Meta Analysis

High uric acid level predicts left atrial thrombus or spontaneous echo contrast detected by transesophageal echocardiography: Meta-analysis and systematic review

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Abstract

Background: Recent observational studies have suggested that the patients with hyperuricemia have a higher risk of having left atrial thrombus (LATH) or left atrial spontaneous echo contrast (LASEC) by transesophageal echocardiography (TEE), while the ultimate predictive value of a high uric acid (UA) level on LATH/LASEC remained obscure.
Methods: We searched the PubMed and Cochrane clinical trials databases up to July 2015. Following screening the 369 initially identified studies, we analyzed six observational studies with 2381 patients.
Results: The meta-analysis of these studies showed that an elevated serum UA level was associated with a higher likelihood of LATH/LASEC ($OR = 1.59$, $95\%CI\ 1.13–2.23$, $P = 0.008$), while significant differences exist among individual trials ($P < 0.00001$ and $I^2 = 85\%$). Sensitivity analysis failed to find any heterogeneity.
Conclusion: An elevated UA level was associated with a higher risk of detecting a left atrial abnormality represented by LATH/LASEC.

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Introduction

An atrial thrombus forming in the left atrial appendage (LAA) in the setting of atrial fibrillation results in a series of adverse outcomes including stroke, myocardial infarction and other severe embolism events. Transesophageal echocardiography (TEE)

is frequently used to look for an LAA thrombus and can be helpful when conducting risk stratification of patients for stroke.[1]

Hyperuricemia has been shown to be an independent predictor of cardiovascular events.[2] Other studies have investigated the relationship between high levels of serum uric acid (UA) and a left atrial thrombus/left atrial spontaneous echo contrast (LATH)/(LASEC) as detected by TEE and there are conflicting results.[3—8] We conducted a comprehensive meta-analysis and systematic review to investigate the potential relationship between the serum UA level and left atrial thrombi detected by TEE.

Methods

We conducted this analysis according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group (MOOSE).[9] Prospective or retrospective observational studies were enrolled with the primary objective of analyzing the association between serum levels of UA and LATH/LASEC. Titles and abstracts of all articles were evaluated and studies were rejected if the following inclusion criteria were not met: 1) human subjects with TEE and corresponding result of LATH/LASEC reported, 2) UA presented as continuous variable, 3) retrospective/prospective cohort studies, 4) baseline data available, 5) detail of LA abnormality detected by TEE mentioned, 6) sample size of more than 50 patients from individual studies.

Search strategies

We performed a search of the on-line databases of PubMed and the Cochrane Controlled Trials Register Databases to July 2015 to identify relevant studies. We used the following keywords: "uric acid", "hyperuricemia" and "atrial thrombus", "spontaneous echo contrast", and "left atrium abnormality". Titles and abstracts as well as the reference lists of all the identified reports were independently examined by two reviewers (E.Z and T.L.) in order to include potentially relevant studies. The two reviewers agreed on the inclusion/exclusion status in 90% of the reviewed studies. Disagreements were resolved after discussion with a third reviewer (L.K.). There was no language restriction for the inclusion of studies. Additionally, we conducted a manual search using review articles, bibliographies of original papers, and abstracts of the scientific sessions of the American Heart Association, the European Society of Cardiology, the Heart Rhythm Society, and the American College of Cardiology from the past two years.

Quality assessment

To limit heterogeneity secondary to differences between study designs, the quality of each study was evaluated according to the guidelines developed by the Evidence-Based Medicine Working Group[10] and the United States Preventive Task Force.[11] We applied the point score system that assessed the following characteristics: (1) clear description of inclusion and exclusion criteria, (2) study sample representative for the mentioned population, (3) clear description of sample selection, (4) full specification of clinical and demographic variables, (5) complete clinical data such as renal function and echocardiogram parameters, (6) no loss of follow-up, (7) cohort study, (8) clear definition of outcomes and outcome assessment, (9) temporality (assessment of UA level before TEE), and (10) adjustment of possible confounders in multivariate analysis. If one of these key points was not mentioned clearly in a study, we considered it not to have been performed properly. Therefore, the possibility of underestimation of the reported characteristics may be present.

Data extraction

Two blind investigators (E.Z. and T.L.) independently performed data extraction with a standard data extraction form to determine eligibility for inclusion. The following collected information was tabulated: 1) publication details, first author's last name and the publication year, 2) characteristics of included studies, the study population, definition of LA abnormality, quality score, cohort design, risk estimate, and the patients' characteristics, 3) baseline data of the studied population, sample size, age, gender, paroxysmal atrial fibrillation (PAF) (%), LATH/LASEC (%), uric acid (μmol/L), creatinine (μmol/L), left atrium diameter, left ventricle ejection fraction, diabetes mellitus (%), hypertension (%), body mass index (kg/m^2), and left atrial appendage flow velocity (cm/s).

Statistical analysis

The magnitude of the association between high serum UA level and the LATH/LASEC detected by TEE was measured by adjusted *OR*, or by an *OR* with 95% confidence intervals (*CI*s). One study[7] only provided a value of *OR* by univariate analysis because there was no association between the serum UA level and the LATH/LASEC following univariate analysis. We used the inverse variance method to weight studies

for the combined overall statistics. Finally, we examined the heterogeneity with the standard χ^2 test of heterogeneity. An $I^2 >50\%$ indicates at least moderate statistical heterogeneity.[12] A pooled effect was calculated with a random-effects model when the χ^2-test for heterogeneity was found to be significant, through which we could take within-study and between-study variance into account. Sensitivity analysis was done by dropping studies and checking the consistency of the overall effect estimate. Statistical significance for the treatment effect was defined at P values <0.05. Publication bias was evaluated using a funnel plot. All the analyses above were performed using Review Manager Version 5.3 (Revman; The Cochrane Collaboration, Oxford, UK).

Results

We identified a total of 369 records following the primary article search. After screening the titles and abstracts, 363 studies were discarded because they were either review articles, laboratory studies, irrelevant to the current analysis, had insufficient statistics, or were non cohort studies. After detailed evaluation, six

observational studies met all inclusion criteria (Fig. 1).[3–8] Overall, there were 2381 patients involved in our analysis. The average UA concentration ranged from 279.5 μmol/L[5] to 368.8 μmol/L.[6] The characteristics of each included study and baseline data of the patients from corresponding studies are depicted in Tables 1 and 2 respectively. Meta-analysis of the included studies demonstrated that a higher level of UA was associated with a higher incidence of LA abnormality ($OR = 1.59$, $95\%CI$ 1.13–2.23, $P = 0.008$, Fig. 2), while there are significant differences between the individual studies ($P < 0.00001$ and $I^2 = 85\%$). Sensitivity analysis was performed to seek the origin of heterogeneity. However, removing any single study did not reduce the heterogeneity. The study from Numa et al[4] set the broadest definition of high risk in TEE, which included LATH, dense LASEC, low LAA flow velocity, and severe aortic atherosclerosis. However, when we exclude this study, the results remained positive, which further supported the close relationship between the high level of UA and the high incidence of LATH/LASEC ($OR = 1.67$, $95\%CI$ 1.10–2.54, $P = 0.02$, Fig. 3). Elimination of any study did not alter the positive association. The funnel plot (Fig. 4) suggested that there was little publication bias,
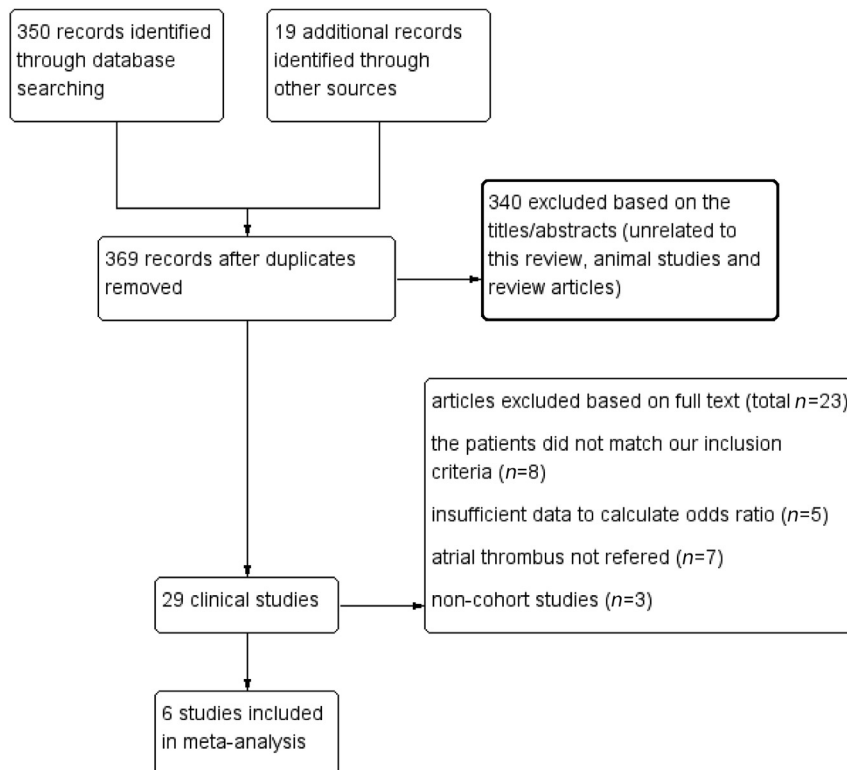

Fig. 1. Flow diagram of study selection process.

Table 1
Characteristics of studies included in meta-analysis.

Investigator	Publication year	Patients (n)	Definition of LA abnormality	Quality score	Cohort study design	Risk estimate	Patients characteristics
Liu	2014	525	LATH/SEC	7	N/A	aOR	AF
Numa	2014	115	TEE thromboembolic risk (TEE risk: low left atrial appendage flow, spontaneous echo contrast, thrombi, or aortic atherosclerosis)	8	retrospective	aOR	CHA2DS2-VASc score = 0 or 1 Non-valvular AF
Ozturk	2014	207	LATH (presence of a clearly defined echogenic intracavitary mass with an echo texture different from that of the underlying endocardium and not due to the pectinate muscle)	7	N/A	aOR	Mitral stenosis and sinus rhythm
Tang	2014	1359	Well-circumscribed echogenic mass with a LATH (unique echo texture contrasting with the adjacent or underlying myocardium) SEC (atrial blood pool in slow turbulent blood flow)	8	retrospective	aOR	Non-valvular AF
Zhao	2015	90	LATH (a fixed or mobile echogenic mass within the left atrium) SEC (a dense persistent echogenic swirling pattern that can be identified in all TEE views regardless of ultrasound frequency or gain setting)	8	retrospective	OR	Non-valvular AF
Akpek	2015	85	SEC (a pattern of slowly swirling intracavity echo densities imaged with gain settings which were adjusted to distinguish background noise)	8	retrospective	aOR	Mitral stenosis

AF: atrial fibrillation; aOR: adjusted odd ratio; N/A: not applicable.
LATH: left atrial thrombus; SEC: spontaneous echo contrast; TEE: transesophageal echocardiography.

Table 2
Baseline clinical characteristics of included studies.

Investigator	Publication year	PAF (%)	LATH/SEC (%)	Age (years)	Male (%)	UA (µmol/L)	LAD (mm)	LVEF (%)	CR (µmol/L)	BMI (kg/m^2)	DM (%)	HTN (%)	LAAfv (cm/s)
Liu	2014	83.0	10.9	60.8	64.2	353.9	37.9	N/A	N/A	N/A	N/A	N/A	N/A
Numa	2014	59.1	28.3	55.4	100	363.0	41.2	58.8	74.3	23.4	N/A	N/A	49.1
Ozturk	2014	SR	10.1	41.9	20.8	279.5	44.8	60.8	79.6	N/A	24.6	29.0	35.3
Tang	2014	65.1	4.5	58.2	70.8	368.8	39.0	63.4	83.6	26.2	13.4	51.7	N/A
Zhao	2015	56.7	27.3	60.1	60.0	325.7	40.4	57.7	77.5	N/A	17.8	52.2	N/A
Akpek	2015	39 AF 46 SR	51.8	46.0	34.1	323.2	N/A	62.9	84.1	22.7	28.2	47.1	N/A

PAF: paroxysmal atrial fibrillation; SR: sinus rhythm; LATH: left atrial thrombus; SEC: spontaneous echo contrast; LAD: left atrium diameter; LVEF: left ventricle ejection fraction; BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; LAAfv: left atrial appendage flow velocity; N/A: not applicable.
UA: uric acid 1 mg/dl = 59.5 µmol/L; CR: creatinine 1mg/dl = 88.41 µmol/L; CHA2DS2−VASc: Congestive heart failure, hypertension, Age >75 years, diabetes mellitus, stroke, vascular disease, Age 65−74 years, sex category.

although the small number of studies made it difficult to interpret.

Discussion

Our results showed that higher levels of UA could predict LATH/LASEC that were detected by TEE. However, when our investigation was restricted to patients with atrial fibrillation, we found that high serum UA level did not predict LATH/LASEC.

As a final enzymatic product of purine metabolism, UA depends on the activity of xanthine oxidase,[13] which participates in the formation of free radical superoxide anions. A study by Dudley et al showed that the xanthine oxidase activity in LAA of the AF group was 4.4 times greater than in the control group[14] resulting in local cellular damage and thrombus formation. The development of LATH/LASEC in AF patients may depend on the type and duration of AF. However, this association was not defined in the enrolled studies.
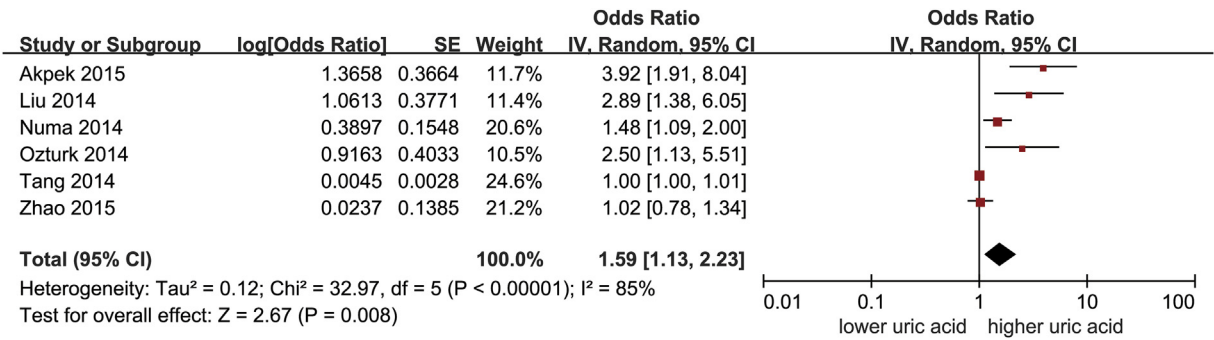
Fig. 2. Forest plot of association between high uric acid levels and left atrial thrombus or spontaneous echo contrast detected by transesophageal echocardiography.
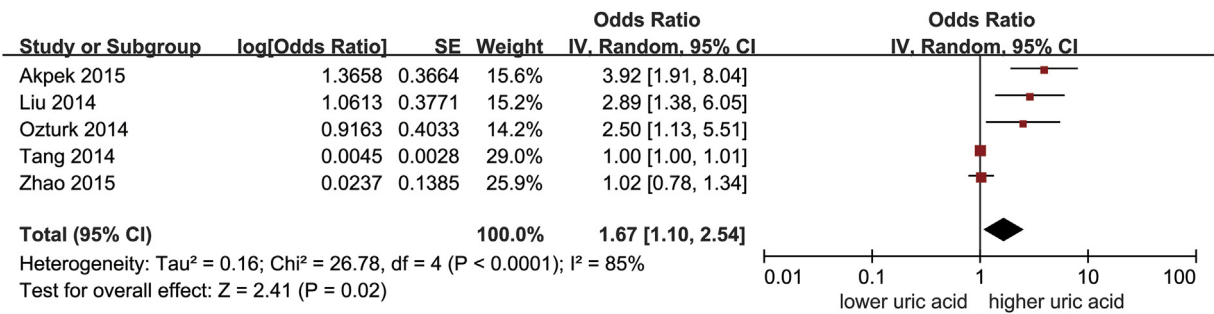

Fig. 3. Forest plot of association between high uric acid levels and left atrial thrombus or spontaneous echo contrast detected by transesophageal echocardiography excluding the study from Numa.[7]
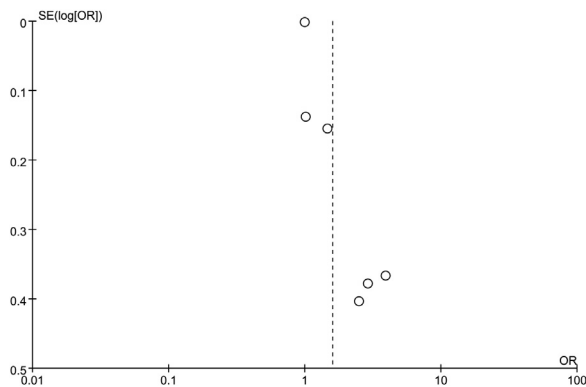

Fig. 4. Funnel plot of the meta-analysis.

Our previous research[15] had showed that there was a close relationship between the presence of AF and elevated serum UA levels in hypertensive patients. Inflammation and oxidative stress have been clearly associated with both progression of AF[16,17] and left atrial abnormality.[13,18] However, it is unclear if there is a direct causal relationship between elevated serum UA levels and AF. We aimed to determine if abnormal serum UA concentrations participate in the development of

LATH/LASEC detected by TEE. To the best of our knowledge, there was no clear evidence supporting the association between higher serum UA levels and the detection of LA abnormalities among patients with AF despite the slight difference found in the total population when the patients with mitral stenosis and sinus rhythm were taken into consideration in the present study.

LATH/LASEC is an important risk factor for stroke in patients with non-valvular AF. A strong association between higher plasma UA levels on admission and poor coronary blood flow was also found in ST-elevation myocardial infarction patients receiving primary PCI. Hypercoagulability and thrombus formation may be reflective of abnormal UA concentrations.[19] Zapolski et al[20] also indicated that elevated serum UA could result in a prothrombotic state. Other epidemiological studies demonstrated a link between hyperuricemia and an increased risk of ischemic stroke and mortality.[21,22] On the other hand, Chamorro et al[23] reported that UA may provide an additional therapeutic effect in the basis of thrombolysis among patients with acute stroke. In addition, some researchers presumed UA elevation had a compensatory protective mechanism with antioxidant action.[24] The conflicting data encouraged us to weigh

the merits and demerits of higher UA in AF patients more carefully.

LATH is a common source of thromboembolism and can be seen frequently in patients with AF[25] and valve disease (especially mitral stenosis).[5,8] However, the precise mechanism of thrombus formation in LA in the setting of high serum levels of UA is unclear. The vascular damage induced by hyperuricemia may be important as indicated by the excessive oxidant generation and inflammatory response in vascular endothelium.[26,27] UA could promote tissue inflammation and deterioration of endothelial function, which may be responsible for AF and accompanying LA thrombus formation.[28] Additionally, hyperuricemia could induce proliferation of vascular smooth Muscle cell and reduce the production of vascular nitric oxide leading to development of turbulent flow and thrombus formation.[29] Moreover, blood flow velocity in LAA may be another precursor of LATH. It was found to have an inverse correlation with serum UA levels among 130 patients with AF.[30]

The mechanism of LATH formation in patients with mitral stenosis involves inflammation, intra-atrial blood stasis, and abnormal platelet size and activation.[31,32] Exposure to high UA levels leads to a hypercoagulable condition and further accelerates the LATH formation.[5]

Conclusion

Our comprehensive meta-analysis shows that increased serum UA levels could be considered an independent predictor for LATH or LASEC detected by TEE. This finding leads to the question of whether pharmacologic reduction of uric acid can reduce the risk of stroke. Large prospective studies will be needed to address this issue.

Limitations

There were several limitations in this meta-analysis. First, the number of enrolled studies was relatively small and limited to an Asian population, despite the large sample size. Second, medications that may have influenced the serum levels of UA were not reported except for two studies,[6,7] and Tang et al[6] excluded patients on diuretics or allopurinol. Third, the disparity in age and sex ratio may have affected the UA level as there are hormonal fluctuations of UA among women at menarche and menopause.[33] Fourth, Numa et al[4] only included patients at low-intermediate clinical risk. Fifth, Ozturk[5] enrolled patients with mitral stenosis and sinus rhythm, which was significantly different from the other

studies. Finally, the endpoints defined by individual studies differ. One study included patients with a low LAA flow and aortic atherosclerosis as well.[4]

Acknowledgments

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