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# Correlation Between Uric Acid and Atrial Electromechanical Coupling Interval in Heart Failure with Reduced Ejection Fraction

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**ABSTRACT**

*Background*: Chronic Heart Failure (CHF) can lead to atrial and structural remodeling that result in non-homogenous impulse propagation and inter and intra-atrial conduction delay. Prolongation of interval of Atrial Electro-Mechanical Coupling (AEMC) in CHF patient was related to atrial electro-mechanical remodeling and Atrial Fibrillation (AF) risk. Hyperuricemia found in CHF played a role in the pathophysiology of AF through neuro-hormonal activation, oxidative stress, inflammation and ionic channel dysfunction. This study aimed to investigate the association between uric acid and AEMC interval in CHF with reduced ejection fraction.

*Methods*: This study was a cross sectional study. Subject were CHF patients with reduced ejection fraction and sinus rhythm who visited cardiology clinic Dr. Hasan Sadikin Bandung between July - September 2018. Blood sampling for uric acid was performed in the morning after fasting 10-12 hours. AEMC interval was measured by echocardiography Tissue Doppler Imaging (TDI) as time interval from onset of P wave in surface electrocardiography to onset of A wave from TDI in lateral atrial wall called lateral PA interval. Statistical analysis was done by linear regression analysis to control confounding variables.

*Results*: This study involved 51 CHF patients with reduced ejection fraction (< 40%) with median age 62 (27 – 81) year, 92% have history of myocardial infarction or coronary revascularization, 16% have diabetes mellitus, 51% have hypertension, and eGFR of 60.9 + 22.1. Mean uric acid was 8.0 + 2.2 mg/dL and mean lateral PA interval was 67.4 + 19.2 ms. Uric acid was significantly associated with lateral PA interval (R : 0.665, adjusted R2 0.407, P < 0.001) after controlling the confounding variables: systolic blood pressure and diastolic function.

*Conclusion*: Uric acid significantly correlated positively with AEMC interval in CHF patients with reduced ejection fraction.

**INTISARI**

*Latar Belakang*: Gagal jantung kronis (GJK) menyebabkan remodeling struktural dan elektrikal sehingga terjadi penjalaran impuls non homogen serta perlambatan konduksi intra dan inter-atrium. Pemanjangan interval atrial electromechanical coupling (AEMC) pada gagal jantung berhubungan dengan remodeling elektromekanikal di atrium dan risiko Fibrilasi Atrium (FA). Hiperurisemia ditemukan pada penderita GJK yang berperan dalam patofisiologi FA melalui aktivasi neurohormonal, stress oksidatif, inflamasi dan disfungsi kanal ion.

*Tujuan*: Penelitian ini bertujuan untuk mencari hubungan antara asam urat dan interval AEMC pada penderita GJK dengan fraksi ejeksi menurun.

*Metode*: Penelitian ini merupakan penelitian potonglintang. Subjek penelitian adalah penderita GJK dengan fraksi ejeksi menurun dan irama sinus yang berobat di Poliklinik jantung RSUP Dr. Hasan Sadikin Bandung bulan Juli-September 2018. Pengambilan sampel darah pemeriksaan asam urat dilakukan di pagi hari setelah berpuasa 10-12 jam. Interval AEMC diukur menggunakan ekokardiografi Tissue Doppler Imaging (TDI) dengan mengukur waktu dari awal gelombang P pada elektrokardiografi hingga awal gelombang A pada gelombang TDI di dinding lateral atrium kiri (Interval PA). Analisis statistik menggunakan uji regresi linier terhadap variabel perancu.

*Hasil*: Penelitian ini melibatkan 51 penderita GJK dengan fraksi ejeksi menurun (<40%) dengan usia median 62 (27 – 81) tahun, 92% memiliki riwayat infark miokard/ revaskularisasi koroner, 16% memiliki diabetes mellitus, 51% memiliki hipertensi dan rata-rata estimated Glomerular Filtration Rate (GFR) 60,9 + 22,1. Rata-rata kadar asam urat adalah 8,0 + 2,2 mg/dL dan rata-rata nilai interval PA lateral adalah 67,4 + 19,2 milidetik. Kadar asam urat berhubungan dengan interval PA lateral secara bermakna (R:0,665; adjusted R2 0,407, p < 0,001) setelah dilakukan pengontrolan terhadap faktor perancu : tekanan darah sistolik dan fungsi diastolik.

*Kesimpulan*: Kadar asam urat berhubungan positif kuat terhadap interval AEMC pada penderita GJK dengan fraksi ejeksi menurun.

## Introduction

Chronic Heart Failure (CHF) and Atrial fibrillation (AF) are frequently found together and are associated with worse long term prognosis and cardio-embolic complication. Stroke is frequently found as the first manifestation of AF.[1] Early identification and prevention was crucial in high risk CHF patient.[2]

CHF could lead to electrical remodeling in atrium through changes in expression and function of ion channels that decrease the action potential duration, decrease effective refractory period, cause conduction slowing and delayed after depolarization that served as a functional re-entry circuit and triggering factor for AF initiation. Structural remodeling as a result of fibrosis and a change in atrial size created an area of conduction slowing, increases anisotropy and cellular uncoupling, and dispersion of refractoriness that serves as a substrate for multiple re-entry circuit in the atrium.[3, 4] Atrial conduction time reflect both electrical and structural remodeling of the atrium. Inter and intra atrial conduction delay and non-homogenous impulse propagation were well known electrophysiological characteristic of atria prone to AF.[5] Atrial conduction properties can be measured invasively by electrophysiological studies and non-invasively by measuring P wave duration on surface electrocardiography (ECG) and signal averaged ECG.

Atrial electro-mechanical activity can also be detected from different atrial region by Tissue Doppler Imaging (TDI) echocardiography with high temporal resolution.[6] The time interval from beginning of electrocardiogram P wave and peak of A wave on TDI (PA interval), termed Atrial Electromechanical Coupling (AEMC) interval, can provide a good estimate of total atrial conduction time.[7] This novel non-invasive TDI echocardiographic parameter can predict Paroxysmal AF and new onset AF in post myocardial infarction and heart failure population.[5, 8,9] Published studies indicated that AEMC interval was increased in patient with CHF.

Uric acid is the end product of purine metabolism. Hyperuricemia found in CHF patient was associated with severity of disease and independent marker of poor prognosis.[10] Xanthine oxidase activation, catabolism and hypoxia in CHF associated with neuro-hormonal activation, inflammation and oxidative stress often result in hyperuricemia. Renal insufficiency and diuretic use also interfere with uric acid level in CHF patient. Meta-analysis and prospective population study showed that hyperuricemia is related to AF risk in hypertension, diabetes, ischemic heart disease, and heart failure patient. Uric acid is involved in pathophysiological AF through inflammation, neuro-hormonal activation, oxidative stress, and ion channel dysfunction. Hyperuricemia is also related to atrial remodeling, such as increased left atrial pressure, reduced atrial kinetic function and increasing left atrial dimension. AEMC interval reflects electro-mechanical remodeling. Uric acid level correlated with interval AEMC in hypertensive patient[11] but this correlation has not been studied in CHF patient with reduced ejection fraction. This study aimed to evaluate the relationship between uric acid and interval AEMC in CHF patient with reduced ejection fraction.

## Methods

*Study Population*

A total of 51 CHF patients (84% male) with reduced Left Ventricular Ejection Fraction (LVEF < 40%) and sinus rhythm were included in this study. None of these patients

had malignancy or history of chemotherapy, end stage renal disease with hemodialysis, thyroid heart disease, autoimmune disease such as systemic lupus erythematosus, restrictive cardiomyopathy, permanent pacemaker, constrictive pericarditis and primary valvular heart disease. Other exclusion criteria such as AF, bundle branch block, atrioventricular block, and premature ventricular complex were confirmed by electrocardiography.

*Data Collection*

This was a cross-sectional observational study. All patients provided informed consent. Local ethics committee approved the study. Detailed medical history and therapies were recorded. Physical examination, 12-lead ECG, and laboratory investigation including complete blood count, blood chemistry and lipid profile were performed for all patients. A 12 lead ECG was recorded from each individual in supine position at paper speed 25 mm/s and gain 10 mm/mV. Serum uric acid was estimated by uricase method.

Transthoracic echocardiography (TTE) were performed with GE Cardiac Ultrasound by 3,5 MHz transducer. All patient were examined by Doppler and TDI according to the standard criteria of American Society of Echocardiography. LVEF were evaluated by Simpson biplane methods. TDI was performed by adjusting spectral pulsed Doppler signal filter until a nyquist limit of 15-20 cm/s and sweep speed set at 50-100 mm/s to optimize the spectral display of myocardial velocities. The time interval from onset of P wave on surface ECG (P) to the beginning of late diastolic wave (A) was termed as atrial electromechanical coupling interval. It was performed in lateral left atrial wall in apical four chamber view and was describe as lateral PA interval. All measurements were calculated in average of three cardiac cycles and corrected with heart rate by dividing with square root of R-R interval.

*Statistical Analysis*

Data analysis was performed using SPSS for windows version 20. This study used three approaches for data analysis, i.e. univariate analysis, bivariate analysis, and multivariate analysis. Bivariate analysis was performed to see the relationship between two variables, by Pearson or Rank Spearman's correlation analysis, where applicable. Multivariate analysis were performed by multiple linear regression analysis. A p value of less than 0.05 was considered to be statistically significant.

## Result

This study comprised of 51 CHF patients with reduced ejection fraction (median age 62 (27 – 81) years, 84% male), most of them (92%) have history of myocardial infarction or prior coronary revascularization (minimum sample size was 47). Mean Body Mass Index was 25.8 $\pm$ 6 kg/m$^2$ with 20% categorized as obese. Mean Systolic Blood Pressure was 137.9 $\pm$ 23.9 mmHg and Mean Diastolic Blood Pressure was 81.6 $\pm$ 14.2 mmHg, 51% subject with history of hypertension, mean left ventricular mass index was 199.6 + 73.3 g/m$^2$, median relative wall thickness 0.30 (0.15 – 0.52). The patients have median fasting blood glucose of 96.0 (74 – 183) g/dL and 16% have history of diabetes with normal mean averaged lipid profile. Mean estimated glomerular filtration rate were 60.9 $\pm$ 22.1. There were no subject with anemia or acute infection. Echocardiographic data showed that subjects have median LVEF 34.5 (17 – 39) %, median Left Ventricular End Diastolic Diameter (LVEDD) was 62.1 (42.9 – 84.5) mm, median left atrial diameter was 44.1 (33.1 – 59.5) mm, and mean left atrial volume index was 40.2 + 13.3 g/m$^2$. Most subjects of this study received beta-blocker (96%), Angiotensin Converting Enzyme Inhibitor (59%), Angiotensin Receptor Blocker (37%), Mineralocorticoid Receptor Antagonist (36%), and diuretic (65%). Most patients also received anti-platelet (89%) and statin (82%). Patient with Spontaneous Echo Contrast in Echocardiography were 47% but only 8% of patients received anti-coagulant therapy. (See Table 1).

Mean uric acid level in this study was 8.0 $\pm$ 2.2 mg/dL and mean lateral PA interval was 67.4 $\pm$ 19.2ms. Bivariate analysis was performed on potentially confounding variable using Pearson, Spearman Rank and bi-serial point correlation. Uric acid (r : 0.564, p < 0.001), diastolic function (r : 0.357, p : 0.01), and systolic blood pressure (r : -0.350, p : 0.012) was found to have correlation with AEMC interval. (See Table 2). Confounding variable included in multivariate analysis were those with significant value (p < 0.05) during bivariate analysis of dependent variable.

Simple linear regression analysis before controlling the confounding variable showed that there was a significant positive correlation between uric acid and AEMC interval (r : 0.564, p < 0.001). Multiple linear regression analysis after controlling the confounding variable showed that there was a significant strong positive correlation between uric acid and AEMC interval (r : 0.665 , adjusted $R^2$ : 0.407, p < 0.001). (See Table 3)

## Discussion

In this study, we demonstrated that TDI echocardiography can be used as a non-invasive method to evaluate atrial conduction time with high temporal and spatial resolution. TDI allowed precise analysis of atrial motion, enabling estimation of time sequence between electrical activation and contraction in different region of the atrium.[12] Left atrial mechanical function were impaired in patients with heart failure. We observed an increase of lateral PA interval in heart failure patients with reduced ejection fraction in contrast to normal value in healthy population from previous study.[6] This observations appeared to be related to the structural remodeling of the atria, characterized by the occurrence of fragmented atrial activity, regions of low voltage, atrial conduction slowing, and interstitial atrial fibrosis. Matrix metalloproteinase and angiotensin II levels appeared to be key factors in atrial remodeling and systolic CHF dependent on severity of hemodynamic overload of the atria.[13, 14]

This is the first study that measured AEMC interval in ischemic cardiomyopathy population. Previous studies evaluated AEMC interval in heart failure population. Study by Bakal et al[15] and Pala et al[16] was conducted in non-

ischemic cardiomyopathy population (LVEF < 40%). Study by Bakal et al[15] was conducted in patients with moderate to severe mitral regurgitation, while Pala et al[16] excluded patients with mitral regurgitation. We did not exclude patients with mitral regurgitation in this study. Study by Waggoner et al[17] was conducted in cardiomyopathy patients with QRS duration > 120 ms that was planned for *Cardiac Resynchronization Therapy* but only 19.5% population of ischemic cardiomyopathy included in this study. We excluded patient with QRS duration > 120 ms in this study. Beeumen et al[18] and Bilgin et al[19] studied heart failure population with reduced and mid-range ejection fraction (LVEF < 50%) but only half of study population consist of ischemic cardiomyopathy (45 % and 54%).

Study conducted by Bilgin et al[19] used a different method to measure AEMC interval by measuring time interval from onset of P wave in surface electrocardiogram to peak instead of initial A wave on TDI echocardiography called peak PA interval. Study conducted by Lee et al showed that both method of AEMC interval measurement (initial PA and peak PA ) had approximately the same ability to discriminate paroxysmal AF from control (Area Under Curved, AUC PA initial 0.743 Vs AUC PA peak 0.718). AEMC interval was slightly better than left atrial volume index (AUC 0.703).[9]

AEMC interval had been found to be increased in paroxysmal AF[20, 21] and other condition with high risk of AF such as mitral stenosis[22], Chronic Obstructive Pulmonary Disease[23], diabetes[24,25], hypertension[26] and hyperthyroid[27]. AEMC interval increase found in this study could be used to identify subject with atrial substrate that was prone to AF development. This theory was supported by prospective study conducted by De Vos et al that found patients with AF have a longer AEMC interval.[28] Antoni et al studied AEMC interval within 48 hours after myocardial infarction found an increase in incident of AF in patient with prolonged AEMC interval.[29] Bertini et al studied heart failure population with ICD implantation and found that prolongation of AEMC interval could predict new onset AF from ICD interrogation.[30]

We found an association between uric acid and AEMC interval in CHF with reduced ejection fraction using simple linear regression analysis. In multivariate model after controlling confounding variables such as diastolic function and systolic blood pressure, there was still a significant strong positive correlation between uric acid and AEMC interval. This finding was supported by previous studies. ARIC study showed that uric acid was an independent predictor of AF.[31] Increasing uric acid level was associated with incident of AF in hypertensive and diabetes mellitus population.[32, 33] Study conducted by Tekin et al in ischemic heart disease found that uric acid had an independent association with AF[34] Study conducted by Letsas et al showed that uric acid level in permanent AF was higher than paroxysmal AF than control.[35] Uric acid correlated with AEMC interval in hypertensive patients.[11] This is the first study that evaluated relationship between uric acid and atrial vulnerability to AF in term of AEMC interval in CHF with reduced ejection fraction.

Uric acid played a role in the pathophysiology of AF through inflammation and independent inflammation pathways. Macrophage that engulfed uric acid crystal could activate NLRP3 inflammasome that stimulate IL-1β and *TGF-β1. TGF-β1* contributed to fibroblast differentiation, collagen deposition, fibrosis, and structural remodeling. IL-1 stimulation decrease *L-type* $Ca^{2+}$ $(IC_{aL})$ current that can caused shortening of action potential duration. Uric acid entered fibroblast through URAT transporter and caused increase intracellular oxidative stress. Uric acid could cause electrical remodeling by shortening of action potential duration by increasing potassium ultra rapid delay rectifier (Ikur) current. Oxidative stress could cause SERCA and ryanodine receptor dysfunction, and together with inflammatory cell would cause disruption in calcium hemostasis that initiate delayed after depolarization as a triggering factor for AF.[36] (See Figure 1)

This study also found the relationship between uric acid and AEMC interval was influenced by hemodynamic parameters, such as diastolic dysfunction (r : 0.357) and systolic blood pressure (r : 0.307). This is supported by the theory that prolongation of atrial conduction time that was associated with development of AF was influenced by not only left atrial enlargement but also by fibrosis and abnormal left atrial function. AEMC interval was more strongly related to AF occurence than left atrial volume.[9] Systolic blood pressure and diastolic dysfunction in heart failure was related to increasing left atrial filling pressure. Study conducted by Hoeper et al and Chrysohuu et al showed that hyperuricemia in heart failure was related to increasing level of left atrial filling pressure and impaired left atrial kinetic function.[37,38] Left atrial hemodynamic burden in heart failure consisted of pressure or volume overload would cause cardiomyocyte stretch. Myocyte stretch could cause calcium ion overload, renin-angiotensin-aldosterone system activation, and release of factors such as endothelin-1, natriuretic peptide, inflammatory factors, and oxidative stress that can cause structural remodeling in the atrium.[39]

The limitation of our study was the small number of patients and small number of female subject so that independent sub-group analysis based on sex could not be performed. The small number of patient made analysis of other various confounding variables impossible to be conducted.

**Table 1.**
Baseline Characteristic

| Baseline Characteristic | n = 51 |
|---|---|
| Age (years), Median (Min - Max) | 62 (27 – 81) |
| Male sex, n (%) | 43 (84) |
| Hypertension, n (%) | 26 (51) |
| Diabetes Mellitus, n (%) | 8 (16) |
| Heart Failure Etiology | |
| Ischemic Heart Disease, n (%) | 47 (92) |
| Hypertensive Heart Disease, n (%) | 6 (12) |
| Dilated Cardiomyopathy, n (%) | 4 (8) |
| Weight (Kg), Mean (SD) | 66.1 (13.4) |
| Height (cm), Median (Min - Max) | 161.5 (136.0 173.0) |
| Body Mass Index (Kg/m$^2$), Mean (SD) | 25.8 (6.0) |
| Obesity, n (%) | 10 (20) |
| Systolic Blood Pressure (mmHg), Mean (SD) | 137.9 (23.9) |
| Diastolic Blood Pressure (mmHg), Mean (SD) | 81.6 (14.2) |
| Heart Rate (bpm), Mean (SD) | 64.8 (11.8) |
| Electrocardiography | |
| Left Atrial Enlargement, n (%) | 34 (67) |
| Old Myocardial Infarct, n (%) | 45 (88) |
| Left Ventricular Hypertrophy, n (%) | 39 (76) |
| PR Interval (ms), Median (Min - Max) | 176 (133 - 233) |
| Laboratory | |
| Haemoglobin (g/dL), Mean (SD) | 14.1 (1.85) |
| White Blood Cell (/mm$^3$), Mean (SD) | 7572 (1930) |
| *Estimated Glomerular Filtration Rate*, Mean (SD) | 60.9 (22.1) |
| *Estimated Glomerular Filtration Rate* < 60, n (%) | 25 (49) |
| Fasting Blood Glucose (mg/dL), Median (Min - Max) | 96 (74 – 183) |
| Total Cholesterol (mg/dL), Mean (SD) | 175 (45) |
| *High Density Lipoprotein* (mg/dL), Mean (SD) | 44 (9) |
| *Low Density Lipoprotein* (mg/dL), Mean (SD) | 114 (38) |
| Triglyceride (mg/dL), Median (Min - Max) | 102 (52 – 341) |
| Hyperuricemia, n (%) | 32 (63) |
| Echocardiography | |
| Left Ventricular Ejection Fraction (%), Median (Min - Max) | 34.5 (17 – 39) |
| E/E'ratio , Median (Min – Max) | 15 (7 – 40) |
| Left Ventricular End Diastolic Diameter (mm), Median (Min - Max) | 62.1 (42.9 – 84.5) |
| Left Ventricular Mass Index (g/m$^2$), Mean (SD) | 199.6 (73.3) |
| Relative Wall Thickness, Median (Min - Max) | 0.30 (0.15 – 0.52) |
| Left Atrial Diameter (mm), Median (Min - Max) | 44.1 (33.1 – 59.5) |
| Left Atrial Volume Index (g/m$^2$), Mean (SD) | 40.2 (13.3) |
| *Spontaneous Echo Contrast*, n (%) | 24 (47) |
| Medication | |
| Angiotensin Converting Enzyme Inhibitor, n (%) | 30 (59) |
| Angiotensin Receptor Blocker, n (%) | 19 (37) |
| Beta blocker, n (%) | 49 (96) |
| Mineralocorticoid Receptor Antagonist, n (%) | 19 (37) |
| Diuretic, n (%) | 33 (65) |
| Antiplatelet, n (%) | 45 (89) |
| *Statin* : Low Intensity, n (%) | 19 (37) |
| : Moderate Intensity, n (%) | 12 (23) |
| : High Intensity, n (%) | 11 (21) |
| Vitamin K Antagonist, n (%) | 4 (8) |

Note:
SD : Standard Deviation,
Min : Minimum,
Max : Maximum

**Table 2.**
Bivariate Analysis Uric Acid, Potentially Confounding Factor an Interval Atrial Electromechanical Coupling

| Variable | Correlation coefficient (r) | *P value* |
|---|---|---|
| Uric Acid [a] | 0.564 | < 0.001* |
| Diastolic function (E/E' ratio) [b] | 0.357 | 0.010* |
| Systolic Blood Pressure[a] | -0.350 | 0.012* |
| Diastolic Blood Pressure[a] | -0.225 | 0.112 |
| Left Ventricular Mass Index[a] | 0.210 | 0.140 |
| Left Ventricular End Diastolic Diameter [b] | 0.180 | 0.207 |
| Left Atrial Volume Index[a] | 0.165 | 0.248 |
| Left Ventricular Ejection Fraction[b] | -0.164 | 0.250 |
| Left Atrial Diameter [b] | 0.136 | 0.340 |
| Sex [c] | -0.114 | 0.426 |
| Age[b] | 0.091 | 0.526 |
| Fasting Blood Glucose [b] | 0.031 | 0.828 |
| TAPSE [b] | 0.044 | 0.759 |
| e-GFR [a] | 0.014 | 0.922 |
| Diuretic Use [c] | -0.011 | 0.941 |
| Body Mass Index[a] | 0.000 | 0.998 |

Dependent variable : Atrial Electromechanical Coupling Interval
Analysis a. pearson, b. rank spearman,
c. point biserial, (*p < 0.05)

**Table 3.**
Multivariate Analysis

| Variable | Unstandardized Coefficient | | Standardized Coefficient | P Value | $R^2$ (adjusted) |
|---|---|---|---|---|---|
| | B | Standard Error | B | | |
| Constant | 27.908 | 8.561 | | 0.002 | 0.318 (0.304) |
| Uric Acid | 4.948 | 1.035 | 0.564 | < 0.001 | |
| Constant | 45.109 | 17.029 | | 0.011 | 0.442 |
| Uric Acid | 4.53 | 0.972 | 0.516 | < 0.001 | (0.407) |
| Systolic Blood Pressure | -0.178 | 0.090 | -0.221 | 0.05 | |
| E/E' Ratio | 0.619 | 0.274 | 0.249 | 0.029 | |

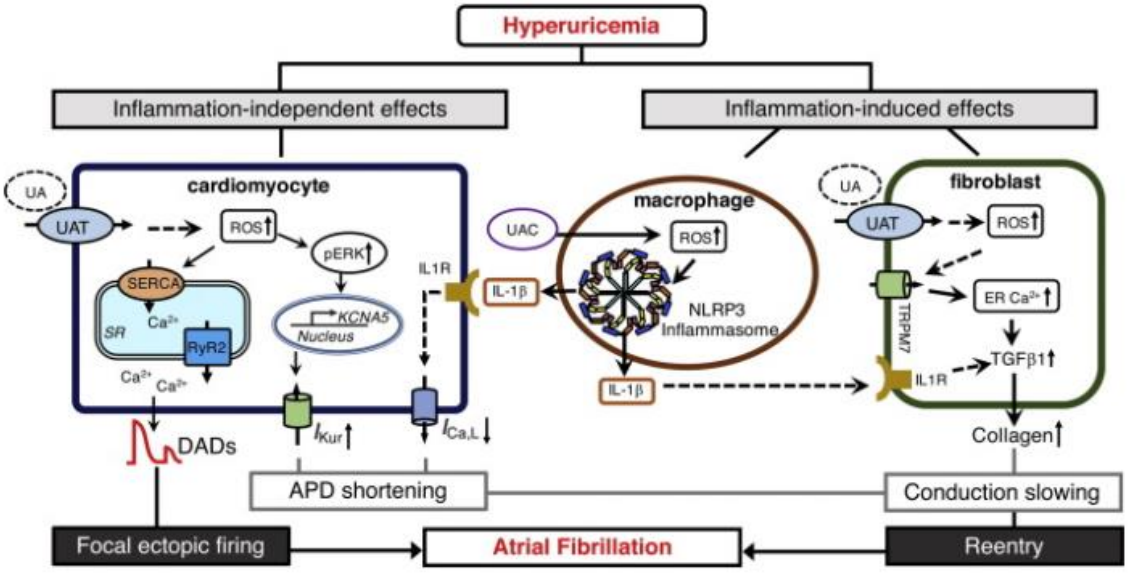


**Figure 1**. Mechanism of Hyperuricemia and Atrial Fibrillation

Adapted from : Li et al36

## Conclusion

AEMC interval prolongation was seen in heart failure with reduced ejection fraction patients. This indicated an increased risk of atrial vulnerability to AF in CHF patients with reduced ejection fraction. In this study, we found a strong significant relationship between uric acid and prolonged AEMC interval in CHF patients with reduced ejection fraction. However, our findings need to be supported by other studies with a large number of patients and a long-term follow-up period.

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