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Significance of high sensitivity C-reactive protein and D-dimer in evaluating intracardiac thrombus and spontaneous echo contrast in patients referred for transesophageal echocardiography: A prospective study

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Abstract

Background: *Intra-cardiac thrombus (ICT) and spontaneous echo contrast (SEC) are considered hypercoagulable and inflammatory conditions. We aimed to determine if high sensitivity C-reactive protein (CRP) and D-dimer (DD), in combination with variables of lower thrombotic risk (normal ejection fraction [NEF], sinus rhythm [NSR]), may predict the absence of ICT/SEC.*

Methods and Results: *Consecutive patients referred for transesophageal echocardiogram (TEE) for evaluation of cardioembolic source were prospectively enrolled. CRP and DD levels were determined at the time of TEE. 124 patients were enrolled, of whom 21 had ICT/SEC. The combination of NSR/NEF had a negative predictive value (NPV) of 98.6% for absence of ICT/SEC. The NPVs of CRP and DD were 93.6% and 85%, respectively. Adding either CRP or DD to NSR/NEF combination increased the NPV to 100%. Log CRP was significantly associated with ICT/SEC.*

Conclusions: *The presence of NSR and NEF may defer the need for TEE for ICT/SEC evaluation. CRP association with ICT/SEC suggests that inflammation plays a role in ICT/SEC formation. Whether CRP and DD should become routine in the triage process of TEE for ICT/SEC evaluation requires further large scale prospective studies.* (Cardiol J 2012; 19, 3: 267–273)

Key words: transesophageal echocardiography, intracardiac thrombus, spontaneous echocardiography contrast, C-reactive protein, D-dimer

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Introduction

Transesophageal echocardiography (TEE) is the most widely used test to evaluate most cardiac sources of thromboembolism, and is considered the gold standard to exclude left atrial (LA) thrombi [1]. Cardiogenic source of embolism is an important contributor to stroke, accounting for approximately 20% of strokes [2]. TEE is semi-invasive, operator-dependent, and requires light sedation with a small but real risk of complications. It would be desirable to identify patients who could be prospectively triaged to distinguish those who would benefit from TEE to detect intracardiac thrombus (ICT) and spontaneous echo contrast (SEC) from those in whom the likelihood of ICT/SEC is very low and who would be just as well served by a transthoracic echocardiogram (TTE).

D-dimer (DD) is an indirect marker of fibrin formation and is an established blood test that reflects activation of the coagulation system. DD is well evaluated in patients with deep venous thrombosis (DVT) and pulmonary embolism (PE), with an excellent negative predictive value [3]. Elevated DD levels have been described in patients with atrial fibrillation (AF) with LA thrombus and LA spontaneous contrast [4, 5]. DD has been associated with the duration of AF [6], as well as left atrial appendage (LAA) dysfunction [7].

High sensitivity C-reactive protein (CRP) is a marker of inflammation and has been shown to increase the risk of stroke [8]. Elevated CRP levels are also seen in patients with AF who have echocardiographic risk factors for thromboembolism [9]. Recently, there has been increasing interest in the inflammatory mechanism of thromboembolism, focusing on the prothrombotic potency of circulating biomarkers.

We sought to determine the value of DD and CRP in evaluating ICT and SEC, and to determine if these markers, when combined with clinical and echocardiographic variables, could help identify patients with low suspicion for intracardiac thromboembolic source in which TEE can be deferred.

Methods

Consecutive patients referred for TEE for evaluation of a cardiac source of thromboembolism at Henry Ford Hospital were evaluated prospectively. Exclusion criteria were: acute coronary syndrome within the previous three months, chronic infection, active bleeding, blood transfusion within the previous month, surgery within the previous three months, DVT or PE within the previous three months, thrombolytic therapy in stroke patients, anticoagulant therapy for more than seven days (since coumadin therapy decreases DD level [10]), malignancy, and autoimmune diseases. The project was approved by the institutional review board. Informed consent was obtained from all enrolled patients.

All TEEs were done after signed patient consent using a combination of midazolam and demerol for sedation. A Philips 5500 (Philips, Andover, MA, USA) Sonos ultrasound machine with an equipped multiplane TEE probe was used for all TEEs. CRP and DD levels were measured at the time of the TEE. All TEEs were performed and interpreted by experienced American Society of Echocardiography Level 2 or 3 equivalent echocardiographers. TEEs were then interpreted for the purpose of this study by an experienced level 3 echocardiographer (KA) who was blinded to the patients' conditions and laboratory results. TEE was considered the gold standard for determining ICT/SEC.

Global left ventricular function was described as normal when estimated ejection fraction (EF) was $\geq$ 50%, and described as reduced when EF $<$ 50%. Mitral regurgitation (MR) was assessed by visual estimation as the percentage of MR jet area to LA area based on American Society of Echocardiography guidelines for quantification for native valve regurgitation [11]. Patients with moderate to severe MR were grouped together as having significant MR, while those with no, trivial or mild MR were labeled as having no significant MR. SEC was defined as a finely reticular pattern of dynamic, swirling intracavitary echoes imaged with gain settings adjusted to distinguish background 'white' noise [12]. SEC was classified as mild when localized to LA or LAA, moderate when seen intermittently with adjustment of gain settings, and severe when present continuously at normal gain settings. ICT was defined as an echodense mass adjacent to the endocardial surface clearly differentiated from such normal structures as pectinate muscles. If thrombus and contrast were seen at the same time, the patient was labeled as having a thrombus only. LAA velocities were measured at end-diastole and averaged over 3–6 cardiac cycles.

CRP assay was manufactured by Behring (part of Siemens Diagnostics). It had a low limit of sensitivity of 0.0176 mg/dL. Intra-assay coefficient of variation was $<$ 0.7%. Inter-assay coefficients of variation were 8% at 0.15 mg/dL and 6% at 0.45 mg/dL. DD assay was manufactured by Stago. DD had a low limit of sensitivity of 0.22 μg/mL (FEU). Intra-assay coefficients of variation were 0.04 SD at

0.29 μg/mL, and 0.06 SD at 2.71 μg/mL. Inter-assay coefficients of variation were 0.05 SD at 0.32 μg/mL, and 0.14 SD at 2.76 μg/mL.

Statistical analysis

SAS version 9.3 software was used for statistical analysis. Categorical data was reported as proportions and continuous data as mean values with standard deviations. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CRP and DD for ICT/SEC were calculated using standard formulas. The median of CRP and DD was used for these calculations since their values were skewed. Sensitivity and specificity of CRP and DD were compared using the receiver operating characteristics (ROC) curve procedure. Spearman's correlation coefficient (r) was calculated to determine the relationship between CRP, DD, and ICT/SEC. Logarithmic transformation was used for CRP and DD to determine their association with ICT/SEC. Stepwise logistic regression analysis using a backward selection process was used to identify independent predictors of ICT/SEC. For all statistical analysis, a p value of less than 0.05 was considered statistically significant.

Results

We prospectively screened 168 consecutive patients referred for TEE for evaluation of a cardiac source of thromboembolism between April 2005 and July 2006. Figure 1 shows the flow-chart diagram of the patients screened and further enrolled. Twenty five patients were excluded as per the exclusion criteria described. In addition, ten patients refused to participate, eight patients were not competent to sign a consent form (Michigan state law does not allow a guardian to sign a consent form for enrolment in a study), and one patient was excluded because of a technically difficult TEE.

Of the patients with ICT/SEC (n = 21), the majority (17 patients) had LA SEC and four had LA/LAA thrombus. One LA thrombus was in the LA, and three were in the LAA. SEC was mild in seven patients, moderate in eight patients, and severe in two patients. ICT/SEC was exclusively seen in the LA/LAA. Furthermore, one patient from the stroke/transient ischemic attack (TIA) group had ICT and four had SEC. Two patients from the AF group had ICT and 11 had SEC; whereas in the group with both stroke/TIA and AF, one patient had ICT and two had SEC (Fig. 1). Figure 2 is a representative example of a study patient with SEC, and Figure 3 of a study patient with a large ICT in the LA.

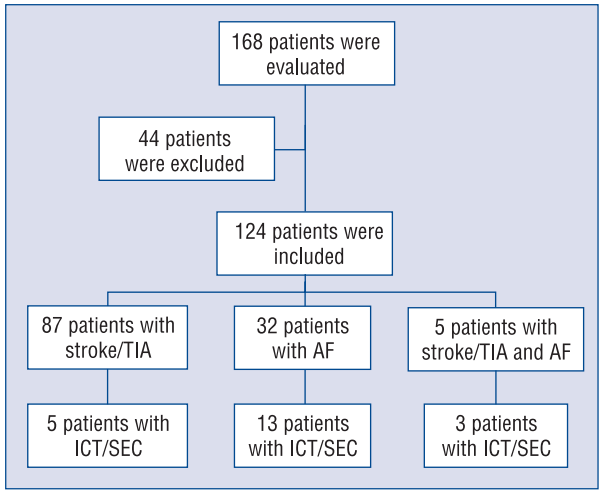

Figure 1. Flow-chart diagram of the patients screened and enroled in the study; AF — atrial fibrillation; ICT — intracardiac thrombus; SEC — spontaneous echo contrast; TIA — transient ischemic attack.

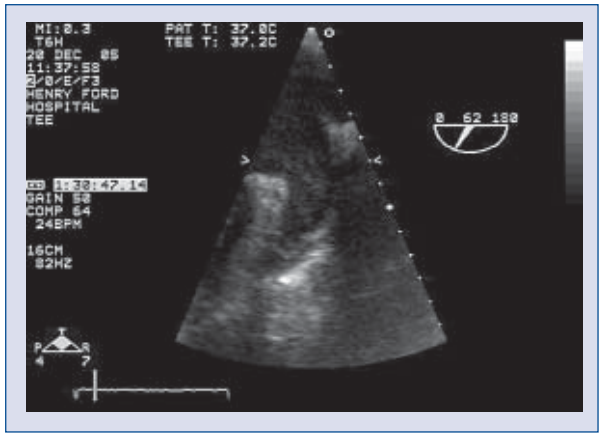

Figure 2. Transesophageal echocardiogram short axis aortic valve level of a study patient showing left atrial appendage on the right side of screen with spontaneous echo contrast.

Mean CRP level was 1.18 ± 2.1 mg/L while mean DD level was 993 ± 2,057 μg/L. Median value for CRP was 0.713 (lower quartile 0.187, upper quartile 1.13) mg/L and for DD 421 (lower quartile 264, upper quartile 866) μg/L. Area under the curve for CRP and DD were 0.77 and 0.69, respectively. Intraobserver (KA) correlation coefficient for both SEC and ICT was 0.98.

Table 1 shows baseline characteristics for included patients according to the presence or absence of ICT/SEC. Patients with ICT/SEC were predominantly male (90% *vs* 58%, p = 0.005) and

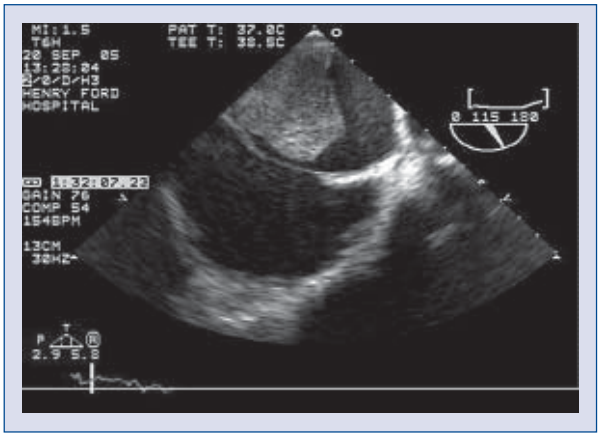

Figure 3. Transesophageal echocardiogram short axis aortic valve level of a study patient showing left atrial appendage (LAA) on the right side of screen with LAA thrombus from a study patient.

with AF (76% *vs* 20%, p < 0.001). Regarding echocardiographic variables, ICT/SEC was associated with lower EF (36 ± 15% *vs* 52 ± 16%, p < < 0.0001), lower LAA velocity (41.3 ± 23.8 cm/s *vs* 70.0 ± 26.3 cm/s, p < 0.001) and increased diastolic LAA area (5.2 ± 2.2 cm^2 *vs* 3.9 ± 1.5 cm^2, p = = 0.017). There was a trend that higher hemoglobin was associated with ICT/SEC (p = 0.055). Patients with ICT/SEC had higher log CRP (p = 0.009), whereas DD level or log DD were not statistically different between the two groups.

Table 2 shows the sensitivity, specificity, PPV and NPV of AF, low EF, CRP, DD, and their combination. As mentioned above, median values of CRP and DD were used for these calculations. A cut-off of 500 μg/L for DD, which is the standard cut-off used in DVT and PE evaluation [13], provided the same results as the median value (420 μg/L) and was used for the analysis. The NPV of AF or low EF was 93–94%. The combination of AF and low EF provided a NPV of 98.6% (71 out of 72 patients). The NPVs of elevated CRP and DD were 93.6% and 85%, respectively. Combining DD and CRP did not enhance NPV (93%). On the other hand, adding either CRP or DD to the combination of AF and low EF increased NPV to 100%.

Table 1. Baseline characteristics.

Clinical, laboratory and echocardiographic variables	No ICT/SEC (n = 103)	ICT/SEC (n = 21)	P
Age [years]	55.8 ± 12.7	53.5 ± 14.9	0.48
Male gender	60 (58%)	19 (90%)	0.005
African-American origin	61 (59%)	13 (62%)	0.82
Atrial fibrillation/flutter	21 (20%)	16 (76%)	< 0.001
Previous stroke	18 (18%)	1 (5%)	0.12
Coronary artery disease	16 (16%)	4 (19%)	0.69
Congestive heart failure	14 (14%)	8 (38%)	0.007
Obesity (BMI > 30 kg/m^2)	47 (46%)	8 (38%)	0.53
Hypertension	71 (69%)	16 (76%)	0.51
Diabetes mellitus	38 (37%)	5 (24%)	0.25
Hyperlipidemia	53 (51%)	8 (38%)	0.26
Smoking	33 (32%)	4 (19%)	0.24
Mean D-dimer [μg/L]	1045 ± 2228	734.8 ± 602	0.23
Log D-dimer [μg/L]	6.3 ± 1.0	6.3 ± 0.7	0.82
Mean CRP [mg/L]	1.1 ± 2.3	1.8 ± 2.2	0.2
Log CRP [mg/L]	–0.8 ± 1.3	0.1 ± 1.1	0.009
Hemoglobin [g/dL]	13.1 ± 1.8	13.9 ± 1.9	0.055
Ejection fraction < 50%	23 (22.3%)	15 (71.4%)	< 0.0001
Mean ejection fraction [%]	52 ± 16	36 ± 15	< 0.0001
Left atrial appendage velocity [cm/s]	70.0 ± 26.3	41.3 ± 23.8	< 0.001
Diastolic left atrial appendage area [cm^2]	3.9 ± 1.5	5.2 ± 2.2	0.017
Left atrial diameter [cm]	4.9 ± 4.8	5.4 ± 0.8	0.36
Aortic valve sclerosis	33 (34%)	6 (30%)	0.71
Significant mitral regurgitation	14 (14%)	5 (24%)	0.24

Continuous variables are expressed as mean ± standard deviation; ICT — intracardiac thrombus; SEC — spontaneous echo contrast; BMI — body mass index; CRP — C-reactive protein.

Table 2. Sensitivity, specificity, PPV and NPV for intracardiac thrombus or contrast.

	Number with ICT and SEC/total number (%)			
	Sensitivity	**Specificity**	**PPV**	**NPV**
AF	16/21 (76%)	82/103 (80%)	16/37 (43%)	82/87 (94.3%)
EF < 50%	15/21 (71%)	80/103 (78%)	15/38 (40%)	80/86 (93%)
CRP > 0.713 mg/L	17/21 (81%)	58/103 (56%)	17/62 (27%)	58/62 (93.6%)
DD > 500 μg/L	11/21 (52%)	57/103 (55%)	11/57 (19%)	57/67 (85%)
AF **and** EF < 50%	20/21 (95%)	71/103 (69%)	20/52 (39%)	71/72 (98.6%)
AF **and** EF < 50% **and** DD > 500 μg/L	21/21 (100%)	45/103 (44%)	21/79 (27%)	45/45 (100%)
AF **and** EF < 50% **and** CRP > 0.713 mg/L	21/21 (100%)	44/103 (43%)	21/80 (26%)	44/44 (100%)
CRP > 0.713 mg/L **and** DD > 500 μg/L	18/21 (86%)	40/103 (39%)	18/81 (22%)	40/43 (93%)

PPV — positive predictive value; NPV — negative predictive value; ICT — intracardiac thrombus; SEC — spontaneous echo contrast; AF — atrial fibrillation; EF — ejection fraction; CRP — C-reactive protein; DD — D-dimer

Table 3. Significant variables with an association with ICT/SEC using stepwise logistic regression analysis with backward selection.

Variable	Odds ratio	95% CI	P
Sinus rhythm	0.04	0.01–0.20	< 0.001
Ejection fraction (change of 1%)	0.75	0.61–0.92	0.0063
Log CRP (change of 0.1 mg/L)	1.08	1.01–1.15	0.023
Significant mitral regurgitation	0.18	0.04–0.97	0.046

ICT — intracardiac thrombus; SEC — spontaneous echo contrast; CI — confidence interval; CRP — C-reactive protein

Log CRP was associated with ICT/SEC (0.1 ± ± 1.1 mg/L *vs* –0.8 ± 1.3 mg/L, p = 0.009), while log DD did not have a significant association. Using stepwise logistic regression with backward selection (Table 3), EF (p = 0.0063 for a change of 1%), AF (p < 0.001), and log CRP (p = 0.023 for a change of 0.1 mg/L), were associated with ICT/SEC. Significant MR was associated with a reduced risk for ICT/SEC (p = 0.046). Multiple regression analysis was also performed by including variables with p < 0.25 in univariate analysis in addition to log DD since it is a variable of interest. In this model, only log CRP (p = 0.01 for 0.1 mg/L change) was associated with ICT/SEC, while significant MR was associated with a reduced risk for it (p = 0.025). In addition, log CRP showed a significant correlation with log DD (r = 0.44, p < 0.0001) and with ICT/SEC (r = 0.24, p = 0.0063).

Discussion

In this prospective study, we evaluated the role of CRP and DD along with TEE to predict ICT/SEC. We found that the combination of normal sinus rhythm (NSR) and normal EF (NEF) identified a group of patients who were unlikely to have ICT/SEC (NPV = 98.6%) and for whom TEE could be deferred. The one patient with ICT/SEC in our study who had NEF and NSR had severe left ventricular hypertrophy and was found to have mild SEC. CRP and DD levels were elevated in that patient. Thus, adding either marker to NSR and NEF increased NPV to 100%.

CRP was significantly associated with ICT/SEC and elevated CRP had better NPV than DD. To the best of our knowledge, this is the first study to have found an association between CRP and ICT/SEC in multivariate analysis. Inflammation may influence the prothrombotic state by the production of tissue factors from monocytes, increased platelet activation, and by endothelial damage [14]. A strong association between increased hematocrit and SEC in patients with AF was demonstrated, and although CRP and interleukin-6 were also univariate predictors, they did not predict SEC.

This and other studies have demonstrated that, at least in AF, a close association exists between a prothrombotic milieu and inflammatory markers such as CRP [15–17]. Our study thus extends the findings of an inflammatory marker such as CRP potentially being of value in predicting the presence of ICT/SEC, in addition to simple variables determined by electrocardiogram and TTE as discussed

above. Previous studies have revealed an association between graded levels of SEC and increased DD levels in patients with nonvalvular AF [5]. However, our study is different in that a different DD assay was used (ELISA), the exclusion criteria were more stringent, and patients with conditions other than AF were also enroled. These could potentially explain the lack of association between DD and ICT/SEC in our study.

Significant MR was found to be protective against ICT/SEC in our study. This association has been described before [18] and could be explained by the washout effect of regurgitant MR jet preventing ICT formation on the atrial surface and in LAA. Our study also demonstrated a trend for an association between ICT/SEC and hemoglobin ($p = 0.055$). This may be explained by increased concentration of erythrocytes or indirectly by promoting stasis due to altered rheology. SEC may represent interaction between erythrocytes and macromolecules during conditions of blood-pool stasis with a higher hematocrit being associated with SEC [14]. However, in the same context, it is interesting to note that low hemoglobin does not necessarily protect against SEC as previously shown by our group [19].

Previous studies have also shown that TEE is a more accurate technique for the evaluation of ICT than TTE [1]. The sensitivity of TTE has been plagued by a lack of adequate visualization of the LAA which harbors over 90% of ICT, particularly in patients with AF. However, predicting the likelihood of thrombus based on the presence or absence of structural heart disease by TTE has been evaluated by other earlier investigations. Ellis et al. [18] described how a structurally normal heart, as determined by TTE, provides 100% NPV for ICT. A large echocardiographic database study of 20,643 TEE examinations in patients with NSR demonstrated only 20 cases of LA thrombi. Twelve out of these 20 patients had underlying mitral or aortic disease or valvular prosthesis [20]. Omran et al. [21] studied 869 patients in two groups: those with AF as the control group ($n = 286$) and those with NSR as the study group ($n = 583$) who were referred for a TEE for evaluation of ICT. All the six (1%) patients with NSR who had ICT had underlying structural heart disease. They concluded that in patients with NSR and no structural heart disease as assessed by TTE, routine TEE was not indicated for the evaluation of ICT.

Several clinical and echocardiographic variables have been proposed as predictors of LAA thrombi by TEE, such as large stroke, history of coronary artery disease, evidence of electrocardiographic ischemia [22], as well as mitral stenosis, AF, tricuspid regurgitation, valvular prosthesis, left ventricular dysfunction, and right ventricular dysfunction [18]. However, our study suggests that two simple parameters, namely NSR and normal LV function, in combination, have a very high NPV (98.6%) which when combined with hematologic markers such as CRP or DD raises the NPV to 100%.

Although our study focused on consecutive patients referred for TEE assessment of ICT/SEC, it raises important questions as to whether routine TEE would be warranted in some patients with NSR and NEF on TTE. This is a particularly hotly debated issue in patients presenting to the echo lab for workup of ischemic stroke, because the role of TEE remains ill-defined [23, 24]. Although previous studies have suggested that TEE is not warranted in all ischemic stroke patients if they are in NSR and have normal TTE [20, 25], others have suggested that TEE adds incremental value for decision making for anticoagulation, and should be part of the routine work-up in patients with ischemic stroke [26, 27].

If the results of our study could be prospectively confirmed in a large series of ischemic stroke patients, more effective use of TEE in selected patients who are candidates for anticoagulation with a high suspicion for atheromatous disease of the aortic arch could be pursued. Lower risk patients can be treated with a diagnostic strategy starting with TTE with harmonic imaging and saline contrast study, along with use of CRP and DD.

Limitations of the study

Conclusions should only be applied to the assay for CRP and DD used in this study. Since two groups (AF and stroke/TIA) were evaluated and ICT/SEC was noticed more in the AF group, it is possible that the association of CRP with ICT/SEC may be secondary to its association with AF. To evaluate this possibility, we compared log CRP between the two groups in patients without ICT/SEC; the difference was not significant ($p = 0.09$). We were unable to evaluate each group separately because of the limited sample size. There was no control population in the study.

Conclusions

The presence of NSR and NEF in patients referred for TEE has a very high negative predictive value for ICT/SEC. This, in combination with simple biomarkers such as CRP or DD, may be helpful in triaging which patients need further semi-invasive tests such as TEE. Thus, further studies ran-

domizing patients to using this strategy of initial TTE, rhythm and inflammatory marker assessment *vs* routine TEE may be helpful in determining the implications of our findings towards selective triage of patients to TEE.

Conflict of interest: none declared

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