

## Study of Cyclophilin\_ A in Egyptian Patients with Chronic Heart Failure Diseases

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### ABSTRACT

**Background.** A Clinical phenomenon that has historically been categorized as a condition where the heart's ability to pump and fill with blood is diminished is known as a Heart failure (HF), which is still the world's number one cause of death.

**Aim of work.** Is to study Cyclophilin- A and evaluate its role and its clinical significance in identifying the patients with heart failure diseases.

**Methods.** On "one hundred and twenty" individuals this work was done, twenty of them were healthy persons (control set), while the other individuals who were recruited from the heart failure clinic and CCU, NHI were divided into two sets, one of both was includes fifty Egyptian HF post myocardial infraction patients (HFpMI), while the left fifty patients were Egyptian HF without MI patients (HFwMI). Cyclophilin-A (CypA) level was assayed by using ELISA technique.

**Results.** Study of lipid profile, cardiac marker for HF diagnosis (proBNP), inflammatory markers (hsCRP and IL-18) and CypA showed that an increasing in the mean value of them in studied groups when compared with control group.

**Conclusion:** The present study showed a significantly increased levels of CypA (P- value < 0.05) in subjects that had previously diagnosed as heart failure patients, suggesting its role in accelerating heart failure progression. It may be considered as biomarker for heart failure and it is reasonable to assume that it could be a target for therapeutic treatment in near future.

**Keywords:** Chronic Heart Failure (CHF); Cyclophilin-A (CypA)

### 1. INTRODUCTION.

Heart failure (HF) is a principal reason of human death worldwide and is the subject of intensive biomedical research. Both physiological and pathological factors for instance (obesity, hypertension, aging, coronary artery disease (CAD), and diabetes are known to contribute to HF (Bozkurt et al., 2021).

Conventional risk factors for CAD include "chronic renal disease (CRD), hyperlipidemia, diabetes mellitus (DM), hypertension, and obesity" (Herrington et al., 2016).

Biomarkers are used for different purposes in HF, where they have an importance in diagnosing HF and help identify the reason of HF. In addition, numerous biomarkers are used as prognostic markers to guide treatment selection, intensity, and response in specific settings. Finally, biomarkers can provide

further vision into specific “pathophysiological mechanisms” of HF (*Schmitter et al., 2014*).

A family of proteins known as cyclophilins (CyPs) are called for their capacity to bind to cyclosporine, that is frequently used to prevent rejection next interior organ transplantations. Cyclophilin-A (CypA), that is found mainly in the cytoplasm. The protein is a member of a family of isozymes that also includes “cyclophilins B, C & cyclophilin-related protein of natural killer cells”. Significant variants have been discovered in individual cells, including the endoplasmic reticulum. ([www.https://en.wikipedia.org/wiki/Cyclophilin](https://en.wikipedia.org/wiki/Cyclophilin)).

The immunophilic protein CypA has “peptidyl-prolyl cis/trans isomerase (PPIase) series (PPIase)” function and is involved in the folding, trafficking, and interaction of proteins. (*Anandan et al., 2021*).

Recent study showed a critical role of CypA in heart diseases in diabetic patients where the increase in macrophage apoptosis atherosclerotic lesions is linked to plaque necrosis and thus vulnerability of the plaque to rupture. Also, CypA, a secreted oxidative stress-induced immunophilin is involved in apoptosis of inflammatory macrophages under high glucose conditions (*Vinitha et al., 2021*).

Activation of this inflammatory signaling pathway promotes more ROS production, which forms a vicious cycle of ROS-CypA-ROS and accelerates the progression of the inflammatory response. Activation of the inflammatory signaling pathway increases the expression of pro-hypertrophic and pro-fibrotic genes (*Mian et al., 2019*).

Endothelial cell adhesion protein expression is induced by extracellular CypA, which encourages Vascular smooth muscle cells migration and proliferation. This actively encourages inflammation, vascular constriction, and the development of atherosclerosis (*Nigro et al., 2013*). Therefore, as shown by earlier studies, CypA may play a

significant part in several stages of atherosclerosis (*Rezzani et al., 2013*).

Atherosclerosis progression which caused by transmigration, differentiation of monocytes and increasing adhesion is mediated by CypA as well as the formation of foam cells (*Ramachandran et al., 2016*).

Aside from their function as protein chaperones, cyclophilins also mediate chemotaxis of neutrophils, eosinophils, and T-cells when secreted from cells in response to oxidative stress (*Satoh 2015*). CypA is also involved in pathological processes underlying several cardiac vascular diseases (CVDs) (e.g., inflammatory cardiomyopathies, cardiac hypertrophy, critical limb ischemia and CAD) (*Dawar et al., 2017*).

Pulmonary hypertension, atherosclerosis & cardiac hypertrophy mainly occurs by inducing “proliferation & inflammatory cell” after binding between CypA and basigin in the plasma membrane (*Satoh et al., 2009; Satoh et al., 2011*). Moreover, it was stated that basigin promotes cardiac failure and fibrosis in left ventricle (LV) in response to continuing pressure excess in mice and that high plasma levels of both soluble form of basigin and CypA were related to poor prediction in subjects with LV failure (*Sunamura et al., 2018*).

More than one study showed that individuals with HF caused by a variety of factors which have significantly higher plasma concentrations of CypA and oxidative stress (OS) (*Huang et al., 2015; Su et al., 2017; Sunamura et al., 2018*), referring to that CypA has an important role as a pro-oxidative & pro-inflammatory factor in the progression from “cardiac hypertrophy and remodeling to HF” (*Satoh et al., 2011*).

After aggregating of inflammatory cells, they continue to cross endothelial cells (ECs) to the sub endothelium, where they differentiate and secrete cytokines like “tumor necrosis factor (TNF), interleukin-6 (IL-6), & interleukin-18 (IL-18)”, which further

promotes “reactive oxygen species (ROS)” production and cause EC activation and apoptosis (Wong *et al.*, 2014).

**The aim of this work** is to study CypA level in Egyptian patients with heart failure diseases in order to detect the role of CypA in progression of heart failure disease.

## 2. SUBJECTS & METHODS.

### 2.1. Subjects.

This study was carried out between December 2021 to February 2022. Control subjects were collected from healthy volunteers, while all patient samples were grouped from the cardiac care unit (CCU) & heart failure clinic, National Heart Institute (NHI), where we selected them according to ejection fraction degree (< 35%) as echocardiography reported within the period between three to six months post the diagnosis of heart failure.

On “one hundred and twenty” individuals this work was done, “twenty” were healthy persons (control set), while the other individuals who were recruited from the HF clinic and CCU were divided to “two” sets, one of both was includes “fifty” Egyptian HF post myocardial infraction (MI) patients (HFpMI), while the left “fifty” patients were Egyptian HF without MI patients (HFwMI).

**Inclusion Criteria:** Patients diagnosed with heart failure with old MI history, hypertension, type II diabetes, obesity and hyperlipidemia.

**Exclusion Criteria:** Severe respiratory diseases, malignancies, Kidney failure & Liver failure

All candidates were subjected for taking a medical history, performing a physical examination (age, gender, height, weight, BP & BMI) and laboratory investigations including [GPT, creatinine, lipid profile tests (total cholesterol, triglycerides, HDL, LDL & VLDL)], highly sensitive C – reactive protein

(hsCRP) and Pro-Brain Natriuretic Peptide (pro-BNP).

### 2.2. Methods.

Peripheral venous blood was collected by vein puncture from all subjects under study. A total of seven ml blood was collected and distributed into two tubes as the following: Two ml was collected into EDTA tube (lab system, Egypt), stored as a whole blood at 4°C until it used to determine HBA1C level within 6 days. A total of five ml blood was collected into uncoated tube, then the serum was separated and stored at -80°C.

GPT, creatinine, total cholesterol, triglycerides, HDL, and LDL were assayed using "RANDOX kit (RANDOX Laboratories LTD, UK)". HBA1C was determined using (Bioscienc, ARENA, turbidimetric kit, Egypt). HBA1C was measured by using (DIALAB DTN-405 Chemistry Analyzer, Austria). hsCRP, IL-18, NT pro-BNP, and CypA were determined by using ELIZA kits "The Eagle Biosciences, INC, Nashua, NH kit", "The Quantikine™ Human Total IL-18/IL-1F4 Immunoassay, USA R&D Systems, Inc. kit ", "FINE TEST COMPANY, Wuhan, China kit " and "KAMIYA BIOMEDICAL COMPANY, USA kit " respectively, according to the manufacturer's guidelines by using the microplate reader (infinite f50, TECAN, Austria, GmbH) and plot software (Curve Expert 1.4).

### 2.3. Statistical analysis.

One-way analysis of variance (ANOVA) was used to compare more than two groups. Receiver – operating characteristic (ROC) curve analysis was used to assessment of sensitivity and specificity. The relationship between variables in the same group was evaluated using spearman correlation coefficient test. Statistical software program specifically, statistical package for the social sciences (SPSS), (version 26, Inc. Chicago, USA) was used for all statistical analysis

(Levesque, R. 2007). The statistical analysis included the arithmetic mean value, standard deviation, hypothesis student “t” test, Pearson correlation “r” and the significance of result (P). P-values of less than 0.05 were considered to indicate statistical significance.

### 3. RESULTS

Our findings showed that there was no significance change among studied sets as regard age & sex (p-value > 0.05), level of ALT within normal range in all studied groups, however, we observed that the percentage of male subjects with HF are more than female subjects within group. Work’s results revealed "a statistically significance" increase in the mean values of HbA1c, Creatinine, triglycerides, total cholesterol, LDL and VLDL as shown in table 1, also, "a significantly increase" (p-value < 0.05) was found in proBNP level in groups under study comparing with the control group, table 1.

Data tabled in table 2 illustrate that there was a meaningfully increase in hsCRP and IL-18 in the studied groups when compared with the control group.

As shown in "table 3 & figure 1" there was a significantly increased level of CypA in studied groups comparing with control set, but it was observed an increasing in HF post MI (group-II) more than (group III), this indicate that CypA has an important role in MI processing and HF.

The data illustrated in table 4 & 5 showed that there was no significant correlation between CypA and neither classical risk factors of cardiac diseases (HBA1c and LDL) nor inflammatory markers.

As regard to data that obtained by ROC curve analysis in patients with HF post MI, CypA at a cut off level >15.1 ng/ml had a diagnostic sensitivity of 0.84, specificity 1.0, with an area under the curve (AUC) 0.883, tables 6, figures 2, while in patients with HF without MI history, cut off level >8.25 of CypA had a diagnostic sensitivity of 0.8,

specificity 1.0 and AUC 0.860, table 7, figure 3.

### 4. DISCUSSION.

A complicated clinical syndrome of inadequate cardiac output brought on by myocardial injury is known as HF. HF is still the world's number one source of illness and death (Ziaean, & Fonarow, 2016). The most typical type of heart failure is chronic heart failure (CHF). Also, it had been known that ischemic heart diseases (IHD), DM & hypertension are the main risk factors which lead to CHF. But there is a further indicator which refer to that “genetic predispositions” plays a critical role in CHF (Hu et al., 2016).

Both of “pro-BNP & troponin T” have used been to help in diagnosis of CHF, while there is no a medical sign predict the progress HF in MI patients (Björklund et al., 2006). Therefore, finding biomarkers that indicate a patient's likelihood of developing HF after an AMI is essential for optimizing management and therapy plans. Our work is to assess the role of CypA in heart failure disease (HFD) as a biomarker.

Our study measured CypA level in cases which have HF post MI and cases which have HF without MI history in assessment with normal subjects, to know their “relation and if the serum CypA has a role in causing and leading to heart failure disease”. So, when we compared between patients with CHF who have not previously experienced MI, CHF patients post MI have CypA level that were “statistically significantly” greater than patients with CHF who had not previously experienced MI. Thus, our findings in agreement with previous studies, that showed that CypA level was increased in the patient who suffered from HF post MI than the normal subjects (Ohtsuki et al., 2017; Hussain et al., 2019; Alfonso et al., 2019; Zaki et al., 2020). Also, a study was estimated that individuals who have “acute coronary

syndrome (ACS)” were had excessed levels of CypA (Yan *et al.*, 2012).

In our work we have been reported that the positive correlation between serum creatinine level in HF patients under study with Pro-BNP level, additionally, when we compared the serum creatinine level of patient groups with the normal subjects, there was a significant increasing. These findings suggest that the present of relation between renal impairment and heart failure disease.

In agreement with our findings, a study by *aimo et al.*, 2019 demonstrated that Creatinine & GFR which are usually used to follow up the effects of HF therapies, “the same parameters are also useful prognostic markers for patients with chronic HF over “NT-proBNP & hs-TnT”.

Other studies support our results, where, a study by *Cole RT et al.*, 2012 showed that both of patients have CHF about (20%: 57%) and about (30: 67%) with Acute HF have renal impairment.

An important increasing in hsCRP was observed in our work, which is in agreement with previous studies (*Guruprasad et al.*, 2012; *Rashidinejad et al.*, 2015).

In the present work, we had reported that significant increasing of lipid profile in subjects within group II (HFpMI) and group III (HFwMI), while, HDL level was within normal level in studied groups when compared with normal subjects in desert set. These findings reflect the effect of lipid profile level in CHF, thus more studies in this point are required.

From advantages of this study, the inhibition for CypA secretion or preventing the binding with its target receptor will be promising therapy for prevention and control in the cardiac disease processing, so CypA can be therapeutic tool for controlling cardiac diseases in the future

This warrants further investigation of the role of CyPA to identify potential CyPA-related therapeutic targets, although further

basic and clinical studies are needed to identify CyPA-related therapeutic targets.

## 5. CONCLUSION

The significance of increasing Serum cyclophilin levels and its association with severity of the disease in patients with heart failure post myocardial infarction injury suggesting the role of this protein in accelerating atherosclerosis following by heart failure, considering the evidence that Cyclophilin A is an inflammatory mediator in atherogenesis.

It may be considered as biomarker for heart failure and it is reasonable to assume that it could be a target for therapeutic treatment in near future.

## 6. RECOMMENDATIONS:

More other studies on greater number of subjects with more and better statistical analysis should be done.

More further studies to emerge the role of cyclophilin A in other cardiac diseases rather than heart failure is needed.

Follow-up study is needed after treatment with anti-cypA to evaluate a CypA protective role for patients.

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**Table 1.** Comparison between studied groups.

Parameter	Group I (n= 20)	Group II (n= 50)	Group III (n= 50)	P-value
SBP(mmHg)	118 ±14.3	125.667	129±18.3	< 0.05
DBP (mmHg)	81 ±6.3	82.333	89±11.2	
Age	56.50 ±6.50	56.48 ±6.0	57.5 ±6.4	> 0.05
Sex (male/female)	13/7	35/15	30/20	> 0.05
HBA1C (%)	4.78 ±0.5	6.93 ±2.2	6.4 ±2.2	<0.05
ALT (U/L)	23.2 ±6.0	29.02 ±6.8	28.78 ±6.3	
Creat. (mg/dl)	0.74 ±0.2	1.82 ±0.6	2.25 ±0.7	
Chol. (mg/dl)	139.85 ±18.0	212.9 ±40.6	171.8 ±45.2	
Trigly. (mg/dl)	76.8 ±24.7	150.38 ±55.8	115.38 ±35.8	
HDL (mg/dl)	60.75 ±11.0	39.66 ±9.7	39.74 ±9.7	
LDL (mg/dl)	63.74 ±16.7	143.16 ±40.9	109.0 ±47.1	
VLDL (mg/dl)	15.36 ±4.9	30.07 ±11.2	23.07 ±7.2	< 0.05
proBNP(pg/ml)	58.38 ±19.84	942.26 ±407.34	927.54 ±356.322	

**Table 2:** Comparison between studied groups according to inflammatory markers

Parameter	Group I (n= 20)	Group II (n= 50)	Group III (n= 50)	P-value
hsCRP (mg/L)	2.2 ±0.9	17.54 ±6.0	21.19 ±8.0	< 0.05
IL18 (ng/ml)	3.11 ±0.5	25.64 ±13.8	18.44 ±6.8	

**Table 3:** Serum Cyclophilin A (CypA) level in control and other studied groups.

PARAMETER	Group I (n= 20)	Group II (n= 50)	Group III (n= 50)	P-value
CypA	3.11±1.0	50.3±13.3	18±3.8	< 0.05

**Table 4:** Correlation between Cyclophilin-A and different parameters under study in group II.

parameters		HBA1C (%)	hsCRP (mg/L)	IL-18 (ng/ml)	LDL (mg/dl)
CypA	r	-.040	.240	.208	.056
	p	.782	.093	.146	.700

**Table 5:** Correlation between Cyclophilin-A and different parameters under study in group III.

Parameters		HBA1C (%)	hsCRP (mg/L)	IL-18 (ng/ml)	LDL (mg/dl)
CypA	R	.012	.044	.206	.146
	P	.932	.760	.152	.311



**Table 6:** ROC Curve analysis for heart failure patients post myocardial infraction (group II).

Test Result Variable(s)	Cut off	AUC	sensitivity	Specificity	PPV	NPV	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
								Lower Bound	Upper Bound
<b>CypA</b>	15.1	0.883	0.84	1.0	100	86.2	0.000	0.800	0.965

The test result variable(s): CypA has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

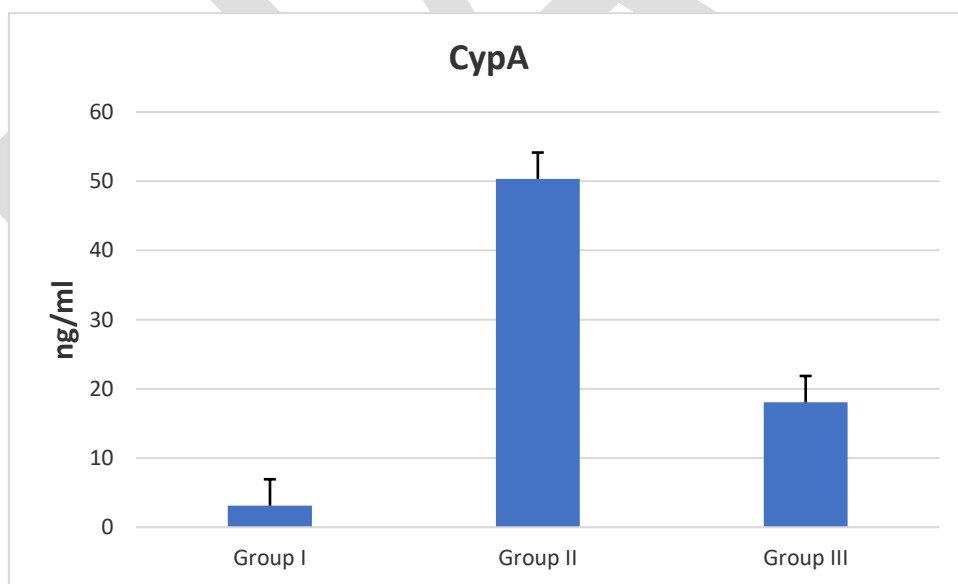
b:Null hypothesis: true area = 0.5

**Table 7:** ROC Curve analysis for heart failure patients without myocardial infraction history (group III).

Test Result Variable (s)	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	Asymptotic Sig. <sup>b</sup>	95% Confidence Interval	
								Lower Bound	Upper Bound
<b>CypA (ng/ml)</b>	8.25	0.860	0.8	1.0	100	83.3	0.000	0.771	0.948

The test result variable(s): CypA has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

b:Null hypothesis: true area = 0.5



**Fig. (1):** Comparison between the different studied groups according to cyclophilin A level.

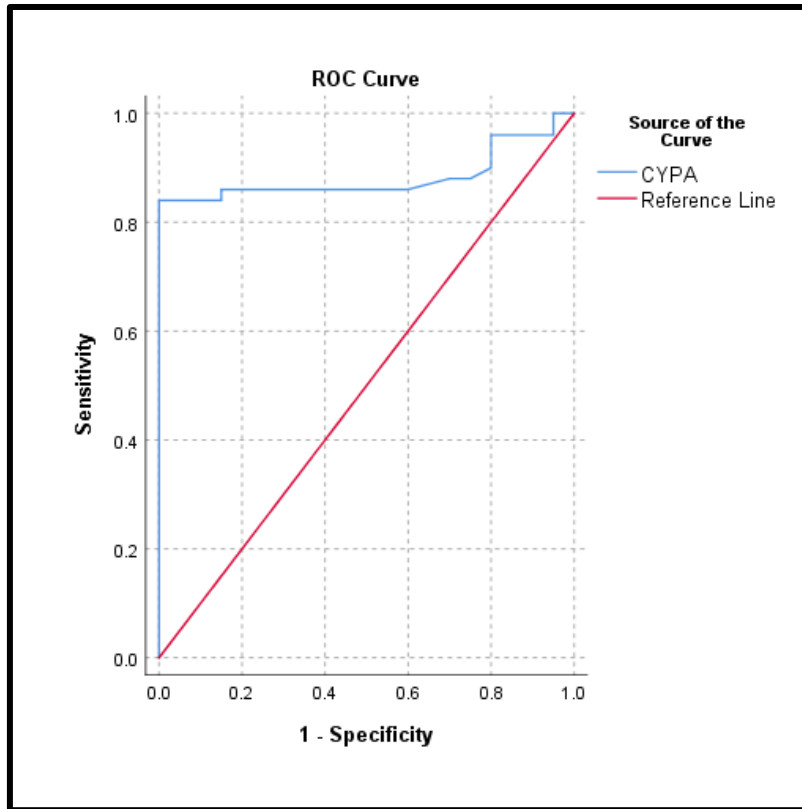


Fig. 2: ROC curve for cyclophilin-A to diagnose heart failure disease post myocardial infarction.

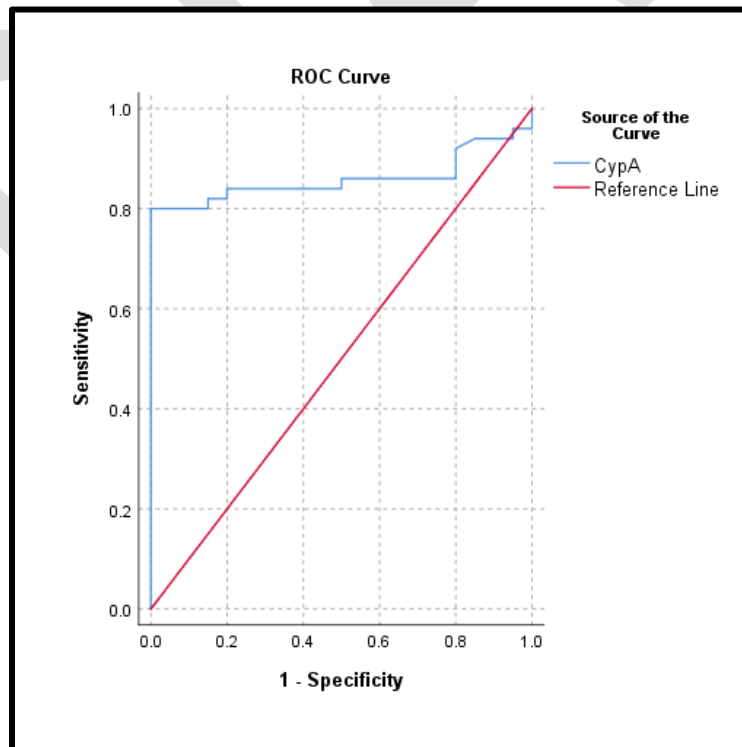


Fig. 3: ROC curve for cyclophilin-A to diagnose heart failure disease without myocardial infarction history.