High-sensitivity C-reactive protein and prediction of thromboembolism in patient with atrial fibrillation

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Abstract

Background: The possibility that the association of inflammation with AF and the related thromboembolic risk could be examined with the use of C-reactive protein(CRP) has captured the attention of many researchers *(Versaci et al., 2002; Boss and Lip 2005; Watanabe et al., 2005; Guazzi and Arena,2009).*

Methods: This study on 100 patients from those referred to transesophageal echocardiography for cardioversion or assessment of left atrial appendage in AFib with stroke. All patients were subjected to history taking (Age, DM, HTN, previous stroke, IHD, PVD). physical examination Resting 12- lead surface ECG. Transthoracic echocardiography to detect LA diameter, LA area and EF. Transesophageal echocardiography to detect LAA SEC, thrombus, emptying and filling velocities. Measurement of hs-crp.

Results: demographic and clinical characteristic including DM, and HTN, IHD,SEX has no significant effect on hs-CRP, but CRP concentration was associated positively with age with significant difference between examined groups ($p = 0.003$) and PVD with significant difference between examined groups ($p = 0.001$). hs- CRP concentration was significantly elevated in patients with prior stroke ($p<0.01$) ,LA/LAA thrombus ($p<0.01$) and spontaneous echo contrast (SEC)($p<0.01$). Additionally, hs-CRP was found to be highly correlated with LAA emptying velocity ($r=-0.521$, $p<0.01$), LAA filling velocity ($r=-0.487$, $p<0.01$), SEC grade($r=-0.521$, $p<0.01$) Also associated positively and significantly with CHA 2DS 2VASc. ahigh CRP cut off of 4.5 mg /d yielded a 95% sensitivity and a 90% specificity for detecting LA/LAA thrombus.

Conclusion: There is astrong association with CRP and clinical and echocardiographic marker of thromboembolism in patients with non- valvular AF .Hs-CRP cut off level of 4.5mg/dl or more is considered to be valuable in predicting the thromboembolic risk in patients with non -valvular AF .

Key Words: HsCRP, Thromboembolism, Atrial Fibrillation.

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Introduction

Atrial fibrillation affects cardiac hemodynamics, resulting in a loss of atrial contraction and a rapid irregular ventricular rate *(Fuster et al., 2011).* Atrial fibrillation is the most common cardiac arrhythmia *(Watanabe et al., 2005)*and is now recognized as the most common cardiac disorder leading to stroke and other thromboembolic events *(Conway et al ., 2004).* Stoke in AF is often sever and results in long- standing disability or death .the rate of ischemic stroke in patients with non –valvular AF is about 5% per year ie 2-7 times that of people without AF *(M.Guazzi and R.Arena,2009).* the possibility that the association of inflammation with AF could be examined with the use of c-reactive protein (CRP) has captured the attention of many researchers (*Versaci et al., 2002; Boss and Lip, 2005; Watanabe et al., 2005; Guazzi and Arena, 2009*). The role of inflammation in the initiation of AF and its outcomes was determined primarily on the basis of observation that inflammatory states, such as myocarditis, pericarditis, and cardiac surgeries were frequently associated with AF*(Cast et al.,1990;Inoue et al .,2003).*Several studies indicate that activated inflammatory cells and inflammatorty mediators may confer aprothrombotic state by promoting endothelial dysfunction and platelet activation in patients with AF *(Inoue et al.,2003).* To our knowledge few data , about the clinical evidence linking inflammation, (as detected by CRP) with the thrombo-embolic risk in patients with AF are found.

Patients and methods

The study population consisted of 100 consecutive patients of both sex with non valvular atrial fibrillation (NVAF). They were referred for trans thoracic and trans esophageal echocardiography.at National Heart Institute (Imbaba-Giza).The study was approved by the ethics committee of faculty of medicine, Banha University. Non valvular atrial fibrillation was documented by 12-lead electrocardiogram (ECG) and continuous monitoring prior to the echocardiographic examination.patients with Advanced terminal illness (e.g. malignancy) were excluded_All patients were subjected to Detailed history and clinical examination with special emphasis on risk factor of thromboembolism which include congestive heart failure, hypertension, diabetes, age 65-75, prior stroke/transient ischemic attack (TIA), vascular disease this is called stroke risk assessment (CHA2DS2-VASc).Standard 12-lead surface electrocardiogram. Two –dimensional echocardiography and Doppler examination with special emphasis on (LA diameter was taken in the para sternal long axis view in M-mode at end systole. Measurements were taken in three beats in atrial fibrillation and the mean values were taken for analysis. LA area by plainmeter around left atrium excluding the junction of pulmonary viens and left atrial appendage if visible. trans thoracic visualization of LA thrombus, the LA was examined in standard parasternal long axis, apical, subcostal and parasternal short axis views with angulation of transducer to enhance the imaging of LA appendage. Ejection faction). Transesophageal Echocardiography (Multiplane 2-D images of the LAA were obtained from the basal transesophageal views. The image plane demonstrating the largest LAA area was used for analysis. LAA was scanned in the mid esophageal from 45° -90°angles. Spectral pulsed Doppler signals were obtained with sample volume approximately 1 cm within the orifice of the appendage. Between each of the five consecutive R-R intervals, the maximal velocity signal directed into (filling velocity) and out of (emptying velocity) the appendage was traced for determination of peak velocity(*Tumura*

et al .,2012). we are focusing on (LA&LAA thrombus. LA spontaneous echo contrast). Laboratoy work up;serum sample from all patients were taken from avein in the arm .no special preparation or fasting is needed. high sensitive CRP immunoassay was evaluated.

Statistical analysis

Correlation between variables was done using correlation coefficient "r". This test detects if the change in one variable was accompanied by a corresponding change in the other variable or not. Receiver operator characteristic (ROC) curve was used for prediction of patients high incidence of THROMBUS from HS –CRP level**.**

Results

Table1: demographic and clinical characteristics of the study population

		N
HTN	Yes	66
	No	34
DM	Yes	32
	No	68
CHF	Yes	28
	No	72
PVD	Yes	10
	No	90
Prior stroke	Yes	9
	No	91
History of IHD	Yes	48
	No	52
SEX	F	64
	M	36
Types of AF	Paroxysmal	32
	Permanent	68
Age	≥65	20
	< 65	80

- There were 66 patients hypertensive and 34 patients normotensive in study group. Mean value of HS-CRP in hypertensive patients was 5.412 ±5.23 mg/l while mean value of HS-CRP in normotensive was 3.118 ±4.652 mg/l. Statistical analysis show no significant difference between hypertensive versus normotensive ($p>0.05$).

- There were 32 patients diabetic and 68 patients non diabetic in study group. Mean value of HS-CRP in diabetic patients was 5.363 ±6.048 mg/l while mean value of HS-CRP in non-diabetic was 4.288 ±4.655 mg/l. Statistical analysis show no significant difference in diabetics versus nondiabetics ($p>0.05$).

-There were28 patients with congestive heart failureand72patients without congestive heart failure in study group. Mean value of HS-CRP in heart failure patients was4.279 ±2.527mg/l while mean value of HS-CRP inthose without heart failure was 4.769 ±5.849 mg/i Statistical analysis show no significant difference in patient with congestive heart failure versus those without congestive heart failure ($p>0.05$).

- There were 10 patients with PVD and 90 patients without PVD in study group. Mean value of HS-CRP in PVD patients was 11.600± 3.578mg/l while mean value of HS-CRP in those without PVD was 3.858 ±4.676mg/l. Statistical analysis show highly significant increase in patient with PVD versus those without PVD ($p<0.01$).

- There were 48 patients with history of ischemic heart disease and 52 patients without history of ischemic heart disease in study group. Mean value of HS-CRP in patients with history of ischemic heart disease was 94.97 ±4.979 mg/l while mean value of HS-CRP in patients without history of ischemic heart disease was 4.312 ±5.815 mg/l. Statistical analysis show no significant difference between patients with history of ischemic heart disease versus without ischemic heart disease ($p>0.05$).

- There were 9 patients with history of prior stroke and 91 patients without history of prior stroke in study group. Mean value of HS-CRP in patients with history of prior stroke was 10.44± 3.220mg/l while mean value of HS-CRP in those without history of prior stroke was 3.900 ±4.728mg/l. Statistical analysis show highly significant increase in patient with versus those without history of prior stroke ($p<0.01$).

- Age of the patients > 65 years with mean value 12.74±9.433 years, while the age of patient < 65 years with mean value 3.097±3.34 years. Statistical analysis show highly significant correlation between hs-CRP and age ($p =0.0001$).

- There were 68 patients had permanent atrial fibrillation (68 % of cases) and 32 patients had paroxysmal type in study group. Mean value of HS-CRP in permanent atrial fibrillation was 5.965±5.719 mg/l while mean value of HS-CRP in paroxysmal type was 1.800 ± 0.996 mg/l. Statistical analysis show highly significant difference between permanent and paroxysmal atrial fibrillation. Hs-crp was higher in permanent atrial fibrillation than paroxysmal. ($p =0.006$)

- There were 36 male patients and64 female patients in study group. Mean value of HS-CRP in male patients was 4.578±6.686 mg/l while mean value of HS-CRP in female

Patients was 4.663±4.106mg/l. Statistical analysis show no significant difference betweenmale or female patients. ($p =0.956$).

Table (2) Correlation of HS-CRP with clinical characteristics comprising the CHA2DS2-VASc stroke risk score

		N	HS-CRP (mg/l)		P
			Mean	±SD	
HTN	Yes	66	5.412	5.236	P >0.05
	No	34	3.118	4.652	
DM	Yes	32	5.363	6.084	P >0.05
	No	68	4.288	4.655	
PVD	Yes	10	11.6	3.578	P<0.01
	No	90	3.858	4.676	
CHF	Yes	28	4.279	2.527	P >0.05
	No	72	7.792	5.849	
Prior stroke	Yes	9	10.44	3.220	P<0.01
	No	91	3.900	4.728	
History of IHD	Yes	48	4.979	4.979	P >0.05
	No	52	4.312	5.815	
SEX	F	64	4.663	4.106	P >0.05
	M	36	4.578	6.686	
Types Of AF	Paroxysmal	32	1.8	.0.966	P<0.01
	Permanent	68	5.965	5.719	
Age	≥65	20	12.74	9.433	P<0.01
	< 65	80	3.097	3.43	

HTN; hypertension, **DM**; diabetes mellitus, **IHD**; ischemic heart disease,

HS-CRP; high sensitivity c reactive protein, **PVD** peripheral vascular disease.

Correlation between HS-CRP and echo cardio graphicdata.

1.Transthoracic echocardiography: (TTE) (table5)

Ejection fraction(EF%)**:** the EF of patients ranges from34%-70%with mean value55.460±8.321%. Statistical analysis show significant correlation between hs-CRP and Ejection fraction.(p =0.025)

Left atrial dimesion (LAD): the LAD of patients ranges from 3.5-6cmwith mean value 4.701±0.719cm. Statistical analysis show highly significant correlation between hs-CRP and Left atrial dimesion. (p =0.001)

Left atrial area:(LAA): the LAA of patients ranges from 16.3-36.2cm with mean value 26.986+5.117 cm. Statistical analysis show highly significant correlation between hs-CRP and Left atrial area.(p =0.001)

Table 3: correlation between HS-CRP and TTE

			HSCRP	
			R	**P.value**
EF%	**Range**	34-70	-0.317	0.025*
	Mean±SD	55.460±8.321		
LA Diameter (Cm)	**Range**	3.5-6	0.628	<0.001*
	Mean±SD	4.701±0.719		
LA AREA (cm^2)	**Range**	16.3-36.2	0.525	<0.001*
	Mean±SD	26.986±5.117		

2.HS-CRP and trans esophageal echo cardiographic (TEE) data

LAA emptying Doppler velocity:it ranges from 12.5-46.2 cm/secwith mean value 24.508±8.962 cm/sec. Statistical analysis show highly significant negative correlation between hs-CRP and Left atrial emptying velocity.(p<0.001, r = - 0.521)

LAA filling Doppler velocity: it ranges from 14.2-46.7 cm/secwith mean value 25.098±8.965 cm/sec. Statistical analysis show highly significant negative correlation between hs-CRP and Left atrial filling velocity. (p <0.001, r = - 0.487)

Spontaneous echo-contrast(SEC): the grade ranges from 0-4 with mean value 1.740±1.337. Statistical analysis show highly significant positive correlation between hs-CRP and Spontaneous echo-contrast grade (SEC). (p<0.001, r =0.612)

THOROMBUS IN LAA: There were 28 patients had thrombus and 72 patients had no thrombus in study group. Mean value of HS-CRP in patients had thrombus was 10.871±6.145 mg/l while mean value of HS-CRP inpatients had no thrombus was 2.206 ±1.000 mg/l. Statistical analysis show highly significant difference between hs-CRP and thrombus. (p<0.001).

Table 4: correlation between HS-CRP and TEE

			Hs-crp	
			R	P. value
LAA emptying velocity cm/s	**Range**	12.5-46.2	-0.521	<0.001*
	Mean±SD	24.508±8.962		
LAA filling velocity cm/s	**Range**	14.2-46.7	-0.487	<0.001*
	Mean±SD	25.098±8.965		
Spontoneus echo contrast Severity grades	**Range**	0-4	0.612	<0.001*
	Mean±SD	1.740±1.337		

Table 5 : correlation between hs-CRP and thrombus in patients groups

THOROMBUS	N	hs.CRP			T-test	
		Mean	±	SD	T	P-value
Negative	72	2.206	±	1.000	-8.313	<0.001*
Positive	28	10.871	±	6.145		

Receiver operator characteristic (ROC) curve for prediction of patient's high incidence of THROMBUS from HS –CRP level (Cut off 4. 5 mg/l)

This curve shows the sensitivity and specificity for the prediction of LAA thrombus ,with Sensitivity 95 % , Specificity 90 %

ROC curve between hs-CRP and THOROMBUS				
Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**
> 4.5	**95**	**90**	**92**	**97**

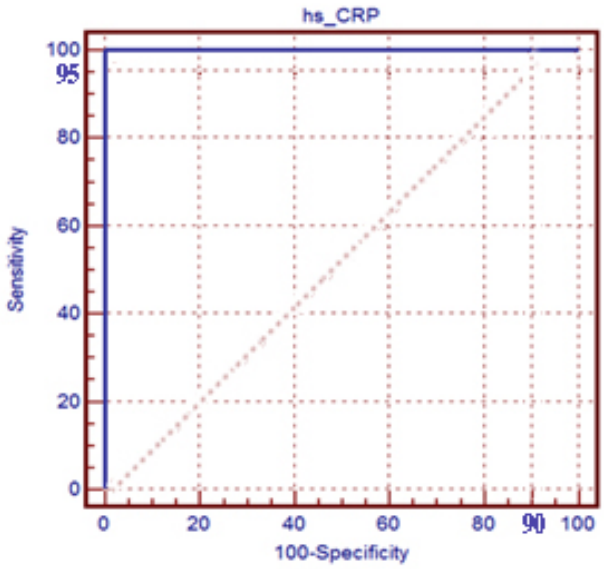
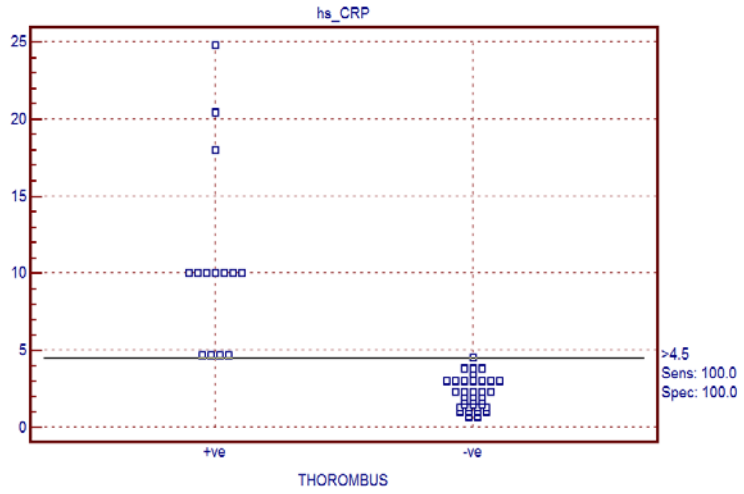


Figure (1) ROC curve for prediction of patients high incidence of THROMBUS from HS –CRP level.



Discussion

Non-rheumatic atrial fibrillation (AF) is a common arrhythmia associated with a prothrombotic or hyper coagulable state which may increase the risk of cerebrovascular events (*Cianfrocca* et al .,*2009)* . Thrombosis appears to be intimately related to inflammation, and it is considerad that AF is associated with an inflammatory state (*Sata et al .,2004).* Abnormal levels of C-reactive protein (CRP) and IL-6 (both indices of inflammation

) have shown to be raised in patients with non valvular AF, independently of other cardio vascular risk factors (*Marin et al.,2004).* The abnormal inflammatory state may "drive" the prothrombotic state in AF, which may contribute to the increased risk of thrombogenesis and, subsequently, thrombo- embolism (*Thambidorai et al.,2004).* The possibility that the association of inflammation with AF and the related thromboembolic risk could be examined with the use of C-reactive protein(CRP) has captured the attention of many researchers *(Versaci et al.,2002;Boss and Lip 2005;Watanabe et al.,2005;Guazzi and Arena,2009).* The aim of this study was to evaluate the relationship between high-sensitivity C- reactive protein (hs-CRP) and the prediction of thrombo embolic complication of atrial fibrillation . We hypothesized that CRP concentration could be related to transesophageal markers of thrombo embolism (severe LA/LAA SEC, LA/LAA thrombus,) and therefore can help to identify the presence of these markers among AF patients in combination with established stroke risk stratification (CHADsVASCs). In our study, demographic and clinical characteristic including DM, and HTN, IHD,SEX has no significant effect on hs-CRP, but CRP concentration was associated positively with age with significant difference between examined groups ($p = 0.003$) and PVD with significant difference between examined groups ($p = 0.001$). Our result are concordant with (*Ederhy et al.,2012)* study which included 178 consecutive patients with Transthoracic echocardiography, TEE, and CRP measurement were performed at admission with non-valvular atrial fibrillation not receiving oral anticoagulant therapy. They found that hs-CRP concentration was associated positively and significantly with age ($p < 0.01$) , but was not statistically associated with any other clinical baseline characteristics . In (*Lip et al.,2007)* study which included 880 consecutive patients with atrial fibrillation , CRP and soluble CD40 ligand were measured by enzyme-linked immunosorbent assay, CRP levels were higher among females ($p = 0.002$) , as well as those patients with raised body mass index ($p < 0.001$) , diabetes($p = 0.006$), and history of hypertension ($p = 0.009$) . CRP was also higher among those patients with comorbidities of ischemic heart disease ($p = 0.002$), peripheral vascular disease ($p = 0.015$), and recent heart failure ($p < 0.001$). This difference between the results of our study and Lip et al study may be return to the difference in number of the patients included i and the different methods of stroke risk stratification, as in our study we used CHA 2DS 2VASc , but Lip et al. used SPAF III, CHADS2, NICE stroke risk stratification. In our study hs- CRP concentration was significantly elevated in patients with prior stroke (10.44± 3.220mg/l vs 3.900 ±4.728mg/l ,$p<0.01$) ,LA/LAA thrombus (10.871±6.145 mg/l vs 2.206 ±1.000 mg/l , $p<0.01$) and spontaneous echo contrast (SEC)(1.740±1.337, $p<0.01$) as shown in table 3,4 figure 7,10 . Additionally ,hs-CRP was found to be highly correlated with LAA emptying velocity (r=-0.521, $p<0.01$), LAA filling velocity (r=-0.487, $p<0.01$),SEC grade(r=-0.521, $p<0.01$) Also associated positively and significantly with CHA 2DS 2VASc. *sa et al .,(2013*) reported that There is a growing body of evidence of the association between this new scoring system(CHA2DS2–VASc) and transoesophageal echocardiography (TEE) findings of high embolic risk, such as left atrial (LA) thrombus and spontaneous echo contrast (SEC). Our results suggest ahigh CRP cut off of 4.5 mg /d yielded a 95% sensitivity and a 90% specificity for detecting LA/LAA thrombus. Our result are concordant with(Lip et al.,2011)who reported that CRP levels increased in apositive fashion with SPAF III,CHADS2,NICE stroke stratification. *Psychari et al.*(2005) reported similar results as regard CRP and LA size .their study included 90 patients with persistent and perrmanent AF ; 46 control patients And found that left atrial size correlates positively with serum levels of CRP . Our result are concordant with Ederhy et al. (2012)as CRP concentration was associated positively and significantly with a reduced left ventricular ejection fraction, increase LA area, presence of LA/LAA SEC or LA/LAA thrombus ,and reduced LAA filling and emptying velocity in absence of oral anticoagulant treatment. additionally Lip et

al(2011) found an association between the clinical and TEE markers of thromboembolism and CRP in patients with AF even in those receiving oral anticoagulant treatment . (Abu-Mahfouz et al., *2012)*, showed that CRP was significantly associated with SEC and intracardiac thrombus . (Cianfrocca et al., *2009)*. Found similar results as the present study.they reported that left atrial appendage mean flow velocity (<25 cm/second) and increasing hs- CRP were significantly associated with high grades of SEC.they added that CRP and LAA velocities are independent determinants of the risk of thrombogenesis in patients with AF. similarly (Maehama et al ., *2010*) observed that raised circulating CRP levels correlated with the presence of LA/LAA thrombi on TEE. In a retrospective study involving 104 patients in atrial fibrillation, *(Thambidorai et al* .,2004) . found that a CRP cut off of 5 mg/dL yielded an 82% sensitivity and a 72% specificity for detecting LA abnormalities and complex aortic plaques. In (AFFLUATE) study (The Atrial Fibrillation and FLUtter And ThromboEmbolism) Ederhy et al,(2012) demonstrates that a CRP value ≤ 3.4 mg/L has a high negative predictive value to exclude transesophageal markers of thromboembolism. Furthermore, (*Prage et al .,2010*) found that a longer duration of AF is associated with higher hs-CRP levels and larger LA/LAA dimensions, supporting a link between the burden of AF, inflammation and thromboembolism. The association of inflammation and AF-related thromboembolism was originally supported by the observation that elevated CRP levels were noted in AF patients with left atrial and/or left atrial appendage spontaneous echocardiography contrast. Recent studies have further demonstrated that IL-6 and CRP are markedly elevated in patients with dilated left atrium and a poorly functioning left atrial appendage (*Chung et al., 2001)*. Proposed mechanisms linking inflammation to thrombosis include endothelial activation and/or damage, production of TF from monocytes increased platelet activation, and increased expression of fibrinogen (*Kallergis et al .,2008).* More than simply a marker of inflammation, CRP may influence directly vascular vulnerability through several mechanisms, including enhanced expression of local adhesion molecules, increased expression of endothelial PAI-1 (plasminogen activator inhibitor 1), reduced endothelial nitric oxide bioactivity, altered LDL uptake by macrophages, with complement within atherosclerotic lesion. *(Boos and Lip GYH ,2005).* Histological evidence to support the association between inflammation and AF has been derived from several sources*(Kamiyama et al .,1998),* Results of atrial biopsies taken from patients in AF compared with controls have demonstrated evidence of inflammatory infiltrates and oxidative damage within the atrial tissue*(Fuster et al., 2006).*

Conclusion

There is astrong association with CRP and clinical and echocardiographic marker of thromboembolism in patients with non- valvularAF . Hs-CRP cut off level of 4.5mg/dl or more is considered to be valuable in predicting the thromboembolic risk in patients with non - valvularAF.

Recommendation

Further studies on large number of patients with follow up period to correlate the level of CRP with clinical outcomes. Hs-CRP may be added to CHA2DS2-VASc to refine the risk of thromboembolism stratification especially in stroke with CHA2DS2-VASc less than 2.

Study limitation

Small number of studied population . Study doesn't include follow up period to demonstrate the association of hs –CRP with clinical outcomes . Other inflammatory markers are not included such as IL-6, leucocytic count, etc .

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