

# Secretion of Atrial Natriuretic Peptide (ANP), Heart Reconditioning and Remolding in Elite Endurance Trained Athletes

HAFEEZULLAH WAZIR ALI<sup>1</sup>, MOHAMMAD ASLAM<sup>2</sup>, SOHAIL AZIZ<sup>3</sup>, MUHAMMAD MAZHAR HUSSAIN<sup>4</sup>

<sup>1</sup>Department of Physiology Northern Border University, Ar'ar, Saudi Arabia

<sup>2</sup>Professor of Physiology Shifa Tameer e Millat University, Islamabad, Pakistan

<sup>3</sup>Professor of Cardiology Fauji Foundation Cardiac Centre of Excellence Rawalpindi, Pakistan

<sup>4</sup>Professor and Head of Physiology Department Vice Principal Fazaia Med College Air University, Islamabad

Corresponding author: Hafeezullah Wazir Ali, Email: [Hafeezullah2k@hotmail.com](mailto:Hafeezullah2k@hotmail.com), Cell: +966536140552

## ABSTRACT

**Aim / Objective:** The aim of this study was to evaluate the effect of maximal exercise on the level of cardiac remodeling and Atrial Natriuretic Peptide (ANP) in elite athletes as compared to sedentary healthy subjects and correlation of ANP with the adaptation of athlete's heart and cardiac remodeling (if any)

**Place and Duration of Study:** The present study was carried out at the Department of Physiology, Army Medical College, with collaboration of Armed Forces Institute of Cardiology (AFIC) Rawalpindi from June 2003 to May 2004.

**Methodology:** A total number of 44 subjects were included in this study. These comprised of 22 elite endurance athletes and 22 healthy sedentary volunteers as controls. All subjects were examined clinically to rule out the cardiovascular and pulmonary diseases on the basis of medical history, physical examination, and echocardiography. All the selected subjects were examined on a Toshiba Power Vision 6000 echocardiograph for assessing and measuring their LV end-diastolic internal diameter (LVIDd), Diastolic interventricular septal thickness (IVSTd), diastolic posterior wall thickness (PWTd). The left ventricular mass was (LVM) was calculated by using the Devereux formula. They were subject to go for ergometer cycle exercise before breakfast. The Blood samples were drawn before and after exercise to assess the level of ANP in their samples.

**Results:** It was found that LVIDd, IVSTd, PWTd, LVM were higher in athletes as compared to their age, sex and BMI matched controls. The ANP levels in athlete's plasma were also high in post and pre exercise sample as compared to controls.

**Conclusion:** Systolic blood pressure, Diastolic Blood Pressure and heart rate are lower in endurance elite athletes than matched sedentary controls. The maximal Exercise increases the level of Atrial Natriuretic Peptide (ANP) in elite athletes significantly as compared to sedentary healthy controls. There was a Positive correlations between ANP and LVIDd, IVSTd, PWTd, and LVM while there was negative correlation between ANP and heart rate, ANP and Blood pressure. However, none of correlation was found to be statistically significant.

**Keywords:** Athlete's Heart, ANP, Cardiac remodeling in athletes, Echocardiography of heart

## INTRODUCTION

The heart of the athlete is strong; the life of the athlete is long, with rare exceptions, these statements are incontrovertible facts supported by a wealth of data<sup>1</sup>. It is a recognized fact that regular endurance exercise training has been promoted as a healthful physical activity associated with multiple benefits and a longer life expectancy<sup>2</sup>. Exercise-induced cardiovascular remodeling is characterized by bilateral dilation of the heart chambers, with supernormal diastolic function, and enhanced arterial vasomotor function<sup>3</sup>. The heart with all these changes<sup>4</sup> including lowering of the heart rate and arterial blood pressure is known as the "athlete's heart."<sup>5</sup> These cardiac remodeling and hemodynamic adaptations results from physiological adaptations to the increased demands of exercise, and left atrial enlargement is a fundamental component of it<sup>6</sup>. When the heart faces a hemodynamic burden, it can do the following to compensate: (1) use the Frank-Starling mechanism to increase cross bridge formation; (2) augment muscle mass to bear the extra load; and (3) recruit neurohormonal mechanisms to increase contractility<sup>7</sup>. The maximum heart rate in athletes remain unchanged having protective effects on their cardiovascular health<sup>8</sup>. These cardiac adaptations include electrical, structural and functional alterations are generally considered benign<sup>9</sup>. The increase in cardiac mass is

maximum over the first few months of training and is directly related to the level of training. The increase in cardiac volume makes the heart more compliant with a larger stroke volume. On the other hand 'bed rest' leads to the reversal of these changes and reduction in volume has been noted in two weeks<sup>10</sup>. Although the controversy about physical activity's optimal load continues, the scientific evidence suggests that the presence of any kind or level of physical activity is much better for an individual than a sedentary lifestyle<sup>11</sup>.

In 1981 it was demonstrated that injections of heart atrial extracts into rats gave rise to pronounced diuresis, natriuresis, and lowered blood pressure. This has led to the isolation and cloning of atrial natriuretic peptide (ANP<sub>99-126</sub>), a hormone synthesized and secreted predominantly by cardiac cells<sup>12</sup>. Within a short time, a peptide with the same biological properties as the crude atrial extracts was isolated and its amino acid sequence was identified in 1983-1984, a 28-amino acid peptide in a pure state and found to elicit potent diuretic and natriuretic activities as well as vasorelaxant activity, when injected into the assay rats and accordingly a name "α-human atrial natriuretic polypeptide (α-hANP)" was proposed for the peptide<sup>13</sup>. The peptide, now known known as atrial natriuretic peptide (ANP), is the first member of a family of peptides known as natriuretic peptides (NPs) synthesizes and secreted by the

mammalian heart and established the heart as an endocrine organ<sup>14</sup>. Mechanical stretch of the atrial wall, due to increased intravascular volume and/or cardiac transmural pressure, and multiple humoral factors is the major stimulus for cardiac ANP release and directly stimulates the transcription and secretion of the peptide<sup>15</sup>. NPs consists of three biologically active peptides: atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Among these, ANP and BNP are secreted by the heart and act as cardiac hormones<sup>16</sup>. Human ANP has three molecular forms,  $\alpha$ -ANP,  $\beta$ -ANP, and proANP (or  $\gamma$ -ANP), with proANP predominating in healthy atrial tissue<sup>17</sup>. In healthy subjects the plasma ANP concentrations were significantly increased during exercise, it is higher in marathon runners than in the controls and judo groups<sup>18</sup>. An intimate link between plasma concentrations of NPs and cardiac morphology was found in different types of athletes, dynamic exercise such as long distance running, cycling, and hand grip exercises have been reported to increase levels of NPs in healthy subjects. Marathon running was associated with progressive left and right atrial remodeling, possibly induced by repetitive episodes of atrial stretching, and reflected by elevated levels of pro-ANP<sup>19</sup>.

**Objectives:** The aim of this study was to evaluate the effect of maximal exercise on the level of cardiac remodeling and Atrial Natriuretic Peptide (ANP) in elite athletes as compared to sedentary healthy subjects and correlation of ANP with the adaptation of athlete's heart and cardiac remodeling (if any)

**Methodology:** The present study was carried out at the Department of Physiology, Army Medical College, with collaboration of Armed Forces Institute of Cardiology (AFIC) Rawalpindi from June 2003 to May 2004. A total number of 44 subjects were included in this study. These comprised of 22 elite endurance athletes and 22 healthy sedentary volunteers as controls.

**Sampling technique:** The subjects were taken by non-probability purposive sampling technique.

**Inclusion criteria:** The subjects were inducted in the study as two groups:

1. **Group-I:** Elite Endurance Athletes (n=22): were recruited from Pakistan Army Their age ranged between 18 -35 years and BMI 19-22 kg/m<sup>2</sup>.

2. **Group-II:** Included the age and BMI matched healthy sedentary controls (n=22)

**Exclusion Criteria:** All subjects were examined clinically to rule out the cardiovascular and pulmonary diseases on the basis of medical history, physical examination (blood pressure  $\leq$ 140/90 mm Hg), and echocardiography. The family history was considered positive if there was a history of coronary artery disease, cardiomyopathy, severe arrhythmias, or any other disabling cardiovascular disease.

**Study Design:** Cross-sectional comparative study.

**Data collection procedure:**

1. **Medical history:** A Proforma as per annexure was filled in for each subject.

2. **General physical examination:**

a) **Height (m) and Weight (kg)**

b) **Body mass index (BMI):** BMI = Weight in Kg/ Height in meters<sup>2</sup> (Kg/m<sup>2</sup>)

c) **Heart Rate:** Heart rate was measured by auscultatory method at mid clavicular line in left fourth intercostal space before and within 3 minutes after exercise.

d) **Blood Pressure:** Arterial blood pressure (mm Hg) was measured after 5 minutes of rest in a seated position by mercury sphygmomanometer.

3. **M-mode echocardiography:** Echocardiographic and Doppler studies were performed using a Toshiba Power Vision 6000 echocardiograph with a 3.7 MHz transducer. Subjects were positioned at 45° left lateral position. To avoid trabeculations in the measurements of wall thickness, an integrated M-mode and two-dimensional studies were done to determine diastolic interventricular septal thicknesses (IVSTd) and left ventricular posterior wall thickness (PWTd) and left ventricular end-diastolic cavity dimension (LVIDd). At first, two-dimensional targeted M-mode recordings were obtained in parasternal long-axis view. Then, septal and posterior wall thickness were measured in parasternal long-axis view between mitral valve tips and papillary muscle from expanded two-dimensional images. Smaller numbers from either M-mode or two-dimensional measurements were accepted to represent the actual thicknesses of septum and posterior wall. The left ventricular mass was (LVM) calculated by using the Devereux formula<sup>20</sup>.

$LVM = 0.8 [1.04 (LVIDd + PWTd + IVSTd)^3 - (LVIDd)^3] + 0.6 \text{ g}$

4. **Bicycle Exercise Test:** The subjects on an electrically braked bicycle ergometer performed a maximal exercise test until exhaustion. The initial load was 50W which was followed by the increments of 10W every 5 minute until exhaustion. During the exercise test, heart rate, arterial blood pressure was recorded. Blood pressure was recorded in the subjects after 5-minute rest in supine position, and at the peak of the exercise immediately before the subject was allowed to stop cycling. The same observer measured blood pressure<sup>21</sup>.

5. **Blood Sampling:** Subjects remained in a relaxed supine position for 20 min prior to blood sampling. A sample of 5 ml of peripheral venous blood was drawn into plastic syringe by observing antiseptic measures from an antecubital vein in each subject and collected into pre-chilled polypropylene tubes containing EDTA (1.5 g/L, blood). All subjects fasted overnight, and the blood samples were collected in the morning (0800 –1000 hours). Then blood was centrifuged at 1600g at 4 °C for 20 minutes and plasma was separated which was kept frozen below -70 °C until determination of proANP.

6. **proANP (1-98):** Plasma concentrations of ANP were measured using a specific Human NT-proANP 1-98 ELISA Kit (Shiono RIA ANP assay kit, Shionogi Co, Ltd). This assay sandwiches  $\alpha$ -human ANP between 2 monoclonal antibodies, one against its carboxy-terminal sequence and the other against its ring structure, and plasma extraction is not required<sup>22</sup>.

7. **Statistical analyses:** The data were entered and analyzed on SPSS Version-12 Computer Software

• **Descriptive Statistics:** Descriptive statistics were used to calculate Means and standard deviations ( $\pm$ SD) of all the variables.

- **Inferential Statistics:** Comparison of means of all parameters between Athletes and Sedentary Controls, using paired Student's t test (Confidence limit 95%).

- **Correlations:** Pearson correlation coefficient and significance of correlation: The values were interpreted as follows;

- r = 0 : No Correlation
- r = 1 : Perfect positive Correlation
- r = -1 : Perfect negative Correlation

**RESULTS**

Present study was designed to work out the correlation between atrial natriuretic peptide (ANP), and cardiac adaptive changes in endurance trained elite athletes. We measured pre and post-exercise heart rate, blood pressure, ANP, levels along with recording the echocardiogram of left ventricle to measure the end-diastolic internal diameter, diastolic interventricular septal thickness, and diastolic posterior wall thickness. The left ventricular mass was calculated by Devereux formula.<sup>20</sup> It was observed that the heart rate and blood pressure of athletes were significantly less than the controls; while left ventricular end-diastolic internal diameter, diastolic interventricular septal thickness, diastolic posterior wall thickness, and mass was greater in athletes than controls. Similarly the plasma levels of ANP was significantly higher in athletes than controls. The results of this study are summarized in tables 1 to 5.

**Table -1** presents the physical data of elite athletes and controls shows mean age and BMI of the elite athletes and controls. The difference between none of these is statistically significant as the controls were carefully matched.

**Table-2** presents heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) in elite athletes and controls before and after exercise. The mean heart rate in post-exercise controls is greater than pre-exercise controls. While in athletes the heart rate is generally less than the sedentary controls. The post-exercise mean heart rate was greater than pre-exercise heart rate of athletes but it was less than the heart rate recorded in controls after exercise. Similarly pre and post-exercise SBP in controls was greater than in athletes. The pre and post-exercise DBP value in athletes was less than that in controls. The heart rate and blood pressure are significantly less in elite athletes ( $p < 0.001$  and  $p < 0.008$  on paired sample 't' test) as compared to the controls.

**Figure-1** presents the heart rate, SBP and DBP in controls before and after exercise. The mean heart rate before exercise is less than that after exercise, pre-exercise SBP is less than post-exercise SBP, while pre-exercise DBP is greater than that in post-exercise, ( $p < 0.001$  and  $p < 0.05$  on paired sample 't' test).

**Figure-2** presents heart rate, SBP and DBP in elite athletes before exercise and after exercise the mean heart rate in pre-exercise is less than that in post-exercise, SBP in pre-exercise is less than that in post-exercise, while DBP in pre-exercise is greater than that in post-exercise, ( $p < 0.001$  and  $p < 0.05$  on paired sample 't' test).

**Table-3** presents ANP, BNP and aldosterone in elite athletes and controls before exercise and after exercise (within ten minutes of exercise till exhaustion). The mean ANP in controls before exercise is less than after exercise

in controls. While in athletes the post-exercise ANP was much greater than pre-exercise ANP levels. All of these are significantly ( $p < 0.001$  on paired sample 't' test) higher in elite athletes as compared with the controls.

Table 1: Comparison of Age and BMI between Elite Athletes and Controls (The Values Of Age And Bmi Are Given As Mean  $\pm$  Sd)

Variables	Elite Athletes (N=22)	Controls (N=22)
Age (years)	22.73 $\pm 3.89$	22.5 $\pm 2.48$
BMI	20.36 $\pm 1.56$	20.89 $\pm 0.96$
Height (m)	1.74 $\pm 0.05$	1.76 $\pm 0.07$
Weight (kg)	61.48 $\pm 2.40$	63.58 $\pm 4.47$

None of the differences is statistically significant

Table 2: Heart rate, Systolic blood pressure, diastolic blood pressure before and after exercise in Athletes and Controls: (The Values Are Given As Mean  $\pm$  Sd)

Subjects n=44)	Variables	Athletes (n=22)	Controls (n=22)
Pre-exercise	Heart rate	55.86** $\pm 3.47$	74.09 $\pm 2.86$
	BP Systolic (mmHg)	107.05** $\pm 7.01$	115 $\pm 5.12$
	BP Diastolic (mmHg)	58.09** $\pm 2.43$	74.55 $\pm 5.1$
	Mean Arterial blood pressure (mmHg)	83.29** $\pm 24.86$	95.00 $\pm 21.05$
Post-exercise	Heart rate	120.82** $\pm 8.27$	136.00 $\pm 6.87$
	BP Systolic (mmHg)	131.36* $\pm 5.16$	139.32 $\pm 9.04$
	BP Diastolic (mmHg)	56.14** $\pm 3.76$	70.68 $\pm 5.19$
	Mean Arterial blood pressure (mmHg)	93.75** $\pm 37.86$	105 $\pm 35.06$

\*: The difference is statistically significant at  $p < 0.008$

\*\*: The difference is statistically significant at  $p < 0.001$

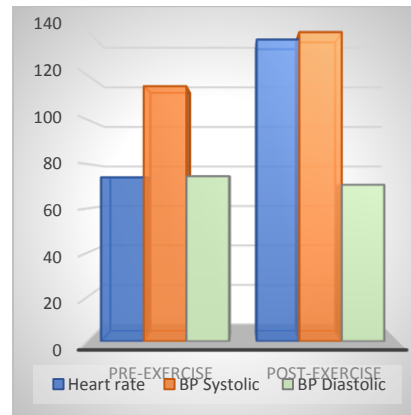


Figure 1: Bar Diagram Showing the Comparison between Pre and Post-Exercise Heart rate and Blood pressure in controls

**Figure-3** presents the comparison between ANP levels in athletes and controls before and after exercise. All of these

parameters are significantly ( $p < 0.001$  on paired sample 't' test) higher after exercise as compared with the pre-exercise values.

**Fig. 4:** Comparison of echocardiographic variables between elite athletes and controls, in it the difference is statistically significant at  $P < 0.001$

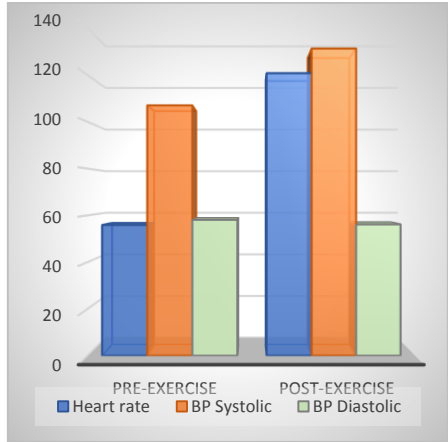


Figure 2: Bar Diagram Showing the Comparison between Pre and Post-Exercise Heart rate and Blood pressure in elite athletes

Table 3: Plasma levels of Atrial Natriuretic Peptide (ANP) before and after exercise in elite athletes and controls: (The Values Are Given As Mean  $\pm$  Sd)

Subjects (n=44)	Variables	Athletes (n=22)	Controls (n=22)
Pre-exercise	ANP (pmol/L)	35.05* $\pm$ 18.39	20.66 $\pm$ 3.76
Post-exercise	ANP (pmol/L)	48.19** $\pm$ 23.07	21.60 $\pm$ 4.02

\*: The difference is statistically significant at  $p < 0.008$   
 \*\*: The difference is statistically significant at  $p < 0.001$

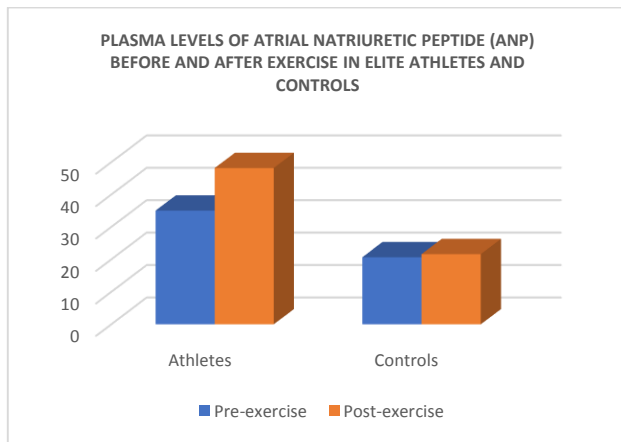


Fig. 3: Plasma levels of atrial natriuretic peptide (ANP) before and after exercise in elite athletes and controls

**Table-4** presents LVIDd, IVSTd, PWTd and LVM in elite athletes and controls. All of these are significantly ( $p < 0.001$  and  $p < 0.008$  on paired sample 't' test) higher in elite athletes as compared with the controls.

Table 4: Comparison of Echocardiographic Variables between elite athletes and controls: (The Values Are Given As Mean  $\pm$  Sd)

Parameter	Elite Athletes (n=22)	Controls (n=22)
LV end-diastolic internal diameter (LVIDd) (mm)	54.63** $\pm$ 1.79	40.6364 $\pm$ 2.08
Diastolic interventricular septal thickness (mm)	9.86** $\pm$ 0.89	8.52 $\pm$ 0.37
Diastolic posterior wall thickness (PWTd) (mm)	8.63* $\pm$ 0.73	8.04 $\pm$ 0.32
Left Ventricular Mass (LVM) (gm)	196.36** $\pm$ 22.86	102.5 $\pm$ 11.01

\*: The difference is statistically significant at  $p < 0.008$   
 \*\*: The difference is statistically significant at  $p < 0.001$

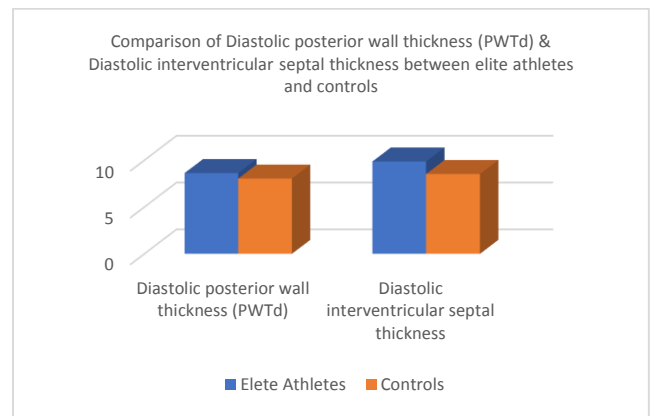


Fig. 4: Comparison of diastolic posterior wall thickness (LVIDD) & Diastolic interventricular septal thickness between elite athletes and controls

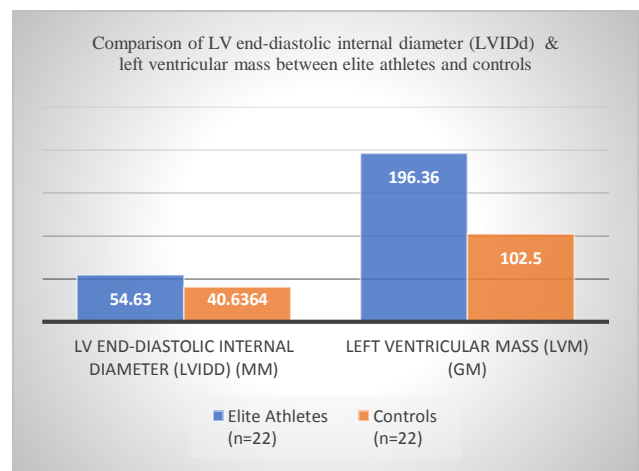


Fig. 5: Comparison of left end-diastolic internal diameter (LVIDD) & left ventricular mass between elite athletes and controls

**Table-5** displays the correlation coefficients (and statistical significance) of ANP with heart rate, blood pressure, LVIDd, IVSTd, PWTd, and LVM in elite athletes and controls. There is a non-significant correlation ( $p > 0.05$ ) between ANP and heart rate, diastolic blood pressure,

LVIDd, IVSTd, PWTd, and LVM in elite athletes and controls. There is significant correlation ( $p < 0.05$ ) between ANP and systolic blood pressure in controls.

However, there is non-significant negative correlation between ANP with heart rate and blood pressure in elite athletes and there is non-significant positive correlation between ANP with LVIDd, IVSTd, PWTd, and LVM in elite athletes.

While in controls, there is non-significant negative correlation between ANP with heart rate and diastolic blood pressure and there is non-significant positive correlation between ANP with LVIDd, IVSTd, PWTd, and LVM

Table 5: Correlation of ANP with Heart rate, Blood Pressure, LVIDd, IVSTd, PWTd, and LVM.

Variables	Elite Athletes		Controls	
	Correlation	Significance	Correlation	Significance
Heart Rate	-0.192	0.392	-0.160	0.477
BP-Systolic	-0.201	0.370	-0.461*	0.031
BP-Diastolic	-0.217	0.333	0.395	0.069
LVIDd	0.013	0.955	0.053	0.814
IVSTd	0.172	0.444	0.064	0.776
PWTd	0.304	0.169	0.156	0.489
LVM	0.208	0.353	0.026	0.909

\* Correlation is significant at  $p < 0.05$  (2-tailed).

## DISCUSSION

This study was carried out to determine pre and post exercise heart rates of elite athletes and sedentary group, measured pre and post exercise blood pressures and carried out echocardiography to determine cardiac adaptive changes in endurance trained elite athletes like wall thickness, internal dimensions, and ventricular mass, and end-diastolic volume of the subjects. We also measured Atrial Natriuretic Peptide levels before and after exercise and try to find any relationship of ANP levels with these changes in endurance trained elite athletes. Over the last two decades and especially in the last five years a lot of research work has been done to determine changes in serum ANP levels associated with long-term endurance exercise. As a result, enough of quality work is now available on the subject. Serum ANP levels are now closer to being declared as established markers of status of athlete's heart. We will also discuss the cardiac adaptive changes and cardiac remodeling which have been observed as increased cardiac parameters (LVIDd, IVSTd, PWTd, LVM), although they are not high enough in this setup but may be alarming if they occur in sedentary population. It was observed that the heart rate and blood pressure of athletes were significantly less than the controls, while left ventricular end-diastolic internal diameter, diastolic interventricular septal thickness, diastolic posterior wall thickness, and mass was greater in athletes than controls.

Similarly the plasma levels of ANP were significantly higher in athletes than controls. Though not significant but positive correlations were found between, ANP and LVIDd, ANP and IVSTd, ANP and PWTd, and ANP and LVM.

While there was negative correlation between, ANP and heart rate, ANP and Systolic Blood pressure, and ANP and diastolic blood pressure.

Here we will attempt to discuss in the light of our findings and in comparison with contemporary works whether ANP have a potential to become an established set for understanding the left ventricular remodeling in athlete's heart due to their relation with type and magnitude of remodeling or not and to which extent it is correlated with cardiac adaptation or remodeling? Regarding cardiac dimensions, it has been found that LVIDd in athletes is increased as compare to sedentary person. Therefore, it was not surprising that in this study the LVIDd was found to be  $54.63 \text{ mm} \pm 1.79 \text{ mm}$  in elite athletes, which is significantly higher as compared to the sedentary controls in whom it was found to be  $40.63 \text{ mm} \pm 2.08 \text{ mm}$ . Lakatos et al found in a large population of highly trained athletes ( $n = 1,777$ ), enlarged LA dimension (23 to 50 mm, mean,  $37 \pm 4 \text{ mm}$ ) in men and 20 to 46 mm (mean,  $32 \pm 4 \text{ mm}$ ) in women and was enlarged (i.e., transverse dimension  $> \text{ or } = 40 \text{ mm}$ ) in 347 athletes (20%), including 38 (2%) with marked dilation ( $> \text{ or } = 45 \text{ mm}$ )<sup>23</sup>. D'Ascenzi et al reported that the mean LVIDd was  $53 \pm 0.5 \text{ mm}$  and maximal wall thickness  $11.2 \pm 0.2 \text{ mm}$  ( $p < 0.01$ ) in elite football players as compared to normal reported control subjects<sup>24</sup>. Similarly D'Andrea et al also observed the same pattern that is Left ventricular end-diastolic cavity dimensions (LVIDd) of  $56 \pm 5.6$  in endurance trained athletes<sup>25</sup>. These Values are close to what we found in our study. In the absence of systolic dysfunction, this cavity dilatation is most likely an extreme physiologic adaptation to intensive athletic conditioning. In our study we found diastolic posterior wall thickness (PWTd) and diastolic Inter-ventricular septal thickness (IVSTd) were significantly more in elite athletes than that in controls. As the mean ( $\pm$ SD) values of PWTd and IVSTd in our elite athletes definitely showed a visible increase, however, looking at the cases individually we found that some athletes had normal PWTd and IVSTd values (mean IVSTd in athletes was  $9.86 \pm 0.89 \text{ mm}$  as compared to controls  $8.56 \pm 0.37 \text{ mm}$ ) ( $p < 0.001$ ). This could be due to the possibility that adaptation to hemodynamic overload induced by training may not be a relevant factor or, at least, it isn't a predominant one. Mean PWTd in this study was calculated to be  $8.63 \pm 0.73$  which is significantly higher than controls  $8.04 \pm 0.32$  ( $p < 0.008$ ). Similar results have been reported by Pellicia et al in their latest study of 2018 on 40 elite male athletes measured the PWTd to be  $9.3 \pm 1.4 \text{ mm}$ , the level close to what we found in present study<sup>4</sup> and Sharma et al in his study also measured mean PWTd levels in elite athletes  $9.5 \pm 1.7 \text{ mm}$  and in controls  $8.4 \pm 1.4 \text{ mm}$  ( $p < 0.0001$ )<sup>26</sup>, Pelà et al reported the maximal wall thickness  $10.3 \pm 1.7$  vs  $8.8 \pm 1.1 \text{ mm}$  ( $p < 0.0001$ )<sup>27</sup>. This high values is probably because of racial difference as Caucasian populations have more body surface area as compared to Asians.

As stated earlier that ANP is released in response of exercise in athletes and sedentary controls. In previous studies it was observed that the cardiac remodeling during endurance training causes an increase in plasma levels of ANP, which is related with type and magnitude of remodeling. Myocyte stretch (e.g. due to increased intravascular volume) is regarded as the central regulator

of ANP secretion.<sup>17</sup> Expression and secretion of ANP is stimulated by various factors and is regulated via multiple signaling pathways it had been found that the ventricular hypertrophy is generally accompanied by increased formation and release of ANP from the heart<sup>28</sup>. Thus, Exertion puts extra strain on heart by increasing the cardiac work load in order to supply more blood to match the increased metabolic needs. The physiological effects of ANP like reduction in heart rate, stroke volume, cardiac output and blood pressure etc are thought to contribute to adaptive changes in periods of cardiovascular stress<sup>29</sup>. ANP plasma level respond differently to the type of exercise. Date et al compared echocardiographic measures and plasma concentrations of ANP in different types of athletes and healthy controls to investigate the relationship between the different types of left ventricular hypertrophy and plasma ANP concentrations. Plasma ANP concentrations were found to be significantly higher in marathon runners ( $11.48 \pm 5.80$  pg/ml = ) than in the control ( $5.33 \pm 1.86$  pg/ml) or judo group ( $5.44 \pm 5.38$  pg/ml) (marathon vs control,  $p < 0.0005$ ; marathon vs judo,  $p < 0.005$ ).<sup>20</sup> The most likely cause of this may be that LV structural changes in elite athletes represent adaptation to hemodynamic overload induced by training and are consistent with different kinds of sports activity. Although ANP is predominantly produced in and secreted from the atria, the ventricular ANP gene is expressed during LV hypertrophy suggesting that the ventricular myocardium produces and secretes ANP into the blood circulation. ANP is stored and released by a regulated pathway in the atrium whereas it is released from the ventricle<sup>30</sup>. Plasma ANP concentrations were high only in the marathon group and correlated with both LAD index and LVD index, suggesting that ANP is secreted from the dilated LA and/or LV<sup>31</sup>. In present study the mean ( $\pm$  SD) plasma level of ANP was found to be elevated ( $35.05 \pm 18.39$  pmol/L) in endurance trained athletes as compared to sedentary controls ( $20.66 \pm 3.76$  pmol/L) before exercise. ( $p < 0.008$ ) while after exercise the ANP level was increased significantly in athletes ( $48.19 \pm 23.07$  pmol/L) as compared to controls ( $21.60 \pm 4.02$  pmol/L). Yan et al in 2017 examined changes of ANP concentration on exercise testing and found that ANP concentration increased significantly immediately after the testing<sup>32</sup>. Several factors have been evaluated as possible stimuli for the release of ANP in healthy individuals on exercise. Exercise intensity has been reported to stimulate the release of ANP. In a study before ours, Wilhelm et al has examined the response of plasma ANP to prolonged strenuous exercise in healthy individuals. He related this rise to exercise which significantly increased ANP levels in healthy men, and could be due to atrial remodeling perpetuated by repetitive episodes of atrial stretching during strenuous competitions, which is reflected by elevated levels of pro-ANP<sup>33</sup>. Mandroukas et al in the study conducted in 2011 concluded that ANP for all athletes was increased significantly in response to not only medium-term exercise but also endurance exercise<sup>34</sup>. Cardiac strain during long-distance running may explain the pronounced increase in ANP level.

Wilhelm et al. found a strong positive correlation between proANP concentration at baseline and after a 10-mile race and right atrial volume among marathon runners compared to non-marathon runners and emphasizes the

importance of right atrial overload following a bout of strenuous exercise.<sup>21</sup> In our study we did not find any significant correlation of ANP with LVIDD, IVSTd, PWTd, and LVM. However, there is non-significant positive correlation between ANP with LVIDD, IVSTd, PWTd, and LVM in elite athletes.

## CONCLUSION

Systolic blood pressure, Diastolic Blood Pressure and heart rate are lower in endurance elite athletes than matched sedentary controls. The maximal Exercise increases the level of Atrial Natriuretic Peptide (ANP) in elite athletes significantly as compared to sedentary healthy controls. There was a Positive correlations between ANP and LVIDD, IVSTd, PWTd, and LVM while there was negative correlation between ANP and heart rate, ANP and Blood pressure. However, none of correlation was found to be statistically significant.

## REFERENCES

- Galanti G, Stefani L, Mascherini G, Di Tante V, Toncelli L. Left ventricular remodeling and the athlete's heart, irrespective of quality load training. *Cardiovasc Ultrasound*. 2016; 14: 46.
- Rubio-Arias JA, Andreu L, Martínez-Aranda LM, Martínez-Rodríguez A, Manonelles P, Ramos-Campo DJ. Effects of medium- and long-distance running on cardiac damage markers in amateur runners: a systematic review, meta-analysis, and meta-regression. *J Sport Health Sci*. 2021 Mar; 10(2):192-200.
- Baggish AL. Focal Fibrosis in the Endurance Athlete's Heart: Running Scarred or Running Scared? *JACC Cardiovasc Imaging*. 2018 Sep;11(9):1271-1273. doi: 10.1016/j.jcmg.2017.09.015. Epub 2017 Dec 13. PMID: 29248664.
- Pelliccia A, Caselli S, Sharma S, Basso C, Bax JJ, Corrado D, D'Andrea A, D'Ascenzi F, Di Paolo FM, Edvardsen T, Gati S, Galderisi M, Heidbuchel H, Nchimi A, Nieman K, Papadakis M, Pisicchio C, Schmied C, Popescu BA, Habib G, Grobbee D, Lancellotti P; Internal reviewers for EAPC and EACVI. European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement: recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete's heart. *Eur Heart J*. 2018 Jun 1;39(21):1949-1969. doi: 10.1093/eurheartj/ehx532. PMID: 29029207.
- Christou GA, O'Driscoll JM. The impact of demographic, anthropometric and athletic characteristics on left atrial size in athletes. *Clin Cardiol*. 2020 Aug;43(8):834-842. doi: 10.1002/clc.23368.
- Diaz Babio G, Vera Janavel G, Constantin I, Masson G, Carrero C, Garcia Botta T, Mezzadra M, Stutzbach P. Atrial size and sports. A great training for a greater left atrium: how much is too much? *Int J Cardiovasc Imaging*. 2021 Mar;37(3):981-988. doi: 10.1007/s10554-020-02082-2. Epub 2020 Oct 26. PMID: 33104945.
- Shah AB, Zilinski J, Brown MG, Neary JH, Weiner RB, Hutter AM, Apple FS, Picard MH, Januzzi JL, Baggish AL. Endurance Exercise Training Attenuates Natriuretic Peptide Release During Maximal Effort Exercise: Biochemical Correlates of the "Athlete's Heart". *J Appl Physiol*. 2018 Oct 11;125: 1702–1709.
- Stamatakis E, Gale J, Bauman A, Ekelund U, Hamer M, Ding D. Sitting Time, Physical Activity, and Risk of Mortality in Adults. *J Am Coll Cardiol*. 2019 Apr 30;73(16):2062-2072. doi: 10.1016/j.jacc.2019.02.031. Erratum in: *J Am Coll Cardiol*. 2019 Jun 4;73(21):2789. PMID: 31023430.
- Lakatos BK, Molnár AA, Kiss O, Sydó N, Tokodi M, Solymosi B, Fábrián A, Dohy Z, Vágó H, Babity M, Bognár C, Kovács A, Merkely B. Relationship between Cardiac Remodeling and Exercise Capacity in Elite Athletes: Incremental Value of Left Atrial Morphology and Function Assessed by Three-Dimensional

- Echocardiography. *J Am Soc Echocardiogr.* 2020 Jan;33(1):101-109.e1. doi: 10.1016/j.echo.2019.07.017.
10. Lampert R, Zipes DP. Updated Recommendations for Athletes with Heart Disease. *Annu Rev Med.* 2018 Jan 29;69:177-189. doi: 10.1146/annurev-med-041316-090402. PMID: 29414256.
  11. García-Manso JM, Martínez-Patiño MJ, de la Paz Arencibia L, Valverde-Esteve T. Tactical behavior of high-level male marathon runners. *Scand J Med Sci Sports.* 2021 Mar; 31(3):521-528.
  12. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci* 1981; 28:89-94
  13. Kangawa K, Matsuo H. Purification and complete amino acid sequence of alpha-human atrial natriuretic polypeptide (Alpha-hANP). *Biochem. Biophys. Res. Commun.* 1984; 118: 131-139.
  14. Goetze JP, Bruneau BG, Ramos HR, Ogawa T, de Bold MK, de Bold AJ. Cardiac natriuretic peptides. *Nat Rev Cardiol.* 2020 Nov;17(11):698-717. doi: 10.1038/s41569-020-0381-0. Epub 2020 May 22. PMID: 32444692.
  15. da Silva GJJ, Altara R, Booz GW, Cataliotti A. Atrial Natriuretic Peptides<sup>1-67</sup>: A Novel Therapeutic Factor for Cardiovascular Diseases. *Front Physiol.* 2021 Jul 8;12:691407. doi: 10.3389/fphys.2021.691407. PMID: 34305645; PMCID: PMC8297502.
  16. Nakagawa Y, Nishikimi T, Kuwahara K. Atrial and brain natriuretic peptides: Hormones secreted from the heart. *Peptides.* 2019 Jan;111:18-25. doi: 10.1016/j.peptides.2018.05.012. Epub 2018 May 31. PMID: 29859763.
  17. Matsuo A, Nagai-Okatani C, Nishigori M, Kangawa K, Minamino N. Natriuretic peptides in human heart: Novel insight into their molecular forms, functions, and diagnostic use. *Peptides.* 2019 Jan; 111:3-17.
  18. Date H, Imamura T, Onitsuka H, Maeno M, Watanabe R, Nishihira K, Matsuo T, Eto T. Differential increase in natriuretic peptides in elite dynamic and static athletes. *Circ J.* 2003 Aug;67(8):691-6. doi: 10.1253/circj.67.691. PMID: 12890912.
  19. Wilhelm M, Nuoffer JM, Schmid JP, Wilhelm I, Saner H. Comparison of pro-atrial natriuretic peptide and atrial remodeling in marathon versus non-marathon runners. *Am J Cardiol.* 2012 Apr 1;109(7):1060-5. doi: 10.1016/j.amjcard.2011.11.039. Epub 2012 Jan 3. PMID: 22221947.
  20. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986 Feb 15;57(6):450-8. doi: 10.1016/0002-9149(86)90771-x. PMID: 2936235.
  21. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Piña IL, Rodney R, Simons-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation.* 2001 Oct 2;104(14):1694-740. doi: 10.1161/hc3901.095960. PMID: 11581152.
  22. Missbichler A, Hawa G, Schmal N, Woloszczuk W. Sandwich ELISA for proANP 1-98 facilitates investigation of left ventricular dysfunction. *Eur J Med Res.* 2001 Mar 26;6(3):105-11. PMID: 11309223.
  23. Lakatos BK, Molnár AÁ, Kiss O, Sydó N, Tokodi M, Solymossi B, Fábíán A, Dohy Z, Vágó H, Babity M, Bognár C, Kovács A, Merkely B. Relationship between Cardiac Remodeling and Exercise Capacity in Elite Athletes: Incremental Value of Left Atrial Morphology and Function Assessed by Three-Dimensional Echocardiography. *J Am Soc Echocardiogr.* 2020 Jan;33(1):101-109.e1. doi: 10.1016/j.echo.2019.07.017. Epub 2019 Oct 1. PMID: 31585830.
  24. D'Ascenzi F, Pelliccia A, Corrado D, Cameli M, Curci V, Alvino F, Natali BM, Focardi M, Bonifazi M, Mondillo S. Right ventricular remodelling induced by exercise training in competitive athletes. *Eur Heart J Cardiovasc Imaging.* 2016 Mar;17(3):301-7. doi: 10.1093/ehjci/jev155. Epub 2015 Jun 18. PMID: 26092834.
  25. D'Andrea A, Mele D, Palermi S, Rizzo M, Campana M, Di Giannuario G, Gimelli A, Khoury G, Moreo A; a nome dell'Area Cardioimaging dell'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). Le "zone grigie" degli adattamenti cardiovascolari all'esercizio fisico: come orientarsi nella valutazione ecocardiografica del cuore d'atleta [Grey zones in cardiovascular adaptations to physical exercise: how to navigate in the echocardiographic evaluation of the athlete's heart]. *G Ital Cardiol (Rome).* 2020 Jun;21(6):457-468. Italian. doi: 10.1714/3359.33330. PMID: 32425192.
  26. Sharma S, Maron BJ, Whyte G, Firooz S, Elliott PM, McKenna WJ. Physiologic Limits of Left Ventricular Hypertrophy in Elite Junior Athletes: Relevance to Differential Diagnosis of Athlete's Heart and Hypertrophic Cardiomyopathy. *J Am Coll Cardiol* 2002; 40:1431-6
  27. Pelà G, Li Calzi M, Crocama A, Pattoneri P, Goldoni M, Anedda A, Musiari L, Biggi A, Bonetti A, Montanari A. Ethnicity-related variations of left ventricular remodeling in adolescent amateur football players. *Scand J Med Sci Sports.* 2015 Jun;25(3):382-9. doi: 10.1111/sms.12238. Epub 2014 Apr 27. PMID: 24766540.
  28. Nishikimi T, Maeda N, Matsuoka H. The role of natriuretic peptides in cardioprotection. *Cardiovasc Res.* 2006 Feb 1;69(2):318-28. doi: 10.1016/j.cardiores.2005.10.001. Epub 2005 Nov 10. PMID: 16289003.
  29. Xiao J, Xu T, Li J, Lv D, Chen P, Zhou Q, Xu J. Exercise-induced physiological hypertrophy initiates activation of cardiac progenitor cells. *Int J Clin Exp Pathol.* 2014 Jan 15;7(2):663-9. PMID: 24551287; PMCID: PMC3925911.
  30. Nakagawa O, Ogawa Y, Itoh H, Suga S, Komatsu Y, Kishimoto I, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy: Evidence for brain natriuretic peptide as an 'emergency' cardiac hormone against ventricular overload. *J Clin Invest* 1995; 96: 1280 - 1287
  31. Kangawa K, Matsuo H. Purification and complete amino acid sequence of  $\alpha$ -human atrial natriuretic polypeptide. *Biochem Biophys Res Commun* 1984; 118: 131 - 139.
  32. Yin R, Yang Z, Peng J, Li B, Fu Y, Zheng Z. Predictive value of exercise-induced atrial natriuretic peptide secretion for the presence of left atrial low-voltage areas in patients with persistent atrial fibrillation. *Acta Cardiol.* 2017 Aug;72(4):433-439. doi: 10.1080/00015385.2017.1335112. PMID: 28768468.
  33. Wilhelm M, Nuoffer JM, Schmid JP, Wilhelm I, Saner H. Comparison of pro-atrial natriuretic peptide and atrial remodeling in marathon versus non-marathon runners. *Am J Cardiol.* 2012 Apr 1;109(7):1060-5. doi: 10.1016/j.amjcard.2011.11.039. Epub 2012 Jan 3. PMID: 22221947.
  34. Mandroukas A, Metaxas TI, Heller J, Vamvakoudis E, Christoulas K, Riganas CS, Sendelides T, Stefanidis P, Kotoglou K, Karamouzis I, Mandroukas K. The effect of different exercise-testing protocols on atrial natriuretic peptide. *Clin Physiol Funct Imaging.* 2011 Jan;31(1):5-10. doi: 10.1111/j.1475-097X.2010.00971.x. Epub 2010 Sep 12. PMID: 20831660.