Vigorous Exercise Effect on Cardiovascular Health

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Abstract
Many studies examine the effects of vigorous cardiovascular exercise on the heart. Intense exercise causes frequent muscle contractions in the heart and specific biomarkers that usually signify a myocardial infarction are released into the bloodstream. However, studies indicate that there might not be a correlation between the release of biomarkers and cardiac function. Another study shows that long term vigorous exercise negatively affects the heart by dramatically increasing the mass and volume of the right and left ventricles, thereby resulting in hypertrophy. The cardiac hypertrophy is still evident even after the subjects have stopped exercising. Cardiac hypertrophy results in myocardial fibrosis and scarring. The percent of myocardial fibrosis in those engaging in long term vigorous exercise was significantly higher than that of the control group. After intense training, tests found a reduced right ventricle ejection fraction due to dilation of the right ventricle while there was no dilation in the left ventricle. In addition, a correlation was found between reduced right ventricle ejection fraction and ventricle arrhythmias. The mortality rate of vigorous exercisers was slightly higher in comparison to those who moderately exercised. Animal studies showed that rats who exercised developed left ventricle hypertrophy, impaired diastolic function, and right ventricle dilation, the symptoms found in humans with an "athlete's heart." Additional research on the effect of vigorous exercise on the heart needs to be conducted to verify these findings.

Introduction

In 490 BCE Pheidippides, a 40 year old courier ran 24.8 miles from Marathon to Athens to announce the Spartan victory over the Persians, and then dropped dead from what is believed to be cardiac arrest. This is the earliest mention of death due to aerobic activity (Trivax & McCullough, 2012). It was not until the 1970s that jogging would become a popular form of aerobic exercise. The many physical and physiological benefits of aerobic exercise caused this phenomenon to grow. In 2010, statistics indicated around 36 million people jog daily. In 2013, 541,000 people completed a marathon (which is an intense aerobic event of 26.2 miles) in the United States alone (Schnohr, et.al. 2013 & Martin, 2014). It has been hypothesized that a person capable of completing a marathon is immune to coronary heart disease (Bassler, 1974). This hypothesis is not fully supported since a six year study from 1975-1980 showed that eleven men died in Rhode Island while running; the cause of death being coronary heart disease (Thompson et. al. 1982). In addition, a study conducted from 2000-2010, shows that out of 10.9 million people who have completed marathons or half-marathons, only 59 have suffered cardiac arrest, majority due to coronary heart disease. (Kim, et.al. 2012).

The World Health Organization endorses at least 150 minutes a week of moderate demanding aerobic activity (such as walking, water aerobics, and bicycling) or 75 minutes a week of vigorous-intensity aerobic physical activity (such as jogging, running, and swimming laps) for significant health benefits (Prevention and Health Promotion, 2014). People may think that exercising vigorously for longer periods of time would increase the health benefits. However, it is unclear whether more intense exercise improves the efficiency of the cardiovascular health or if it overexerts the heart and thereby puts the individual's health at risk. By examining the data and studying trends associated with extreme exercise and productivity of the heart, this review will try to determine if prolonged vigorous exercise is detrimental to a person's cardiovascular health.

Methods

This comprehensive review was written through the critical analysis of clinical research papers and peer reviewed journal articles. The necessary material was found using Touro College's online databases, such as Pubmed, Medline and EBSCO. Google and Google Scholar were used to search specific keywords related to the topic.

Discussion

The Mechanism of Cardiac Contraction

Cardiac muscle contraction and relaxation has been studied on the cellular and molecular level. The overall mechanism for muscle contraction is known as excitation–contraction coupling. In excitation–contraction coupling, an electrical stimulus (action potential) transforms into a mechanical response (muscle contraction). In cardiac muscle, excitation–contraction coupling occurs by a more specific mechanism of calcium-induced calcium release, a positive-feedback system where calcium induces the release of more calcium from intracellular Ca2+ supplies. The internal conduction system initiates an action potential that progresses along the t-tubules of the cardiomyocytes, resulting in the opening of voltage-gated L-type calcium channels. This allows extracellular calcium to flow into the sarcoplasmic reticulum causing a stimulation of the ryanodine receptors (RyR) of the sarcoplasmic reticulum which results in a bulk release of calcium into the cytoplasm. Binding of the cytoplasm calcium to troponin C (a subunit of the troponin complex), results in conformational changes of the tropomyosin complex allowing for cross bridging to occur between the actin and myosin (excitation–contraction coupling mechanism). Contraction occurs as the actin filaments are pulled toward each other. All this transpires through the hydrolysis of ATP in the mitochondria mainly found around the

ryanodine receptors. The cardiac muscle cell relaxes/repolarizes once there is not any calcium left in the cytosol; this is achieved through the different ion channels that sequester the calcium back into the sarcoplasmic reticulum, an ATP dependent action. The more intense the exercise, the more frequently this process happens and a variety of toxic molecules are produced (Bers, 2001).

Biomarker Release

The troponin complex comprises of three subunits of proteins: troponin I (TnI), troponin T (TnT), and troponin C (TnC). Each of the three subunit proteins has specific interactions with the actin filaments that help regulate muscle contraction. Necrosis of myocardiocytes results in loss of membrane integrity, resulting in the release of cardiac troponin T and cardiac troponin I into the bloodstream. Troponin T and troponin I are considered leakage markers since cardiac muscle has a different isoform than skeletal muscle does for each of these respective troponins. Usually, an increase in troponin T and troponin I in the blood is an early warning sign of a myocardial infarction. It has been hypothesized that the elevated cardiac troponin markers found in the bloodstream after vigorous exercise is from the cytosolic pool rather than from physically bound cardiac troponin (the breakdown of the myocyte). This means that cardiac muscle contraction is not affected by the increase in troponin levels in the bloodstream due to vigorous exercise since the damage to the membrane is reversible (Wells & Sleeper, 2008). A study examined the relationship between cardiac troponin T and left ventricle function in 52 runners who just completed a marathon. The 52 runners were screened with an echocardiogram to determine left ventricle function and a blood sample assessing for cardiac troponin T before and after the race. The 99th percentile for cardiac troponin T in the serum assay of normal subjects is 0.01 micrograms per liter. The cardiac troponin T was not detected in all the participants before the race. However, significant increases of cardiac troponin T levels were observed after the race in all the marathon runners. Twenty runners had values above the acute myocardial infarction cut off of 0.05 micrograms per liter. The study did not find a link between these elevated levels of cardiac troponin T and left ventricle function. This supports the notion that the cardiac troponin T released into the bloodstream during extreme exercise is from the cytosolic pool (Whyte, et.al. 2005).

A study of fourteen amateur runners who completed a marathon were tested pre and post marathon for myoglobin, creatine kinase (both also biomarkers for detecting a myocardial infarction) and cardiac troponin T along with a cardiac magnetic resonance to detect myocardial necrosis. The study was performed to determine whether elevated biomarkers due to vigorous exercise had a relation to myocardial necrosis. Before the race, myoglobin, creatine kinase, and cardiac troponin T serum levels were normal. Post marathon there was a significant increase in the assay serum levels of all the three biomarkers. If these results were found in a person who did not partake in vigorous exercise it would be cause for alarm. When cardiac magnetic resonance imaging was done there was no evidence of myocardial edema on T2 imaging or delayed enhancement of the left ventricle myocardium. Within one week of the race, all the biomarker levels returned to normal. Some might say vigorous exercise is fine since there is not an immediate relationship found between elevated biomarker levels and cardiac function. However, constant vigorous exercise might affect cardiac function in the future depending on whether the increased biomarker levels are from the cytosolic pool or from physically bound cardiac troponin (Mousavi, et.al. 2009). These two studies provide some evidence to the above hypothesis however further studies must be conducted to understand the exact reason for the increase in biomarker levels.

The Heart Rate Effect

The body's cardiac output increases during aerobic activity, due to the greater demand for oxygenated blood that the body has during exercise. The two defining qualities of cardiac output is stroke volume (the amount of blood forced out of a ventricle during one contraction [mm/Hg]) and heart rate (the amount of times the heart contracts in one minute [beats/min]). The stroke volume is determined by three factors: the blood that fills the heart during diastole (preload), the force with which the blood leaves the heart during systole (afterload) and, the resistance of the aorta or pulmonary arteries. Cardiovascular exercise causes more blood to be pumped out of a ventricle, resulting in an increased stroke volume. There is a maximum capacity that the stroke volume can increase to before it levels off. At this point, the heart rate responsible for the cardiac output pumps blood to the rest of the body (McArdle, et. al. 2006).

In a recent study, fifty healthy females ages 18 to 24 were randomly selected to examine the benefits that moderate and vigorous exercise training has on a person's heart rate and blood pressure (systolic and diastolic). Participant's heart rate and blood pressure were measured before and after actively engaging in an exercise regimen. The exercise regimen included a thirty minute combination of walking (moderate exercise) and running (vigorous exercise) over a three month period. The heart rate and blood pressure was considerably lower after the three months of aerobic training (see Figure 1 on next page) (Munisekhar, et. al. 2014). This data shows that moderate exercise training is beneficial for improved cardiovascular health due to a decreased resting heart rate and blood pressure. In addition, there is reduced stress on the heart and artery walls. A slower heart rate also gives the coronary arteries more time to fill with blood and oxygenate all the heart cells (Harvard, 2008).

Figure 1

	HEART RATE (BEATS/MIN)		DIASTOLIC BLOOD PRESSURE (mm/Hg)		SYSTOLIC BLOOD PRESSURE (mm/Hg)	
	Before Training	After Training	Before Training	After Training	Before Training	After Training
	Mean		Mean		Mean	
Resting	78.1	68.1	66.2	62.15	99.6	95.1
Walking	126.2	106.58	76.65	67.75	115.88	102.5
Running	169.25	127.93	77.7	72.3	144.85	124.35

Mean heart rate, blood pressure (diastolic & systolic) of the 40 participants before and after their training: Modified from (Munisekhar, et. al. 2014).

Long Term Exercise Conditioning

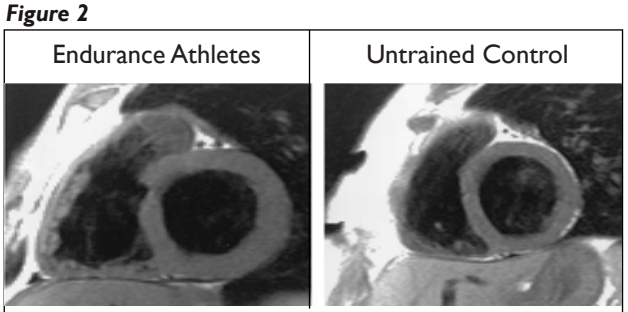
To attain the physiological condition of "athlete's heart" there must be a decrease in heart rate and an increase in hemodynamic demands, which modifies the stroke volume loading. As a result of increased hemodynamic demand there is a change in the left and right ventricle mass and volume; the result of which is cardiac hypotrophy. Due to the limitation of imaging tools, this has been shown in the past to be predominately on the left ventricle. Echocardiography and MRI were used in order to study the effect that prolonged vigorous exercise has on both the right and left ventricles' mass and volume. Twenty-one healthy male endurance athletes, with a history of exercise and a control group of twenty one untrained males were used in the study. In order to meet the criteria of an "athlete's heart", the heart volume of the twenty one endurance athletes had to be at least 13 ml/kg. Results showed that in the hearts of endurance athletes, the mass of the left ventricle was 200 grams while in the control group the mass of the left ventricle was 148 grams. In the hearts of endurance athletes, the mass of the right ventricle was 77 grams while in the control group the mass of the right ventricle was 56 grams. This is a significant increase in the mass of the left and right ventricles and reaches the criteria for hypertrophy. The left ventricle and right ventricle end-diastolic volumes were also substantially increased in the endurance athletes compared to the control group (Figure 2) (Scharhag, et.al. 2002). This study shows that an "athlete's heart" has a balanced enlargement of the left ventricle and right ventricle, which in turn indicates a benign balanced cardiac hypertrophy.

In another study echocardiography and electrocardiography was used to look at left ventricle hypertrophy remodeling in forty elite endurance male athletes after termination of systematic training (deconditioning). Of the forty endurance athletes, fifteen stopped all physical activity and the other twenty five changed from doing intense exercise to doing moderate exercise. The forty athletes had left ventricle cavity enlargement of more than 60mm or wall thickness of more than 13mm at the beginning of the study. After the average deconditioning period of six years, the dimensions of the left ventricle during end-diastolic shrunk by seven percent. The left ventricle cavity size still remained enlarged; more than 55mm in 85 percent of the athletes and more than 60mm in 22 percent of them. The average wall thickness decreased by fifteen percent from 12mm at peak training to 10.1mm after deconditioning. There was not any difference between the fifteen that stopped all physical activity and the other twenty five that changed from intense to moderate exercise. The study showed that once there is substantial left ventricle dilation (hypertrophy), there is only a slight reversal in left ventricle hypertrophy, even after ceasing to do exercise for a long period of time (Pelliccia, et.al. 2006).

Myocardial Fibrosis

La Gerche et al. (2012) found that five of the participants (13%) who had greater prior exposure to vigorous exercise displayed delayed gadolinium enhancement (DGE) in their cardiac magnetic resonance imaging baseline test. More specifically, they showed fibrosis and scarring in the interventricular septum. Another study which contained 102 healthy male runners between 50 –72 years were matched with 102 control subjects who were non-runners. In order to be included in the experiment the runners had to have completed at least five marathons in the past three years. The results showed that 12% of marathon runners had myocardial fibrosis and patchy scarring, as demonstrated by delayed gadolinium enhancement with cardiac magnetic resonance imaging. This rate was three times higher than in the control group, who had a 4% occurrence of myocardial scarring. The study also did a 21 month follow up on all the participants and found the rate of coronary heart disease was higher in the runners with myocardial scarring and fibrosis then in the control group. Even though the percentage of marathon runners with scarring or fibrosis is low, compared to the control group, the incidence of scarring is greatly higher. This author proposes that the development of myocardial scarring may be correlated

Figure 2



Comparison of volume and mass of both ventricles in endurance athlete's vs untrained Control (Scharhag et.al. 2002.)

to prolonged engagement in vigorous exercise; in this case, the marathon running (Breuckmann, et.al. 2009).

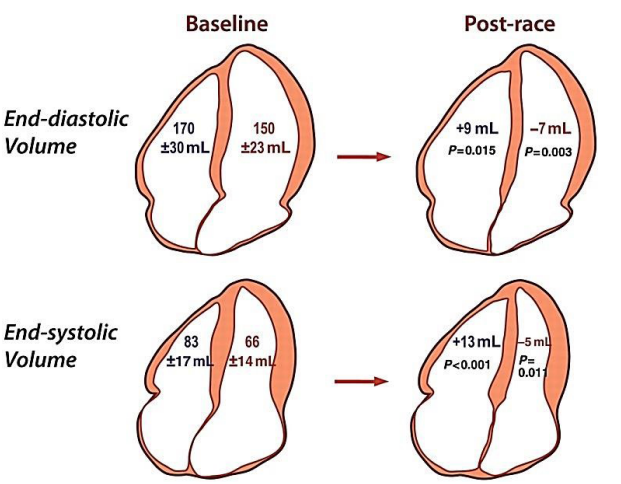
A study on myocardial fibrosis resulting from extreme training was performed on twelve lifelong veteran male endurance athletes, twenty age-matched controls and seventeen younger male endurance athletes. Veteran male athletes had to have 35–52 years of continuous intense training and younger male athletes had to have 11–31 years of intense continuous training. Just as in the previous study, delayed gadolinium enhancement with cardiac magnetic resonance imagining was performed to evaluate myocardial fibrosis. Results showed that in six of the twelve veteran athletes (50%), the existence of myocardial fibrosis and scarring was present. There was no sign of myocardial fibrosis found in the age-matched veteran controls or the younger athletes. The extensiveness of myocardial fibrosis in veteran athletes was not correlated to the age of the athlete, but rather to the amount of years spent training and to the amount of marathons completed. Even though the previous two studies were a small sample size, they still add validity to the correlation between extreme exercise and myocardial fibrosis (Wilson, et.al. 2011).

Right Ventricle Dysfunction Immediately After Exercise

Vigorous aerobic activity increases the average cardiac output of 5 liters per minute to a maximum of 35 liters per minute (McArdle, et. al. 2006). This increase puts a strain on the heart causing the right atrium (RA) and right ventricle (RV) to dilate. A one-time event will not have a negative impact since the heart will return to its normal size. However more consistent vigorous exercise can cause myocardial scaring due to the volume load and cardiac strain because of the chronic dilation of the right atrium and right ventricle. In fact, a study using cardiovascular magnetic resonance (CMR) showed that running a marathon causes acute right atrium and right ventricle dilation and reduces the right ventricle ejection fraction (RVEF). The participants in the study were randomly selected; 25 healthy participants from a pool of 425 volunteers. Cardiovascular magnetic resonance imaging was conducted four weeks before and after the race. The mean age of the participants was 38 years and the mean time for completing a marathon was 256 minutes. "Cardiovascular magnetic resonance showed before and after marathon left ventricular ejection fractions were comparable, 57.7 ± 4.1% and 58.7 ± 4.3%. Right atrial volume index increased from 46.7 ± 14.4 to 57.0 ± 14.5 ml/m2 .Also, right ventricular end-systolic volume index increased from 47.4 ± 11.2 to 57.0 ± 14.6 ml/m2 whereas the right ventricular ejection fraction dropped from 53.6 ± 7.1 to 45.5 ± 8.5%". This data shows that marathon running causes a decrease in right ventricular ejection fraction due to a dilation of the right atrium and right ventricle. However, according to the study it does not appear to result in ischemic injury to any of the chambers (Trivax, et.al. 2010).

Forty healthy endurance athletes were studied following a vigorous event (duration of between 3-11 hours) to assess cardiac function at baseline, immediately post-race, and 1 week post-race. The authors found a reduced right ventricular ejection fraction after the race, which was connected to the dilation of the right ventricle after the event. This follows the Frank–Starling mechanism, which states that an increase in the volume of blood stretches the ventricle causing the heart to contract more forcefully. Thus, in these extreme conditions it causes a dysfunctional heart which is evident by the right ventricular ejection fraction. A greater dilation of the right ventricle caused a slight decrease in left ventricle volume (figure 3) (La Gerche, et.al. 2012). This may be explained because the increase in ventricular load due to intense exercise is greater for the right ventricle then the left ventricle (La Gerche, et.al. 2010). The study also showed that the extent of right ventricle deformation is directly correlated to the event period. A week after the event, all of the cardiac dysfunction returned to their baseline readings (La Gerche, et.al. 2012).

Figure 3



Intense exercise effect on right and left ventricle. The change in volume from baseline is showed on the left (La Gerche, et.al. 2012).

There was a correlation found between a decrease in right ventricular ejection fraction and ventricular arrhythmias (VA) in endurance athletes. This was a result of right ventricle dysfunction in 82 percent of the cases. The study performed right ventricle angiography on three groups: 22 athletes with ventricular arrhythmias, 15 athletes without ventricular arrhythmias and 10 control non-athletes. The study defines an athlete as one who has 6 hours a week of endurance exercise (running or cycling) for more than 5 years. Results showed that those athletes with ventricular arrhythmias showed a substantial decrease in right ventricular ejection fraction versus athlete without ventricular arrhythmias (49.1 ± 10.4 vs. 63.7 ± 6.4%). It was also revealed that the athletes who participated in vigorous exercise have

enlarged right ventricles while the control group right ventricles were normal, these findings are consistent with previous studies (Ector, et.al. 2007).

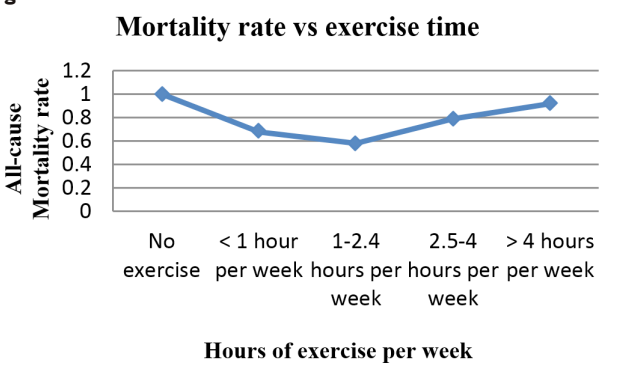
Mortality Rate

The positive effects of exercise on health are numerous. The greatest benefit is the overall decrease of the mortality rate due to physical activity. A 21 year study observed 55,157 adults from the age of 18 to 100 (mean age 44) to determine the correlation of running with all-cause and cardiovascular mortality risk. Individuals with any health issues prior or present were excluded from the experiment. There was a questionnaire that was distributed to participants which asked specific questions regarding a person's exercise training (figure 4). Of the 55,157 participants 24% of them were involved in weekly running of some sort. The study found that runners had a 30% lower all-cause and 45% lower cardiovascular mortality rate then compared with non-runners. The cardiovascular mortality life expectance decreased in non-runners by 4.1 years. These results were similar, as long as the weekly running time was kept under 175 min/week (less than 1840 MET -min/week). Exercising more than 175 min/week slightly increased the mortality rate but was still less than the non-runners mortality rate. This was not only the case for time spent running but also for speed, frequency, and distance (Figure 3) below for the given data (Lee, et.al. 2014).

In the Copenhagen heart study, similar results were found after it was adjusted to a comparable set of confounders found in the previous study. The authors reported with less than 150 minutes of exercise a week there was a decrease in all-cause mortality. However, exercise time greater than 150 min/week did not make a difference in all-cause mortality between runners and non-runners. These results produced a U-curve with regard to jogging time versus mortality rate (figure 5) (Schnohr, et.al. 2013). One of the reasons may be because in this study there were only 1,878 joggers which caused wide confidence intervals since there were not enough runners to equally distribute in all the different exercise categories. On the other hand in the previous study by Lee et.al. there were approximately 13,000 joggers which allowed an equal distribution in the different dose running times.

Another observational study was done by the British Regional Heart Study in 1978 on the decreased risk of coronary heart disease due to physical activity. There were a total of 7,735 male participants aged between 40 and 59. The male participants were randomly chosen from general practices in 24 British towns without distinguishing whether they had pre-existing coronary heart disease. A typical questionnaire was conducted which asked questions on exercise and leisure activities (such as walking, weight lifting, and jogging). After eight years, results showed that the male participants without any pre-existing coronary heart disease who partook in moderate exercise (such as walking at 4 miles per hour) had decreased the risk of coronary heart disease by 50 percent, compared to those who were inactive. The participants with coronary heart disease conditions in the past showed a comparable inverse relationship: decreased risk of coronary heart disease with increased moderate exercise. However, those partaking in vigorous aerobic activity (such as jogging or running) had a higher rate of a heart attack than those participating in moderate exercise (Shaper, et.al. 1991). These three studies show that those who participate in weekly moderate exercise versus those who do not do any exercise have less of a risk of developing coronary heart disease, and a lower all-cause and cardiovascular mortality rate. However these studies also show that there is an upper limit to these benefits and over exercising slightly reverses these positive effects and the mortality rate is similar to those who do not exercise.

Figure 4



Hazard ratio of all-cause mortality versus the amount of time spent exercising per week. Graph produces a U shaped curve with an optimal exercise time between 1-2.4 hours per week (Schnohr, et.al. 2013).

Animal Studies

In order to achieve a post-mortem look at the effect intense exercise training has on cardiovascular health, it is necessary to perform studies using animals. Rats were used to examine the long term intense exercise effect on cardiac function; more precisely fibrosis, which can induce cardiac arrhythmias. The Wister rats were separated for 16 weeks (this is equivalent to around 10 years in humans) into exercise and sedentary control groups. After the 16 week experiment, some of the rats from the exercise group were held for another eight weeks without exercise. This was done in order to see if the effect that intense exercise has on the heart is reversible. At the end of the experiment, all of the rats were euthanized and their hearts were removed for dissection. The exercise rats were put on a treadmill for five days a week, at 60 centimeters per second. In order to keep the rats running, a small shock was provided however, it was extremely low so that a stress response would not be elicited. Results showed that after 16 weeks of training, the exercise rats developed left ventricle hypertrophy, and impaired diastolic function; which is related to the left atrium dilatation. There was also right ventricle dilatation,

impaired diastolic and systolic dysfunction. All these symptoms are also found in humans with "athlete's heart". Right ventricle fibrosis was found in the histological sections. This can be due to the higher loading conditions on the right ventricle versus the left which is also consistent in humans. TGF-β1, a fibrotic marker, was found in high levels in both atrium and right ventricle. TGF-β1 is a collagen stimulator that leads to development of fibrosis. Another component that was observed was the surge in collagen-I [determines stiffness of cardiac muscle] protein expression in the right atria and ventricle, collagen-III [distensible] remained unchanged. This shows that the diastolic dysfunction of the right atria and ventricle could be due to the increased cardiac stiffness. Intense long term exercise effect on cardiac arrhythmias was evaluated in vivo, by attaching a modified catheter to the right ventricle apex. Inducible ventricle tachyarrhythmia was found in 42% of the exercise rats compared to 6% of the control rats. A possible explanation for the higher prevalence of arrhythmias in exercise rats could be linked back to cardiac fibrosis. After the eight week deconditioning period, all the exercise rats had almost all the cardiac remolding mentioned above revert to the control rats levels. (Benito, et.al. 2011) There have been other animal studies conducted that show similar results to this one. Even though there are some similarities between cardiac remodeling in animals and humans, researchers cannot be certain that cardiac remodeling in both is exactly the same.

Conclusion

After intense exercise immediate testing resulted in dilatation of the right ventricle and atrium, reduced right ventricular ejection fraction, and elevated levels of biomarkers found in the blood. Even though there was a correlation found between reduced right ventricular ejection fraction and ventricle arrhythmias, the sample size was too small to fully determine the validity of the correlation. Further research needs to be conducted on the effect and mechanism of elevated biomarkers found in the bloodstream after vigorous exercise. Testing after many years of intense aerobic activity show that balanced cardiac hypertrophy is normally found in a person with the condition known as "athlete's heart." Even after many years of deconditioning, the heart does not return to its normal size. A result of cardiac hypertrophy is myocardial fibrosis and scarring. The percent of myocardial fibrosis in those participating in prolonged vigorous activity is low; however, compared to the control group, the percent is significantly greater. Studies also show that while moderate exercise is beneficial to lowering a person's all-cause mortality rate and cardiovascular mortality rate, intense exercise reverses this positive effect slightly. Humans share similar results found in dissections of rats that underwent exercise training. Though intense exercise does not have a positive effect on cardiovascular health, more studies involving a greater sample size have to be conducted to determine the extent to which vigorous exercise damages the heart. In addition to the negative effects that intense exercise has on the heart one has to consider the adverse effects that it has on the body and more specifically the skeletomuscular system.

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