JBAAR

Journal of Bioscience and Applied Research

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Estimation of insulin-like growth factor binding protein -1 in premature heart contraction patients

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DOI: 10.21608/jbaar.2025.455422

Abstract

This study was conducted to provide an approach for the diagnosis and prognosis of atrial and ventricular presystole, with a particular focus on insulin-like growth factor-binding protein (IGF-1). The research was conducted in Najaf Governorate, Iraq, from July 1, 2024, to December 1, 2025, with monthly patient follow-ups. A total of 90 participants were enrolled, including 60 patients diagnosed with PVS and 30 healthy individuals as controls. The results were stratified into subgroups according to age, PVS type (atrial or ventricular), diagnosis status (newly diagnosed or under treatment), disease duration, blood pressure status, and body mass index (BMI) category. The results revealed a significant increase in IGF-1 levels among patients compared to the control group. Male patients showed significantly higher levels than female patients. Elderly patients (60-69 years old) showed a significantly higher incidence of ventricular fibrillation compared to other age groups. Additionally, newly diagnosed patients had a significantly higher incidence of ventricular fibrillation compared to treated patients. Hypertensive patients showed a significantly higher incidence of ventricular fibrillation compared to normotensive individuals. Regarding disease duration, those aged 1 week to 1 month showed significantly higher values compared to patients aged 1-5 years and older than 5 years. Patients with obesity had a significantly higher incidence rate compared to the control groups. In conclusion, the study suggests that insulin-like growth factor-1 (IGF-1) binding protein is a novel biomarker for atrial and ventricular fibrillation. It may serve as a valuable diagnostic and prognostic tool, potentially helping to reduce future complications associated with this condition.

Keywords: Premature atrial contraction, sex, age, atrial.

Introduction

Premature atrial and ventricular contractions are defined as extra heartbeats that originate in the upper chambers of the heart, giving the sensation of a skipped beat. These contractions arise from sites apart from the sinus node, leading to disturbances in the normal heart rhythm (1, 2). Insulin-like growth factor binding protein-1 (IGFBP-1) belongs to a protein family characterized by disulfide-linked cysteines in the N-terminal domains and has a molecular weight of approximately 30 kDa. The combined N-terminal and C-terminal domains confer high-affinity binding to insulin-like growth factors (IGFs). Within its central domain, IGFBP-1 contains serine phosphorylation sites that, when phosphorylated, significantly increase its ability to inhibit IGF-1 availability to type 1 IGF receptors (3, 4). Elevated IGFBP-1 levels have been reported in several diseases, including cardiovascular disease, atherosclerosis, heart failure, cerebrovascular

Received: January 11, 2025. Accepted: March 11, 2025. Published: September 19, 2025

disorders, and peripheral vascular disease (5- 7). Recent evidence suggests that IGFBP-1 also plays a role in both atrial and ventricular fibrillation (8). Primarily produced in the liver, IGFBP-1 regulates IGF activity involved in growth and metabolism. Its expression is inhibited by insulin, influenced by sex and age, and stimulated by proinflammatory cytokines. Increased levels of IGFBP-1 have been strongly associated with cardiovascular diseases (9, 10).

Materials and Methods

Subjects

The present study included a total of sixty (60) patients diagnosed with premature heart contractions and thirty (30) apparently healthy individuals who served as the control group. Patient samples were obtained from individuals attending the Al-Najaf Center for Cardiovascular Surgery and Cardiac Catheterization, as well as from private laboratories in Al-Najaf Al-Ashraf Province, during the period from July 1, 2024, to December 1, 2025. The patients were further classified into subgroups based on age, sex, type of arrhythmia (atrial or ventricular), clinical diagnosis, disease duration, presence of hypertension, and body mass index (BMI). Insulin-like growth factor binding protein -1 was estimated by using ELISA kits

Inclusion criteria

The current study includes patients suffering from atrial and ventricular premature contraction and different ages and both sexes and diagnosed as new or treated with different body mass index (normal, overweight, and obese), with hypertensive or normotensive status, and of different durations of disease.

Exclusion

Many of the patients' complaints were excluded, including heart failure, myocardial infarction, and other conditions such as kidney failure, liver disorders, diabetes, and blood diseases.

Experimental design

The total number of patients was 60, with the control group comprising 30 men. The patients were divided into several subgroups:

1. Patients with atrial fibrillation (AF) included 30 patients, and those with ventricular fibrillation (VF) included 30.
2. New patients who were not treated included 25 patients, and those receiving treatment included 35.
3. Patients were divided according to disease duration (1 week point - 1 month), 25 patients with 1-5 years, and 15 patients with more than 5 years of disease.
4. Patients were divided according to hypertension (40 patients with hypertension) and normal blood pressure (20 patients).
5. Patients were divided according to body mass index (BMI), including 20 patients with normal weight, 15 patients with overweight, and 26 patients with obesity.
6- According to gender, the study included 25 males and 35 females.
7- According to age, the number of patients aged 30-39 years was 15 patients, the number of patients aged 40-49 years was 10 patients, the number of patients aged 50-59 years was 20 patients, and the number of patients aged 60-69 years was 15 patients.

Biostatistical analysis

The data analysis was performed by SPSS version 20, where used t-test independent to compare patients and controls, and correlation was used in this study.

Results

Insulin-like growth factor binding protein-1 level in premature heart contraction patients and controls.

Figure 1 indicates a significant increase ($p< 0.0001$) in premature heart contraction patients (3054 ± 399.3) in comparison with the control group (372.6 ±11.03).

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 level according to sex.

The present results in Figure 2 revealed a significant in (P< 0.0001) in males (5304 ± 564.4) in increase to females (1447 ± 362.4).

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 level according to age.

The current study, Figure 3, indicates a signification increase (P < 0.0001) in ages (60-69) years (6884 ± 490.4) in comparison with age (50-59) years (2777± 569.1), (40-49) years (1570 ± 760.0), and (30-39) years (551.4 ± 22.07).

Also, other age groups, 50-59 years (40-49) years, showed significant increases with age (30-39) years.

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 level according to atrial and ventricular types.

Figure 4 revealed a significant increase (P 0.0118) in atrial premature contraction (2064 ± 466.2) in comparison with ventricular (4046 ± 603.0).

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 level according to diagnosis.

The results illustrated in Figure 5 show a significant increase (P<0.0001) in new diagnosis patients (4810 ± 644.0) compared with treated (1792 ± 393.3).

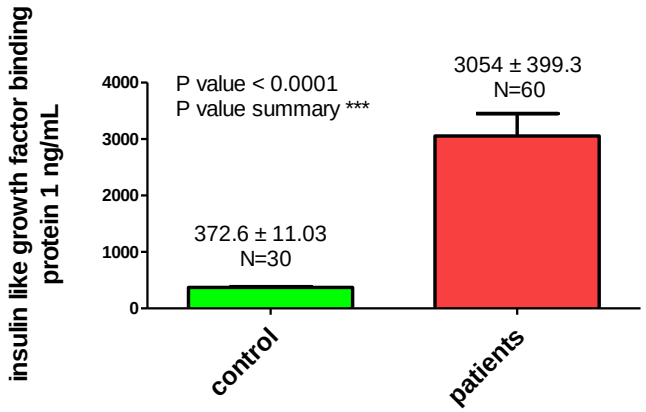

Figure 1: Insulin-like growth factor binding protein-1 Level in patients compared with the control group

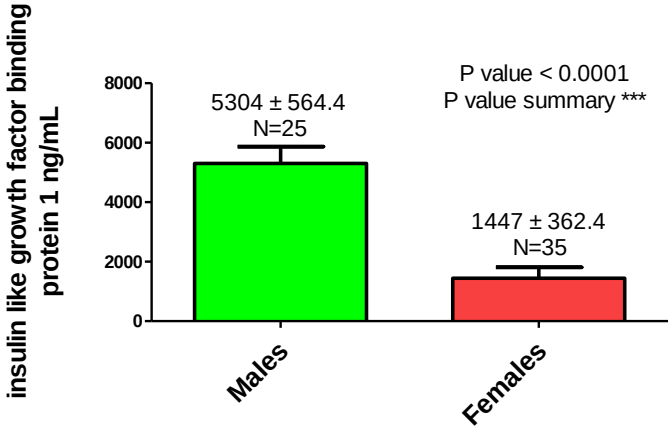

Figure 2: Insulin-like growth factor binding protein-1 Level in Male patients compared with Female patients

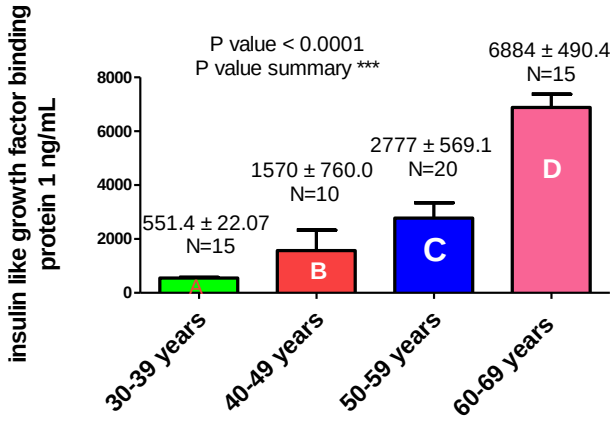

Figure 3: Insulin-like growth factor binding protein-1 Level in different ages.

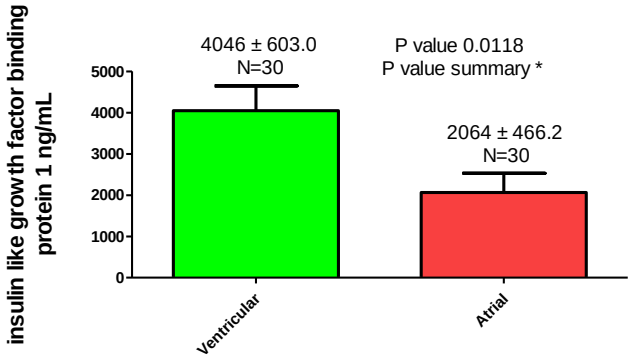

Figure 4: Insulin-like growth factor binding protein-1 Level in ventricular compared with atrial patients.

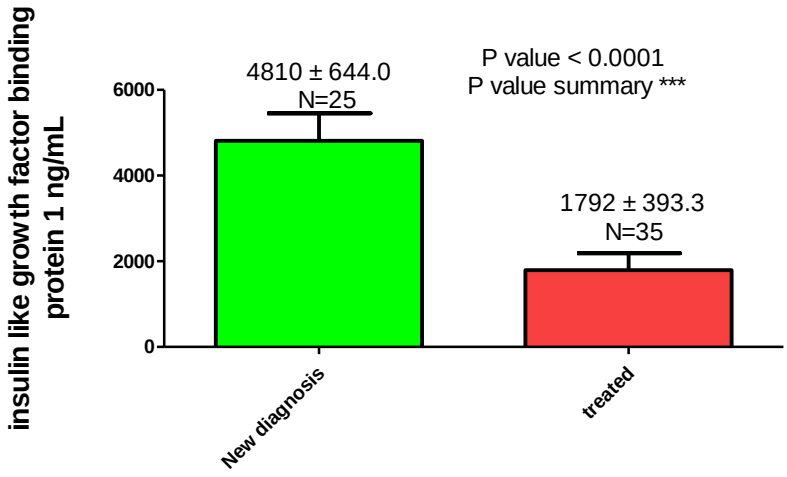

Figure 5: Insulin-like growth factor binding protein-1 Level in new diagnoses compared with treated patients.

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 according to hypertension.

In Figure 6 documentation shows that significant increase (P = 0.0068) in hypertensive patients (3804 ± 522.1) compared with normotensive (1556 ± 434.3).

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 according to duration of disease.

Figure 7 showed a significant increase (P<0.0001) in duration of disease (1 weak-1 month) (6536 ± 480.5) in comparison with other durations (1-5) years (1768 ± 406.6) and (>5) years (554.7 ± 21.13). The results also indicate a significant increase in duration of disease (1-5) years in comparison with (>5) years.

Comparison between premature heart contraction patients in insulin-like growth factor binding protein-1 according to body mass index.

The present results in Figure 8 proved that there was a significant difference (P 0.0007) in obese patients (5236 ± 597.6) in comparison with overweight (1725 ± 701.0) and normal weight (1232± 180.3), also overweight patients showed a significant increase (P 0.0007) in comparison with normal weight.

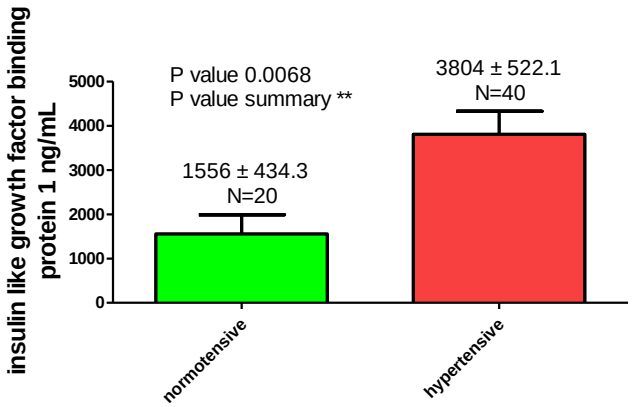

Figure 6: Insulin-like growth factor binding protein-1 Level in normotensive compared with hypertensive patients

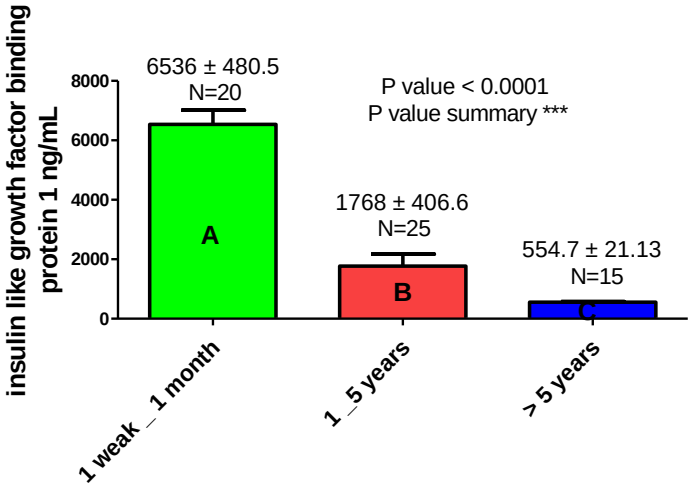

Figure 7: Insulin-like growth factor binding protein-1 Level according to the duration of patients

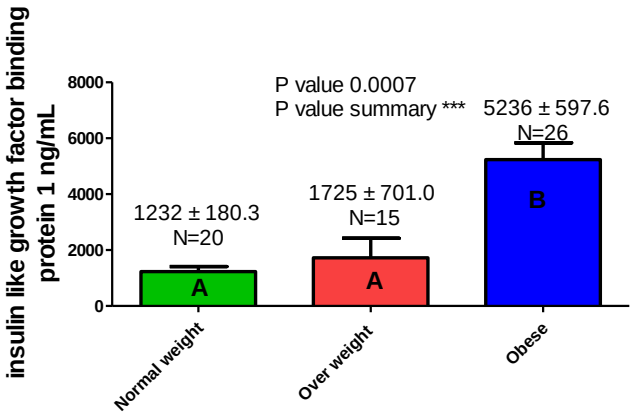

Figure 8: Insulin-like growth factor binding protein-1 Level according to body mass index in patients.

Discussion

The results of the current study showed a significant increase in premature cardiac contraction compared to the control group. These findings are consistent with a study (11) that showed that IGFBP-1, a biomarker, increases the risk of atrial and ventricular fibrillation when measured at elevated levels. Other studies have suggested that IGFBP-1 affects atrial fibrillation by stimulating or inhibiting insulin growth factor (IGF) expression (12, 13). Other recent studies have suggested a relationship between BNP, IGFBP-1, and IGF-1 and left ventricular hypertrophy (LVH) after select participants underwent echocardiography (14). A recent study revealed that increased circulating IGFBP-1 levels are due to phosphorylated serine receptor sites in the central domain. Phosphorylation of these domains has a high affinity for the insulin growth factor receptor-1, leading to suppression of IGF-1 levels due to inhibition of the insulin growth factor receptor 1 (IGF1R) in cardiovascular disease and premature cardiac contraction (15, 16). A previous study indicated that elevated IGFB-1 levels, associated with pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukins Iβ (IL)-Iβ, may have a stimulating effect on free radicals such as H_2O_2 and nitric oxide, which play an important role in the elevation of inflammation in many tissues and organs, such as the heart and the conductive system (17-20). Recent research has shown that low IGF-1 levels combined with high concentrations of IGFB-1 with NT-pro BNP are associated with atrial fibrillation and ventricular ejection fraction and are considered a significant risk factor for these diseases. This study is based on several hypotheses that have demonstrated the antiarrhythmic effect of IGF-1 at normal levels and its protective effect against atrial apoptosis. Therefore, high levels of IGFBP-1 combined with low levels of IGF-1 may induce atrial apoptosis (19-23). A previous study revealed that overexpression of IGF-1 in most models may alleviate both atrioventricular and ventricular pathological conditions and reduce atrial and ventricular fibrillation (24). The second mechanism reported that normal levels of IGF-1 have antioxidant and anti-inflammatory effects and that low levels induce reactive oxygen species and inflammatory responses affecting the atria and ventricles (25, 26). The third hypothesis proposed that low levels of the growth hormone-IGF-1 axis (growth hormone/IGF-1) may increase sympathetic tone, shorten the refractory

period, and affect atrial contractility. Impaired intracellular calcium balance also leads to changes in the atrial substrate (27, 28). Many studies have postulated that attenuated cardiac growth with reduced IGF1R signaling is associated with cardiac disease and both atrial and ventricular contraction in mice, and concluded that there is an association between IGF1R and cardiac health (29, 30). Based on the correlation results, the positive association between NF-pro-BNP and IGFBP-1 has been studied through numerous studies. It has been concluded that both biomarkers with high levels of IGF-1 are associated with increased cardiac output and are considered diagnostic markers for ventricular hypertension and elevated blood ejection fraction (31). Several studies have also shown a correlation between β-type natriuretic peptide and IGFB-1 in the detection of primary atrial fibrillation and ventricular ejection fraction and their use as diagnostic markers (32). IGFBP-1 may also cause changes in cardiac electrical activity through atrial hypertrophy and myopathy with prolonged P-R waves. This interpretation is based on the relationship between BNP and IGFBP-1, as shown in (33). The current study also indicated that IGFBP-1 is higher in males than in females. These results are consistent with a study (34), which showed higher levels of IGFBP-1 in females than in males. This phenomenon may be due to the role of estrogen, especially in postmenopausal women. No previous study has indicated differences between males and females in atrial or ventricular premature contraction. The higher IGFBP-1 levels in males may be due to testosterone, which is considered a risk factor for atrial fibrillation in males of all ages. Maintaining normal levels appears to mitigate atrial and ventricular fibrillation. Therefore, any disturbance in testosterone may increase IGFBP-1 levels by decreasing IGF-1 and insulin levels (35). The results also showed a significant increase in IGFBP-1 in the elderly (60–69 years) compared to other ages. The results of this study are consistent with other research that has shown that aging is strongly associated with decreased IGF-1 levels, a positive correlation with IGFBP-1 levels, and an increased risk of atrial and ventricular arrhythmias (36). Recent studies have also indicated that aging is associated with increased regulation of IGFBP-1 and increased hepatic production, as well as an increased risk of atrial fibrillation (Estefsar). The results revealed a significant increase in IGFBP-1 in patients with atrial fibrillation compared to ventricular fibrillation. These results could be explained by IGFBP-1's greater effect on atrial wall expansion compared to the ventricles, increased depolarization in the atrium, and disturbances in electrical waves such as P waves and P-Q waves, which are more pronounced than those in the ventricles. It also had a greater effect on the sinoatrial node than the A-V node, and finally, the induction of apoptotic cells in the atrium may be greater than in the ventricles (37).The results also indicated a significant increase in IGFBP-1 in newly diagnosed patients, compared to patients who received treatment and had a longer disease duration (1 week to 1 month). Numerous studies have documented that several proteins, such as IGFBP-1, are diagnostic or prognostic markers for atrial and ventricular fibrillation and are associated with an increased risk of these diseases, especially in patients with early onset or diagnosis (38). While the duration of the disease (1 week - 1 month) is associated with newly diagnosed patients who did not receive any type of medication or treatment, it is considered an early predictor of the disease with a high level of IGFBP-1 (39).The results also indicated that IGFBP-1 levels were higher in hypertensive patients compared to patients with normal blood pressure, especially in patients with premature atrial fibrillation. Previous studies have revealed a positive relationship between IGFBP-1 and systolic blood pressure and atrial pulmonary hypertension, while they did not change or correlate with right ventricular systolic pressure. Therefore, they are not considered biomarkers of biventricular hyperplasia, which is consistent with the results of

our study (40). Finally, the results of the study indicated that IGFBP-1 levels were higher in obese patients compared to overweight and normal-weight patients. These results are consistent with other previous studies that have shown inhibition of IGFBP-1 in obesity and an inverse relationship between obese patients and IGFBP-1 due to elevated IGF-1 levels, insulin resistance, insulin secretion, and lipolysis in adipose tissue (41-43). The levels of IGFBP-1 in the current study in patients are related to high blood pressure as well as obesity, as premature atrial and ventricular contraction may occur in obese patients with abnormal ECG when compared to obese patients with normal ECG (44).

Conclusion

The current findings concluded that disease severity was more associated with males than females with high levels of both biomarkers. Furthermore, it can be argued that newly diagnosed patients' disease duration (from one week to one month) was significantly affected by both biomarker levels. Furthermore, advanced age, high blood pressure, and a high body mass index (BMI) are risk factors for high levels of premature myocardial infarction.

Conflict of interest: NIL

Funding: NIL

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