Journal of Clinical & Experimental Cardiology
ISSN: 2155-9880

Kim et al., J Clin Exp Cardiolog 2016, 7:7
DOI:10.4172/2155-9880.1000456

Research Article Open Access

Factors Associated with Left Atrial Enlargement in Patients with Anemia Caused by Uterine Myoma

Soo Ho Kim[1], Min-Kyung Kang[1*], Han-Kyul Kim[1], Kwang Jin Chun[1], Jaehuk Choi[2], Seonghoon Choi[1], Jung Rae Cho[1] and Namho Lee[1]

[1]*Cardiology Division, Kangnam, Hallym University Medical Center, Seoul, South Korea*

[2]*Cardiology Division, Hangang Sacred Heart Hospital, Hallym University Medical Center, Seoul, South Korea*

[*]**Corresponding author:** Min-Kyung Kang, MD, PhD, Cardiology Division, Kangnam Sacred Heart Hospital, Hallym University Medical Center, Seoul, South Korea, Tel: 82-2-2820-5294; Fax: 82-2-2846-4669; E-mail: homes78@hallym.or.kr

Received date: April 11, 2016; **Accepted date:** July 11, 2016; **Published date:** July 22, 2016

Copyright: © 2016 Kim SH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Uterine myoma (UM) is common among female gender, and it often causes anemia. Left atrial enlargement (LAE) is commonly detected in patients with anemia as well as caused by uterine myoma. Therefore, this study was aimed to investigate the clinical implications of LAE and its associating factors in patients with anemia caused by UM.

Methods: This is a retrospective observational cross sectional study and it considered 139 female patients with UM who had undergone preoperative echocardiography. Patients were sorted into 2 groups according to the presence of LAE (n=60) or not (n=79). LAE was defined as LA volume index (LAVI) was 35 ml/m^2 or more

Results: Patients with LAE (LAVI: 41.0 ± 5.3 ml/m^2) showed larger left ventricular (LV) dimension and increased LV mass index (LVMI) than patients without LAE (LAVI: 27.9 ± 3.9 ml/m^2). Patients with LAE were older, showed slower heart rate (HR) and further decreased level of hemoglobin. Older age, slower HR, level of hemoglobin, larger LV, increased LMI, E/E', right ventricular systolic pressure and decreased S' velocity were shown to be correlated with increased LAVI. Among them, older age (OR: 1.119, 95% CI: 1.014-1.236, p=0.026) and slower HR (OR: 0.926, 95% CI: 0.878-0.977, p=0.005) were independently associated with LAE in patients with anemia caused by UM.

Conclusion: LAE was often noticed in patients with anemia caused by UM and older age and slower HR were seemed to be its associating factor.

Keywords: Anemia; Left atrium; Uterine myoma

Introduction

Left atrial (LA) enlargement is associated with poor prognosis and cardiovascular events such as cerebral infarction and heart failure (HF) and as well as adverse overall outcomes [1-3]. There are several factors that determine LA size, i.e. age, gender, body size; therefore we use LA volume indexed to body surface area (BSA) as more precise method to examine LA size [4]. In terms of pathophysiologic aspects, mitral stenosis and left ventricular (LV) dysfunction induce LA pressure overload [5]. In addition, LA volume overload resulting from mitral valve regurgitation, arteriovenous fistula, left to right shunt, or high cardiac output state can also contribute to LA enlargement (LAE) [5]. However, there are controversies that "high cardiac out HF" is misnomer or not, because some authors suggest that high out state is intrinsically normal and capable of generating a high cardiac output [6]. Others have suggested that high output HF occurs only when there is the presence of underlying heart disease [7]. Among them, chronic anemia is a major cause of high cardiac output state which we easily encounter in daily practice [8]. However, there are only few studies exist which evaluating cardiac enlargement [9] or clinical implications [10,11] in patients with chronic anemia. Most recently, Hammoudi et al. reported that LA volume is not an index of LV diastolic dysfunction in patients with sickle cell anemia [12], however, sickle cell anemia is very rare in South Korea. Uterine myoma (UM) is well known cause of anemia because of high frequency of menorrhagia [13] occurring 5 to 20% of women [14]. LAE is common in patients with anemia caused by UM even they did not have overt heart disease. However, frequency or degree of LAE and its clinical implications have not been investigated in those patients. Therefore, we aimed to study on factors associated with LAE and its clinical implications in patients with anemia caused by UM in South Korea.

Materials and Methods

Study design and participants

We conducted a retrospective observational cross sectional study. In this study, we enrolled 139 female patients who were admitted to Kangnam Sacred Heart Hospital and diagnosed anemia caused by UM from April 2012 to December 2015. Anemia was defined when hemoglobin level was lower than 12 g/dL for women [15]. LAE was defined as LA volume index (LAVI) was 35 ml/m^2 or more [4]. Patients with chronic kidney disease, systolic blood pressure ≥ 160 mm Hg, decreased LV EF<50%, regional wall motion abnormalities, arrhythmia, severe valvular heart diseases, pericardial diseases, thyroid disease, moderate to severe pulmonary hypertension, sepsis, hemodynamic instability, and age ≥ 80 years were excluded from this study. The participants underwent transthoracic echocardiography and

we collected participant data on demographic, anthropometric, and laboratory parameters.

Transthoracic echocardiography (TTE)

TTE was performed using standard techniques with a 2.5-MHz transducer. The standard 2-D and Doppler echocardiography was performed using a commercially available echocardiographic machine (Vivid 7R GE Medical System, Horten, Norway). LV end-diastolic dimensions (LV EDD), end-diastolic interventricular septal thickness, and end-diastolic LV posterior wall thickness were measured at end-diastole according to the standards established by the American Society of Echocardiography [4]. LV ejection fraction (EF) was determined by the biplane Simpson's method [16]. Maximal LA volume was calculated using the biplane Simpson method [17] and indexed to the body surface area as LAVI. LV mass was calculated using the Devereux formula [18]=1.04 [(LVEDD + IVSTd + PWTd)^3 – (LVEDD)^3] – 13.6. Thereafter, the LV mass index (LVMI) was calculated and indexed to body surface area (BSA). Mitral flow velocities were recorded in the apical four-chamber view. Mitral inflow measurements included the peak early (E) and peak late (A) flow velocities and the E/A ratio. The tissue Doppler of the mitral annulus movement was also obtained from the apical four-chamber view. A 1.5-mm sample volume was placed only at the septal side of the mitral annulus. The analysis was performed for early diastolic (E') and late diastolic (A') peak tissue velocities. As a noninvasive parameter for LV stiffness, the LV filling index (E/E') was calculated by the ratio of transmitral flow velocity to annular velocity. Adequate mitral and tissue Doppler image (TDI) signals were recorded in all patients [19]. Right ventricular systolic pressure was evaluated by calculating right ventricle-right atrium (RV-RA) pressure gradient (PG) using the modified Bernoulli equation (4 V^2). Using the peak tricuspid regurgitation jet velocity as V, the RV-RA PG can be calculated [20]. RA pressure was determined by assessing IVC size and collapsibility. There was no patient with intra-cardiac shunt in this study.

Statistical analysis

All continuous data are expressed as mean ± SD, and all categorical data are presented as percentage or absolute numbers. Continuous variables were analyzed using Student's t-test and dichotomous variables were analyzed using the chi square test. In addition, multivariate analysis (logistic and linear regression, SPSS for Macintosh, version 23, SPSS, Inc., and Chicago, Ill., USA) was performed. All variables that had a p value of 0.05 or less were considered statistically significant.

Results

Echocardiographic parameters of the study population

Echocardiographic measurements are showed in Table 1. Patients with LAE showed larger LV than patients without LAE. More dilated LV and more increased LVMI were noted in patients with LAE. However, most patients with anemia showed normal LV diastolic function and variables associated with LV diastolic function (E and A velocities, E/A ratio, DT, E' velocity, E'/A' ratio, E/E') even though they had enlarged cardiac size. Only E/E' was slightly but significantly elevated in patients with LAE (10.0 ± 2.6 vs. 8.4 ± 2.2, p<0.001). There was no significant difference of EF between the two groups, but S' which related to LV systolic function, was slightly lower in patients with LAE (S': 7.8 ± 1.3 vs. 8.3 ± 1.4 cm/s, p=0.039). In addition, right ventricular systolic pressure was slightly higher in patients with LAE (34.5 ± 8.5 vs. 29.9 ± 5.5 mm Hg, p<0.001).

_	LAE (n=60)	No LAE (n=79)	p
LAVI (ml/m2)	41.0 ± 5.3	27.9 ± 3.9	<0.001
LVMI (g/m2)	91.9 ± 21.1	79.3 ± 16.6	<0.001
RWT	0.31 ± 0.05	0.31 ± 0.06	0.664
LV EDD (mm)	52.0 ± 3.3	49.3 ± 3.4	<0.001
LV ESD (mm)	33.3 ± 3.2	31.9 ± 3.0	0.011
LV EF (%)	66.4 ± 4.9	66.0 ± 4.8	0.563
E velocity (cm/s)	89.9 ± 19.3	84.5 ± 18.5	0.096
A velocity (cm/s)	71.6 ± 19.1	68.3 ± 17.3	0.279
E/A ratio	1.36 ± 0.54	1.31 ± 0.44	0.573
DT (ms)	170.5 ± 27.4	178.2 ± 23.3	0.078
E' velocity (cm/s)	9.4 ± 2.3	10.5 ± 2.7	0.08
A'	8.6 ± 2.3	9.1 ± 2.8	0.336
E'/A' ratio	1.20 ± 0.54	1.27 ± 0.49	0.456
E/E'	10.0 ± 2.6	8.4 ± 2.2	<0.001
S' velocity (cm/s)	7.8 ± 1.3	8.3 ± 1.4	0.039
RVSP (mm Hg)	34.5 ± 8.5	29.9 ± 5.5	<0.001

Diastolic grade			0.105
normal	31 (52%)	54 (68%)	–
Grade 1	17 (29%)	17 (22%)	
Grade 2	12 (20%)	8 (8%)	
Data are represented as mean ± SD or n (%). LAVI: Left Atrial Volume Index; LVMI: Left Ventricular Mass Index; LV EDD and ESD: LV End-Diastolic and Systolic Dimension; EF: Ejection Fraction; DT: Deceleration Time.			

Table 1: Echocardiographic parameters of the study population.

Clinical parameters of the study population

The clinical characteristics of the patients are showed in Table 2. The study population included 60 patients with LAE and 79 patients without LA). Patients with LAE were slightly older (mean age: 48.9 ± 7.3 vs. 45.0 ± 7.4 years, p=0.003) and heart rate (HR) was slower (66.7 ± 12.4 vs. 77.0 ± 15.6, p<0.001). In laboratory parameters, level of hemoglobin was more lowered in patients with LAE (6.7 ± 1.9 vs 7.4 ± 1.7 g/dl, p=0.024).

–	LAE (n=60)	No LAE (n=79)	p
Age (years)	48.9 ± 7.3	45.0 ± 7.4	0.003
Systolic blood pressure (mm Hg)	114.5 ± 16.1	110.9 ± 14.6	0.2
Diastolic blood pressure	70.7 ± 8.9	70.0 ± 10.7	0.646
Heart rate (beats per min)	66.7 ± 12.4	77.0 ± 15.6	<0.001
Body surface area (m^2)	1.59 ± 0.13	1.60 ± 0.14	0.639
Body mass index (kg/m^2)	24.8 ± 5.2	24.2± 4.6	0.414
Hypertension	4 (7%)	3 (4%)	0.465
Diabetes	4 (7%)	4 (5%)	0.726
Stroke	0 (0%)	1 (1%)	1
History of CHD	0 (0%)	1 (1%)	1
Serum creatinine (mg/dl)	0.64 ± 0.14	0.64 ± 0.12	0.959
Hemoglobin (g/dl)	6.7 ± 1.9	7.4 ± 1.7	0.024
Hematocrit	22.7 ± 4.9	24.5 ± 4.5	0.028
RDW	17.7 ± 2.6	18.0 ± 6.6	0.74
CBC	5692 ± 2435	6086 ± 2641	0.368
Platelet	314.9 ± 139.6	307.4 ± 117.0	0.731
Ferritin	47.6 ± 181.1	21.2 ± 54.7	0.294
Iron	28.2 ± 44.1	29.9 ± 58.8	0.881
TIBC	386.2 ± 93.5	407.5 ± 80.7	0.235
Data are mean ± standard deviation (SD) or or n (%). CHD: Coronary Heart Disease; RDW: Red Blood Cell Distribution Width; CBC: Complete Blood Count; TIBC: Total Iron-Binding Capacity.			

Table 2: Clinical and laboratory parameters of the study population.

Correlations of continuous variables with LAVI in patients with anemia

As shown in Table 3, age and slower HR were significantly correlated with LAVI, whereas body mass index and serum creatinine level did not. Echocardiographic findings showed enlarged LV and increased LVMI were closely correlated with increased LAVI. Of the tissue Doppler parameters, deceleration time (DT) of E velocity, E' and S' velocity showed negative correlation with LAVI, and E velocity and E/E' showed were closely correlated with LAVI.

–		P value
Age	0.192	0.024
BSA	0.03	0.727
BMI	0.071	0.407
HR	-0.265	0.008
Serum cr.	0.044	0.608
Hemoglobin	-0.15	0.077
LV EDD	0.446	<0.001
LV ESD	0.301	<0.001
LV EF	0.067	0.431
LVMI	0.321	<0.001
E	0.182	0.032
A	0.028	0.743
E/A	0.148	0.082
DT	-0.257	0.002
E'	-0.231	0.006
A'	-0.132	0.123
E'/A'	-0.027	0.755
E/E'	0.368	<0.001
S'	-0.226	0.008
RVSP	0.375	<0.001

Table 3: Correlation of clinical and echocardiographic variables with left atrial volume index.

Multivariate analysis

The results of multivariate analysis using parameters had significant correlations with LAVI were shown in Table 4. Among variables found to be correlated with LAE, older age (OR: 0.192, 95% confidence interval: 1.014-1.236, p=0.026) and slower HR (OR: 0.926, 95% confidence interval: 0.878-0.977, p=0.005) were independently associated with LAE. It shows positive correlation of age and LAVI and 1-B showed negative correlation of HR and LAVI.

_	Odds ratio	95% CI	p
Age	1.119	1.014-1.236	0.026
HR	0.926	0.878-0.977	0.005
Hemoglobin level	0.8	0.508-1.260	0.336
LVEDD	1.218	0.944-1.572	0.13
LVESD	0.92	0.734-1.152	0.466
LVMI	1.011	0.975-1.048	0.559
E velocity	1.079	0.987-1.179	0.095
DT	0.986	0.959-1.013	0.301
E/E' ratio	0.609	0.293-1.268	0.185
S' velocity	1.117	0.692-1.802	0.65
RVSP	1.045	0.942-1.160	0.405
LVEDD: Left Ventricular End-Diastolic Dimension; LVESD: Left Ventricular End-Systolic Dimension; LVMI: Left Ventricular Mass Index; DT: Deceleration Time.			

Table 4: Multiple logistic regression analysis to predict high left atrial volume index in patients with anemia.

Discussion

We found that almost half of patients with anemia caused by UM showed LAE (60/139, 43%). Older age, slower HR, lower level of hemoglobin, dilated LV, increased LVMI, shortened DT, elevated E/E' ratio and right ventricular systolic pressure, and decreased S' velocity were found to be associated with LAE in patients with anemia. Among them, older age and slower HR were independently related to LAE according to our study. Furthermore, even patients with anemia showed LAE, they did not have significant clinical and/or echocardiographic problems which supposed to be associated with LAE.

Sanghvi et al. reported that 120 of 155 patients reported cardiac enlargement by chest X-ray, and enlargement disappeared rapidly in 92 patients with correction of the anemia in 1960 [9]. More recently than previous study, Naito et al. showed that chronic iron-deficiency anemia leads to LV hypertrophy and HF in molecular level among animals [10]. Metivier et al. reported that anemia-related LV hypertrophy which is mainly due to increased cardiac output - mediated by lower afterload, increased preload, and positive inotropic and chronotropic effects - are reversible, not associated with impaired diastolic dysfunction [11]. However, even in the absence of underlying cardiovascular disorders, severe anemia (hemoglobin concentration <4-5 g/dl) could leads to congestive HF. All previous studies mentioned above were mainly focused on LV hypertrophy, not LAE, and the report from Metivier et al. was on patients with end-stage renal disease [11]. Rather different from previous studies, we focused on LAE which is very common in patients with anemia without underlying heart diseases or end-stage renal disease.

It is well known that patients with established cardiovascular disease and HF, the presence of anemia is associated with disease severity and affects outcome unfavorably [21-23]. Furthermore, Klip et al. recently published that hemoglobin level affected on new onset HF as U shaped pattern [24]. In terms of low hemoglobin level, only severe anemia increased annual HF incidence, not just anemia. In addition, Kim et al. reported that the presence of anemia was significantly associated with elevated LV filling pressure and LV structural changes – increased LVMI and LAVI, like our studies – in newly diagnosed hypertensive patients over 50 years old even before development of overt HF [25]. However, it has not been studied about clinical implications or its associating factors of LAE in anemic patients without underlying heart disease or other significant systemic diseases. Patients with anemia showed LAE comparable to patients with diastolic dysfunction, and showed even more dilated LV with increased LVMI according to our study likewise previous studies. However, most patients with anemia showed normal LV diastolic function and more favorable LV diastolic indices. Interestingly, patients with LAE showed slightly but significantly decreased S' velocity than patients with anemia even though there was no difference in EF at all. TDI allows the quantitative evaluation of myocardial function [26,27] and it is well known that TDI is more sensitive to detect subclinical abnormalities in systolic and diastolic LV function over conventional echocardiography [28,29]. Decreased S' velocity was well represent with subtle LA or LV dysfunction in asymptomatic individuals with cardiovascular risk factors [30].

Conventionally, chronic severe anemia is known to be often associated with various degree of salt and water retention [31-33]. Study from Anand et al. in 1993 told us that patients with chronic severe anemia (hematocrit 9-16%) had edema caused by retention of salt and water, reduction of renal blood flow and glomerular filtration rate, and neurohormonal activation similar to that seen in patients with edema caused by myocardial disease [34]. However, none of anemic patients used diuretics to eliminate congestion in our study because none of patients had significant pulmonary congestion. In addition, there are only small patients (14/139, 10%) showed severe anemia (hematocrit lower than 16%) in our study.

Our findings were similar to the recent study by Hammoudi et al., which reported that LAE is common in sickle cell anemia and related to age, hemoglobin concentration and LV morphology [12], however, sickle cell anemia is very rare in South Korea. Even we did not investigate the duration of anemia, when consider their cause of anemia, which were mostly UM or iron deficiency anemia-, their duration of anemia might be not acute event, rather several months exist. That is supposed to be why older age and slower HR were independently associated with LAE in patients with anemia caused by UM in this study. The longer anemia existed, the larger LA developed and slower HR represents its chronicity and adaptation. Nevertheless, patients with anemia or even with severe anemia did not have any clinical problems even cardiac enlargement detected by echocardiography.

Limitations

This study has lots of limitations. First, relatively small number of study population was one of major limitation. Second, we did not

investigate longevity of anemia, because most patients were asymptomatic until they found their anemia via routine health check-up. Therefore, our results may be different from other chronic severe anemia. However, this study might be useful in treating patients with mild to moderate anemia showing LAE without other problems. Third, the most common cause of anemia was caused by UM in this study and we exclude few men patients with anemia. Therefore our results were impossible to translate all anemic patients. Fourth, some laboratory data – brain natriuretic peptide, anemia study such as ferritin, iron, total iron-binding capacity, were not examined in whole study population. Therefore, important laboratory data associated with anemia were not fully investigated in this study. At last, we did not perform follow-up echocardiography after correction of anemia (i.e. myoma operation, blood transfusion). Therefore, we could not see if there was a reversal of LA or LV enlargement. It is important to see atrial reverse remodeling after proper therapy, because of high occurrence of atrial fibrillation (AF) in patients with LAE [35]. Patients with non-ischaemic dilated cardiomyopathy performed cardiac resynchronization therapy had less occurrence of AF if they had favorable atrial and ventricular reverse remodeling [36,37]. Therefore, it would be needed to see the relation between occurrence of AF and presence of atrial reverse remodeling in patients with anemia in the future study.

In summary, patients with anemia showed LAE even absence of underlying heart diseases but had favorable LV diastolic and systolic function. Older age, lower level of hemoglobin, dilated LV, increased LVMI, shortened DT, elevated E/E' ratio, right ventricular systolic pressure and decreased S' velocity were associated with LAE in patients with anemia caused by UM. Among them, older age and slower HR were independently related LAE. In conclusion, LAE is common in patients with anemia caused by UM without significant clinical implications.

Acknowledgements

This research received no specific grant from any funding agency.

References

1. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D (1995) Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation 92: 835-841.
2. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, et al. (2006) Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: Strong Heart Study (SHS). Am Heart J 151: 412-418.
3. Takemoto Y, Barnes ME, Seward JB, Lester SJ, Appleton CA, et al. (2005) Usefulness of left atrial volume in predicting first congestive heart failure in patients > or=65 years of age with well-preserved left ventricular systolic function. Am J Cardiol 96: 832-836.
4. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, et al. (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28: 1–39.
5. Leung DY, Boyd A, Ng AA, Chi C, Thomas L (2008) Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J : 1506-1564.
6. Anand IS, Florea VG (2001) High Output Cardiac Failure. Curr Treat Options Cardiovasc Med 3: 151-159.
7. Braunwald E, Grossman W (1992) Clinical aspects of heart failure. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine, 4th edn. Philadelphia: Saunders: 444.
8. Mehta PA, Dubrey SW (2009) High output heart failure. QJM 102: 235-241.
9. Sanghvi LM, Misra SN, Banerjee K (1960) Cardiac enlargement in chronic severe anemia. Circulation 22: 412-418.
10. Naito Y, Tsujino T, Matsumoto M, Sakoda T, Ohyanagi M, et al. (2009) Adaptive response of the heart to long-term anemia induced by iron deficiency. Am J Physiol Heart Circ Physiol 296: 585-593.
11. Metivier F, Marchais SJ, Guerin AP, Pannier B, London GM (2000) Pathophysiology of anaemia: focus on the heart and blood vessels. Nephrol Dial Transplant 15 Suppl 3: 14-18.
12. Hammoudi N, Charbonnier M, Levy P, Djebbar M, Stankovic Stojanovic K, et al. (2015) Left atrial volume is not an index of left ventricular diastolic dysfunction in patients with sickle cell anaemia. Arch Cardiovasc Dis 108: 156-162.
13. Adachi T (2008) Anemia in the field of obstetrics and gynecology. Nihon Rinsho 66: 548-552.
14. Mochizuki M, Kuwabara Y (1996) Standard Textbook? Obstetrics and Gynecology. Igaku-Shoin, Tokyo 107-113.
15. Beutler E, Waalen J (2006) The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration. Blood 107: 1747-1750.
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American society of echocardiography committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. J Am Soc Echocardiogr 2: 358-367.
17. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, et al. (2006) Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 47: 1018-1023.
18. Devereux RB, Reichek N (1977) Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 55: 613-618.
19. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, et al. (2007) Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation 116: 637-647.
20. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA (2002) Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 15: 167-184.
21. Lawler PR, Filion KB, Dourian T, Atallah R, Garfinkle M, et al. (2013) Anemia and mortality in acute coronary syndromes: a systematic review and meta-analysis. Am Heart J 165: 143-153.
22. Kengne AP, Czernichow S, Hamer M, Batty GD, Stamatakis E (2012) Anaemia, haemoglobin level and cause-specific mortality in people with and without diabetes. PLoS One 7: e41875.
23. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, et al. (2008) Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol 52: 818-827.
24. Klip IT, Postmus D, Voors AA, Brouwers FP, Gansevoort RT, et al. (2015) Hemoglobin levels and new-onset heart failure in the community. Am Heart J 169: 94-101.
25. Kim YR, Pyun WB, Shin GJ (2010) Relation of anemia to echocardiographically estimated left ventricular filling pressure in hypertensive patients over 50 year-old. J Cardiovasc Ultrasound 3: 86-90.
26. Uematsu M, Miyatake K, Tanaka N, Matsuda H, Sano A, et al. (1995) Myocardial velocity gradient as a new indicator of regional left ventricular contraction: detection by a two-dimensional tissue Doppler imaging technique. J Am Coll Cardiol 26: 217-223.

27. Palka P, Lange A, Fleming AD, Fenn LN, Bouki KP, et al. (1996) Age-related transmural peak mean velocities and peak velocity gradients by Doppler myocardial imaging in normal subjects. Eur Heart J 17: 940-950.
28. Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, et al. (2001) Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. Am J Cardiol 88: 53-58.
29. Derumeaux G, Mulder P, Richard V, Chagraoui A, Nafeh C, et al. (2002) Tissue Doppler imaging differentiates physiological from pathological pressure-overload left ventricular hypertrophy in rats. Circulation 105: 1602-1608.
30. Miyoshi H, Oishi Y, Mizuguchi Y, Iuchi A, Nagase N, et al. (2014) Influence of comorbid cardiovascular risk factors on left atrial-left ventricular interaction in asymptomatic patients: clinical application of two-dimensional speckle-tracking echocardiography. Int Heart J 2: 138-135.
31. Varat MA, Adolph RJ, Fowler NO (1972) Cardiovascular effects of anemia. Am Heart J 83: 415-426.
32. Graettinger JS, Parsons RL, Campbell JA (1963) A correlation of clinical and hemodynamic studies in patients with mild and severe anemia with and without congestive failure. Ann Intern Med 58: 617-626.
33. Sanghvi LM, Sharma VS, Mansharamani G (1963) Mechanism of oedema in chronic severe anaemia. Br Heart J 25: 89-96.
34. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC (1993) Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. Br Heart J 4: 357-562.
35. Petersen P, Kastrup J, Brinch K, Godtfredsen J, Boysen G (1987) Relation between left atrial dimension and duration of atrial fibrillation. Am J Cardiol 60: 382-384.
36. D'Ascia SL, D'Ascia C, Marino V, Lombardi A, Santulli R, et al. (2011) Cardiac resynchronisation therapy response predicts occurrence of atrial fibrillation in non-ischaemic dilated cardiomyopathy. Int J Clin Pract 65: 1149-1155.
37. Santulli G, D'ascia SL, D'ascia C (2012) Development of atrial fibrillation in recipients of cardiac resynchronization therapy: the role of atrial reverse remodelling. Can J Cardiol 28: 245.