Check for updates

Original Article

Phlebology

Phlebology
0(0) 1–6
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0268355521994997
journals.sagepub.com/home/phl
SAGE

Association between lower extremity venous insufficiency and duration of atrial fibrillation

Zeynep Yapan Emren[1], Sadık Volkan Emren[2], Fatih Ada[3], Sefa Erdi Ömür[3] and Ferhat Dindaş[3]

Abstract

Objective: Physiologic studies have shown that atrium has an active role in venous blood return from lower extremity. In this context we investigated the association between AF and chronic venous disease (CVD).

Methods: In this observational study we included 392 AF patients which were divided into two groups (chronic AF, 218 (56%)) and non-chronic. AF, 174 (44%)). These two groups were compared in terms of CVD after matching conventional risk factors for CVD.

Results: CEAP classification was different between chronic and non-chronic patients (C0–C2: 72% vs 47%; C3–C6: 28% vs 53% <0.001). Chronic AF patients had also higher rate of venous reflux on Doppler ultrasound (38% vs 16% $P < 0.05$). There was a correlation between AF duration, right atrial volume index and CEAP classification respectively (rho:0.314 $p < 0.001$), (rho:0.258, $p < 0.001$).

Conclusion: Prevalence of CVD is higher in patients with chronic AF. In addition, atrial volume is directly correlated with CVD.

Keywords

Atrial fibrillation, venous disease, atrium

Introduction

From a historical view atrium has been considered to have only pump function which contributed to stroke volume. However, it has been demonstrated that atrium has three functions including pump, reservoir and conduit functions which have a hemodynamic importance for cardiac function.[1] The complex function of atrium is deemed to contribute venous return from peripheral veins. During atrial diastolic phase negative pressure in atrium suck the venous blood from vena cava which leads to opening of venous valves in lower extremities. Furthermore, it has recently shown that opening and closing of venous valves are synchronous with cardiac cycles.[2]

There is no doubt that - venous valves are essential in conveying venous blood from lower extremity to heart.[3] Dysfunction in lower extremity venous valves cause venous insufficiency. The physiologic interaction between atrial and venous function brings a question that whether loss of atrial function during AF lead to impair venous valve function. During atrial fibrillation in addition to rhythm disturbances extensive structural and functional abnormalities also occur.[4] Atrium not only loss of pump function but also reservoir and conduit function with the duration of atrial fibrillation.[5] Although both AF and venous insufficiency commonly encountered in clinical practice and prevalence of these diseases increase with aging. It is not clearly known whether chronic AF may link to CVD. In this study

[1]Department of Cardiology, Çiğli Training and Education Hospital, Izmir, Turkey
[2]Department of Cardiology, Izmir Katip Celebi University School of Medicine, Izmir, Turkey
[3]Department of Cardiology, Cumhuriyet University School of Medicine, Sivas, Turkey

Corresponding author:
Sadık Volkan Emren, Department of Cardiology, Izmir Katip Celebi University School of Medicine, Izmir 35160, Turkey.
Email: vemren@hotmail.com

we searched the association between CVD and duration of atrial fibrillation.

Methods

In this observational study, we included 392 patients over 18 years old with a documented AF either on electrocardiography or rhythm Holter monitoring between 2017–2019. Patients were divided into two groups based on the duration of AF. Patients having AF lasting more than 12 months consisting patients with long lasting and permanent AF were included in one group (group 1), those having AF lasting less than 12 months including paroxysmal or persistent AF were included in another group (group 2).[6] All the patients were examined by an experienced clinician in terms of venous disease severity. To decide the venous disease distribution, investigators used Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification.[7] According to CEAP classification patients were given 0 to 6 based on the disease distribution using only clinical (C) parameter. CEAP venous disease classification is graded as follows C0: no visible sign of venous disease, C1: Telangiectasia or reticular veins, C2: Varicose veins, C3: Edema, C4: Changes in skin (pigmentation or eczema, lipodermatosclerosis or atrophie blanche) and subcutaneous tissue edema C5: Healed ulcer, C6: Active ulcer. The two AF groups were matched in terms of conventional risk factors for CVD such as gender, BMI, family history CVI, sedentary lifestyle, sitting occupation and age.

Patients with hypo and hyperthyroidism, cancer, heart failure with reduced or preserved ejection fraction, moderate to severe valvular disease, prosthetic valve implantation, chronic kidney disease, previous deep vein thrombosis or pulmonary embolism, history of pulmonary hypertension, lymphedema, hypoalbuminemia and lower extremity fracture were excluded from study. Those patients using anticoagulant treatment less than 14 days for deep vein prophylaxis or anything else without having venous, cardiac or thrombophilia were included. If the AF patients were need to use anticoagulation for the prophylaxis of ischemic or peripheral arterial embolism based on the risk scores, they were included as well. However those needing long term anticoagulant therapy due to chronic venous disease, mechanical heart valve, coagulopathy were excluded.

AF was defined as an irregular rhythm with an indistinct rapid oscillations or f waves instead of p waves lasting more than 30 s on Holter monitoring or 10 s on electrocardiography tracing.[8] Body mass index (BMI) was calculated as weight divided to square of height (kg/m^2). Hypertension was present if the patient was on hypertension treatment or newly diagnosed hypertension as the consecutive blood measurement over 140/90 mmHg. If patient was on diabetes treatment or fasting blood glucose over 126 mg/dl or HbA1c level over 6.5 gr/dl was defined as diabetes. Patients were categorized as with peripheral disease if an ankle brachial index was lower than 0.9 or there was an atherosclerotic stenosis at the carotid, vertebral, upper extremity, mesenteric, renal, or lower extremity arteries with doppler ultrasonography, computed tomography, magnetic resonance angiography, or duplex subtraction angiography.[9] Stroke was determined based on past stroke or central cerebral damage due to cerebral infarct, intracerebral or subarachnoid hemorrhage. Coronary artery disease was defined if %50 or more stenosis was present in any of coronary territory.[10] Chronic obstructive pulmonary disease was determined with spirometry in patients with cough, sputum, and dyspnea lasting longer than 3 months.[11] This study was approved by local ethical committee. A written informed consent was attained from all participants.

All patient underwent echocardiographic examination to asses ejection fraction and valvular severity and to rule out cardiac diseases associated with lower extremity edema. Echocardiographic examinations were performed by using IE33 (Philips Company) instruments, with 1.5–4.0 MHz transducer. Images and doppler measurements were obtained according to American Society of Echocardiography and European Association of Cardiovascular Imaging (EACVI) guidelines.[12] Left atrial volume and right atrial volume was calculated by using Simpson method from apical four chamber view. To obtain left atrial volume index (LAVi) and right atrial volume index (RAVi), left and right volume was divided to body surface area.

Duplex ultrasound imaging of lower extremity venous system were performed by an experienced radiologist, who was blinded to the presence of AF using the HI VISION Ascendus system (HITACHI ALOKA Medical, Tokyo, Japan) with a high-frequency linear surface probe (7.5–10MHz). Bilateral major venous segments of the lower extremity were examined by the combination of B mode gray scale and color duplex ultrasound. In examination of venous insufficiency, vessels were examined both spontaneously, manual compression and during a Valsalva maneuver. Venous reflux was defined as reflux time of >0.5 seconds for superficial veins and 1.0 second for deep veins.[13]

Statistical analysis

Statistical analyses were conducted using SPSS software version 23.0. Variables were analyzed using

visual and analytical methods to determine normal distribution. Mean and standard deviation and median and interquartile range was used for descriptive statistics. Chi-square test was used to compare nominal and categorical variables. Parametric and non-parametric data was compared using independent sample t-test and Man Whitney U test respectively. Correlation between CEAP classification and left and right atrial volumes and correlation between AF duration and CEAP classification was determined using Pearson correlation analysis. Two sided P-value <0.05 was considered statistically significant.

Results

Among patients 218 (56%) patients had an over one-year duration of AF either chronic or long-standing AF (group 1) while 174 (44%) patients had less than one-year duration of AF either paroxysmal AF (98, 25%) or persistent AF (76, 19%) (group 2). Mean duration of AF in group 1 and 2 was 1971 ± 1825 and 44 ± 72 days respectively. HT, DM, CAD and stroke rate was higher in group 1. With regard to echocardiographic parameters LAVi and RAVi was higher in group1 whereas group 2 patients had higher ejection fraction ($p < 0.05$) Table 1.

Group 1 patients had also higher rate of venous reflux on Doppler ultrasound examination compared to group1 patients (38% vs 16% $P < 0.05$). CEAP classification was different between chronic and non-chronic AF patients (C0–C2: 72% vs 47% $P < 0.001$; C3–C6: 28% vs 53% $P < 0.001$). Figure 1 showed the detailed distribution of CEAP classification according to AF duration.

There was a moderate correlation between AF duration and venous disease distribution based on the CEAP classification (rho:0.314 $p < 0.001$). In addition, left atrial volume and right atrial volume was also correlated with CEAP score (rho:0.208, $p = 0.003$ and

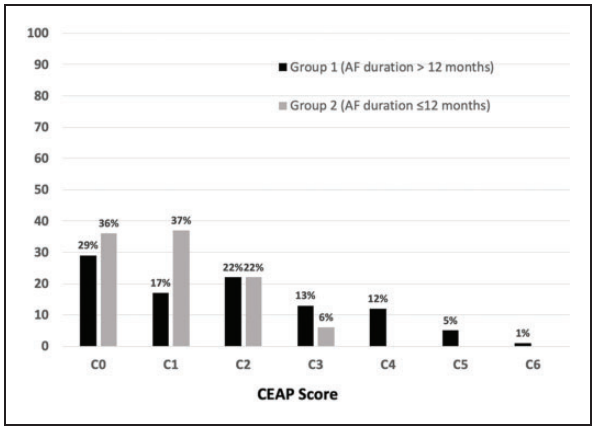

Figure 1. Distribution of CEAP score according to duration of atrial fibrillation.

Table 1. Clinical end echocardiographic variables among patients.

	Group 1 (AF lasting >12 months) N:218	Group 2 (AF lasting ≤12 months) N:174	*P*
Age, years mean ± sd	68.2 + 8.7	67.7 + 10.4	0.630
Female n (%)	93 (43%)	88 (51%)	0.127
BMI kg/m^2 mean ± sd	31.2 + 5.2	30 + 6.7	0.063
Sitting Occupation n (%)	177 (81%)	136 (78%)	0.527
Hypertension n (%)	192 (88%)	101 (58%)	<0.001
Diabetes Mellitus n (%)	99 (45%)	60 (34%)	0.030
Coronary Artery Disease n (%)	138 (63%)	83 (48%)	0.002
Vascular disease n (%)	64 (29%)	66 (38%)	0.084
Stroke n (%)	22 (10%)	4 (2%)	0.002
Cancer n (%)	4 (2%)	2 (1%)	0.697
Smoking n (%)	18 (8%)	12 (7%)	0.704
Sedentary lifestyle n (%)	54 (25%)	45 (26%)	0.816
Family history of CVI n (%)	36 (16%)	24 (14%)	0.483
Pregnancy history n (%)	93 (43%)	78 (45%)	0.683
Ejection Fraction (%)	55,2 + 1,89	56,4 + 2,78	<0.001
LAVi ml/m^2 mean ± sd	46.1 + 4,6	43,8 + 3,4	<0.001
RAVi ml/m^2 mean ± sd	46.1 ± 4.6	43.8 ± 3.4	<0.001
Venous reflux on doppler ultrasound n(%)	83 (38%)	28 (16%)	<0.001
CEAP classification			
C0–C2	102 (47%)	126 (72%)	<0.001
C3–C6	116 (53%)	48 (28%)	

BMI: Body mass index; CEAP: Clinical-Etiology-Anatomy-Pathophysiology; CVI: Chronic venous insufficiency; LAVi: left atrial volume index; RAVi: right atrial volme index; IQR: Interquartile Range; N: number.

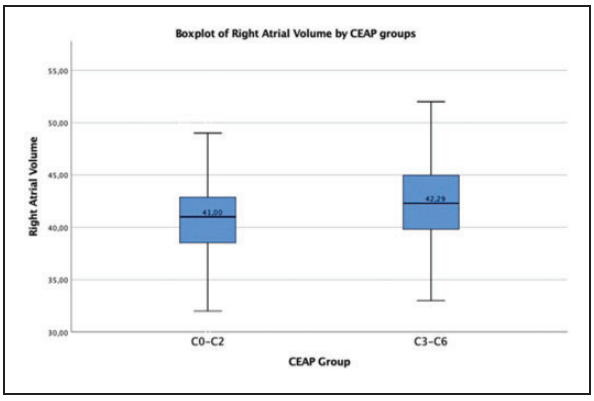

Figure 2. Right atrial volume index regarding CEAP classification.

rho:0.2258, $p < 0.001$ respectively). When the patients were divided into two groups regarding CEAP score (C0-2 vs C3-6) RAVi was higher in C3-6 compared to C0-2 (41 ± 4.5 vs 42.4 ± 4.6 $P = 0.006$) (Figure 2).

Discussion

Two common cardiovascular diseases in clinical practice; VI and AF have always been considerate as a completely different entity thus far. To our knowledge this is the first study investigating the association between AF and CVD. According to our study, prevalence of CVD was higher in chronic or long-standing AF patients. In addition, severity of CVD has a strong correlation with AF duration.

CVD describes the term of incompetent valves and higher venous pressure in lower extremities.[14] CVD consists of CVI and varicose veins. Prevalence of CVI and varicose veins vary from 1 to 40% and 1 to 73% respectively.[15] Prevalence of CVD increases in elder population with a prevalence of 36.7% (14.6% in males and 22.1% in females) over 60 years old in Turkish population.[16] In our study rate of CVI is comparable the literature. There are some well-known risk factors for CVI such as age, female gender, smoking, obesity, inheritance, pregnancy and previous leg injury or operation.[17] Also occupational and environmental factors requiring prolong sitting or sitting position are associated with CVI.[18,19] Beside these conventional risk factors some cardiac mechanical and functional abnormalities has shown to be related to CVI. The two hallmark mechanisms in CVI are impaired vein valves and increased central vein pressure. Increase of right atrial pressure in some cardiac disease conveys to pressure to central veins. In this regard increase of pressure in central veins reflects to peripheral veins that forces the valves and lead to VI. Previous studies demonstrated that the rate of VI was higher in patients with chronic pulmonary obstructive disease and pulmonary hypertension. VI was correlated with the severity of pulmonary arterial pressure.[20,21] Besides, Aldemir et al showed increase of venous insufficiency in patients with primary pulmonary hypertension despite having preserved right ventricle function.[22]

Apart from anatomical factors, there are several physiological mechanisms affecting venous return. Abdominal and thoracic pressure changes are determinative of venous valve opening. During expiration, with the decrease of abdominal pressure blood return increases by the opening of venous valves and vice versa.[23] The relation between atrial mechanics and venous return has not been elucidated. For a long period of time atrium has been considered to have a passive role for venous return. However recent studies have shown that atrium has an active role for venous return from peripheral veins. In a study by Rai et al. motions of peripheral venous valves are synchronous to cardiac cycle. During atrial diastole venous valves open whereas venous valves close simultaneously with the atrial systole.[2] Furthermore, another experimental study demonstrated that negative pressure during atrial diastole pose a suction effect on venous system which lead to open venous valves and transfer venous blood to heart. On the other hand, loss of the negative pressure during atrial systole and force of gravity prompts to close lower extremity venous valves to avoid reflux.[24] In healthy individual's atrium has three major hemodynamic functions: reservoir, conduit and booster pump. Reservoir function describes the expansion of atrium due to venous filling during left ventricle systole. Conduit function represents blood flow from atrium at early phase of left ventricle diastole. Booster-pump is defined as the atrial kicking at late phase of left ventricle diastole which accounts for 15% to 30% of ventricle filling.[25] In case AF, atrial functions are deteriorated. After initiation of AF, reservoir function of left and right atrium has reduced due to impaired diastolic atrial compliance.[26] As the AF continues progressive functional changes are accompanied with the increase of fibrosis.[27] Among AF patients, patients with persistent AF have more structural and functional impairment compared to those with paroxysmal AF.[28] Furthermore, patients with persistent AF have more deteriorated atrial reservoir, conduit, and booster pump functions compared to those with paroxysmal AF as demonstrated by cardiac magnetic resonance imaging.[27]

In this study prevalence of long standing or permanent AF is about 50% consistent with the previous studies.[29] The findings of our study suggest that the loss of atrial reservoir and conduit function due to impaired atrial diastolic distensibility in long lasting AF hampers venous blood return from lower

extremities. Moreover, irregular rhythm in AF may cause the irregularity of valve motion in peripheral veins. As the AF progresses for a long period of time these functional and structural changes give rise to VI.

Study limitations:

In this study we used two-dimensional echocardiography to calculate left and right atrial volume. However, it might be more accurate to obtain these measures by three-dimensional echocardiography or cardiac magnetic resonance imaging. CVD is analyzed only by the C parameter of the CEAP classification. Although this study showed an association between AF and CVD. There need to be a prospective cohort studies to delineate to cause effect relationship between this two-common disease.

Conclusion

This is a complementary study of previous physiological studies which have demonstrated the role of atrial function on peripheral venous return. Based on this study findings, there is an association between AF duration and CVD. Furthermore, increment in atrial volume is related to venous disease severity

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

The ethics committee of Sivas Cumhuriyet University approved this study (REC number: 2020-02/49).

Guarantor

None.

Contributorship

ZYE and SVE researched literature and conceived the study. FA and SEÖ was involved in protocol development, gaining ethical approval. FD was involved in patient recruitment and data analysis. SVE wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ORCID iDs

Sadık Volkan Emren https://orcid.org/0000-0002-7652-1123

Fatih Ada https://orcid.org/0000-0002-6953-5906

Acknowledgements

None.

References

1. Grant C, Bunnell IL and Greene DG. The reservoir function of the left atrium during ventricular systole. An angiocardiographic study of atrial stroke volume and work. *Am J Med* 1964; 37: 36–43.
2. Rai DB. The motion of venous valves in humans – a new discovery. *Int J Angiol* 2006; 15: 141–145.
3. Tansey EA, Montgomery LEA, Quinn JG, et al. Understanding basic vein physiology and venous blood pressure through simple physical assessments. *Adv Physiol Educ* 2019; 43: 423–429.
4. Morillo CA, Klein GJ, Jones DL, et al. Chronic rapid atrial pacing: Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* 1995; 91: 1588–1595.
5. Wang Z, Tan H, Zhong M, et al. Strain rate imaging for noninvasive functional quantification of the left atrium in hypertensive patients with paroxysmal atrial fibrillation. *Cardiology* 2008; 109: 15–24.
6. Kirchhof P, Benussi S, Kotecha D, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Kardiol Pol* 2016; 74: 1359–1469.
7. Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004; 40: 1248–1252.
8. Kirchhof P, Bax J, Blomstrom-Lundquist C, et al. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. *Eur Heart J* 2009; 30: 860–885.
9. Aboyans V, Ricco J-B, Bartelink M-L, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS) document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal. *Eur Heart J* 2018; 39: 763–816.
10. Members TF, Montalescot G, Sechtem U, et al. ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
11. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017; 195: 557–582.
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16: 233–271.
13. Coleridge-Smith P, Labropoulos N, Partsch H, et al. Duplex ultrasound investigation of the veins in chronic

venous disease of the lower limbs–UIP consensus document. Part I: basic principles. *Phlebology* 2006; 21: 158–167.
14. Raffetto JD and Eberhardt RT. Chronic venous disorders: general considerations. *Rutherford's Vasc Surg* 2014; 1: 842–857.e4.
15. Beebe-Dimmer JL, Pfeifer JR, Engle JS, et al. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol* 2005; 15: 175–184.
16. Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO study. *Neurology* 2000; 54: 1064–1068.
17. Scott TE, LaMorte WW, Gorin DR, et al. Risk factors for chronic venous insufficiency: a dual case-control study. *J Vasc Surg* 1995; 22: 622–628.
18. Phillips AM. The influence of environmental factors in chronic bronchitis. *J Gnathol* 1963; 26: 468–475.
19. Lacroix P, Aboyans V, Preux PM, et al. Epidemiology of venous insufficiency in an occupational population. *Int Angiol* 2003; 22: 172–176.
20. Erdogmus B, Annakkaya AN, Yazici B, et al. The prevalence of venous insufficiency in patients with chronic obstructive pulmonary disease evaluated by color duplex ultrasonography. *Wien Klin Wochenschr* 2006; 118: 549–553.
21. Doepp F, Bähr D, John M, et al. Internal jugular vein valve incompetence in COPD and primary pulmonary hypertension. *J Clin Ultrasound* 2008; 36: 480–484.
22. Aldemir M, Emren SV, Balçık Ç, et al. Primary pulmonary arterial hypertension with preserved right ventricular function leads to lower extremity venous insufficiency. *Vascular* 2018; 26: 183–188.
23. Normahani P, Shalhoub J and Narayanan S. Repurposing the systemic venous return model for conceptualisation of chronic venous insufficiency and its management. *Phlebology* 2020; 35: 749–751.
24. Rai D. The dynamic function of the atrial diastole of the heart and motion of venous valves in humans. *Int J Angiol* 2013; 22: 37–44.
25. Mehrzad R, Rajab M and Spodick DH. The three integrated phases of left atrial macrophysiology and their interactions. *Int J Mol Sci* 2014; 15: 15146–15160.
26. Leistad E, Christensen G and Ilebekk A. Effects of atrial fibrillation on left and right atrial dimensions, pressures, and compliances. *Am J Physiol - Hear Circ Physiol* 1993; 264: 1093–1097.
27. Kuppahally SS, Akoum N, Burgon NS, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: Relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging* 2010; 3: 231–239.
28. Schneider C, Malisius R, Krause K, et al. Strain rate imaging for functional quantification of the left atrium: Atrial deformation predicts the maintenance of sinus rhythm after catheter ablation of atrial fibrillation. *Eur Heart J* 2008; 29: 1397–1409.
29. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014; 6: 213–220.