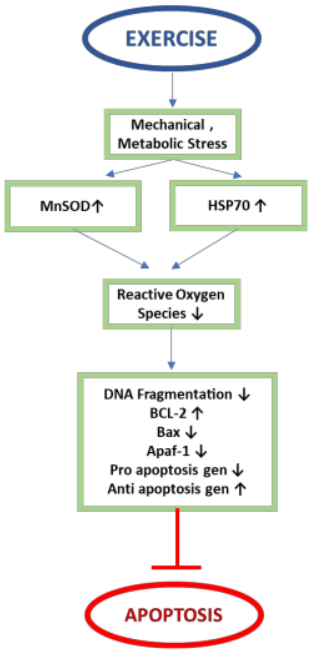

Figure 1. Role Of Physical Exercise In Inhibiting Apoptosis *(adapted from Kwak,2013)*[2]

According to a study conducted by Siu et al (2004), regular moderate-intensity physical exercise can impact the apoptosis process in young rat cardiomyocytes.[4] This study showed a positive correlation between the HSP70 and the Bcl-2 levels protein/mRNA. Conversely, there was an opposite correlation observed between the levels of HSP70 and Bax mRNA. In addition, the study also indicated that MnSOD protein showed a positive correlation with Bcl-2 transcription and HSP70 protein, while there was a negative correlation observed with the apoptosis index and caspase-3 activity. These findings suggest that HSP70 and MnSOD may play a significant role in regulating the homeostasis of apoptotic factors in cardiomyocytes.[4,15]

Physical exercise has been found to have a positive impact on the apoptosis process. In particular, moderate-intensity physical exercise can reduce DNA fragmentation, increase protein and transcription levels of Bcl-2, and lower Apaf protein levels in cardiomyocytes of mice. These changes are not observed in mice that do not undergo physical exercise. Mitochondrial pathway (intrinsic pathway) is affected by reactive oxygen species, which can disrupt the stability of mitochondrial membrane homeostasis, leading to the formation of permeable mitochondrial pores and releasing pro-apoptotic factors such as cytochrome-c.[4]

Bcl-2 family proteins play a crucial role in modulating the formation of permeable pores in the mitochondrial membrane, thereby regulating apoptosis through the intrinsic pathway. In a research study involving mice who underwent eight weeks of endurance physical training, the Bcl-2 protein, which is an anti-apoptotic gene product, increased, while the Bax protein, which is a pro-apoptotic gene product, decreased.[4,15]

The study also found that exercise can increase the levels of important endogenous antioxidants such as Cu/Zn-SOD, catalase, glutathione peroxidase, glutathione reductase, and MnSOD. In particular, the antioxidant MnSOD increased in mice who underwent endurance physical training for eight weeks compared to the control group. The study also showed that MnSOD was negatively correlated with the apoptotic levels and caspase-3 activity and positively correlated with the transcriptional activity of Bcl-2 and HSP-70. Thus, reduced apoptosis in cardiomyocytes is potentially related to increased antioxidant capacity and modulation of oxidative stress levels caused by physical exercise.[2,8]

Physical exercise has been found to reduce apoptosis, or programmed cell death, through a variety of mechanisms. One such mechanism is by increasing the expression of endogenous antioxidants and the HSP70 protein.[24] Additionally, physical exercise can alter the expression

of several proteins involved in apoptosis, such as pro-apoptotic proteins like Bax, caspase, and Apaf-1, and anti-apoptotic proteins like Bcl-2. By increasing the expression of anti-apoptotic proteins and decreasing pro-apoptotic proteins, physical exercise can help prevent cell death. Furthermore, physical exercise can also reduce the expression of death ligands like Fas-L and TNF-α, as well as death receptors such as the TNF receptor, further inhibiting apoptosis. HSP70 has also been shown to inhibit the activity of Bax, AIF, Apaf-1, and death receptors like the TNF receptor and Fas receptor.[2,4,15]

6. CONCLUSION

In summary, the aging process induced upregulation of mitochondrial-mediated apoptotic signaling cascades, encompassing heightened expression of pro-apoptotic effector proteins including Bax, an increased Bax/Bcl-2 expression ratio, as well as amplified caspase-9 and cleaved caspase-3 activity, culminating in intensified apoptotic events. However, chronic endurance exercise training attenuated these amplifications in apoptotic signaling and apoptosis, indicating that such physical conditioning confers anti-apoptotic defensive effects upon cardiac tissue. Nevertheless, additional investigation remains imperative to elucidate the precise cellular and molecular pathways through which endurance training mitigates aging-associated apoptosis in cardiac myocytes.

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