European Heart Journal Supplements (2017) **19** (Supplement B), B35–B39
The Heart of the Matter
doi:10.1093/eurheartj/suw063

Arterial stiffness and atrial fibrillation: a new and intriguing relationship

Stefano Fumagalli[1,*], Serena Boni[1], Simone Pupo[1], Ilaria Giannini[1], Anna T. Roberts[1], Claudia Di Serio[1], Alessandra Scardia[1], Carlo Fumagalli[1], Francesca Tarantini[1], and Niccolò Marchionni[1]

[1]Department of Experimental and Clinical Medicine, University of Florence and AOU Careggi, Geriatric Intensive Care Unit and Research Unit of Medicine of Aging, Viale Pieraccini 6, 50139 Florence, Italy

KEYWORDS
Atrial fibrillation;
Arterial stiffness;
CAVI;
Elderly

Atrial fibrillation (AF) and arterial stiffness (AS) greatly increase with age. In elderly patients, AF is often a marker of frailty and is frequently associated with important diseases and complications, such as stroke, heart failure, dementia, chronic obstructive pulmonary disease, pneumonia, acute myocardial infarction and urinary infections. Little is known about the influence of vascular properties on AF. In a first experiment, to verify the existence of a possible association between arrhythmia and vascular properties, we evaluated the Cardio-Ankle Vascular Index (CAVI), a measure of AS, in 33 patients (age: 73 ± 12 years) at 5 h from effective external cardioversion (ECV) of persistent AF. We found that CAVI was a direct independent predictor of left atrial diameter. This association did not exist in a healthy control population ($N = 18$). In a second experiment, conducted in 31 patients (age: 78 ± 7 years), we studied the possible association between AS and AF after ECV of the arrhythmia. At follow-up (on average at 6 months), we observed the arrhythmia in 48% of cases and found that its presence was directly related to CAVI values and CHA_2DS_2-VASc score.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in elderly people.[1] The prevalence of AF greatly increases after 60 years of age, being higher than 20% in subjects $\geq$85 years.[2] In a population of 'oldest old' subjects evaluated by general practitioners in a large British community, the prevalence of the arrhythmia was similar to that observed for chronic obstructive pulmonary disease, heart failure (HF), and osteoporosis.[3] This relevant epidemiological trend is due to the aging process of the cardiovascular system and to the increase of comorbidities. In fact, in elderly patients, AF is often associated with HF, pneumonia, acute myocardial infarction and urinary infections,[4] and it can be considered a marker of frailty.[5] AF can also determine severe complications, such as stroke[6] and dementia.[7] Interestingly, epidemiological data show that old patients with AF have a median of six different diagnoses, among which hypertension, coronary artery disease, hyperlipidemia, diabetes mellitus, and chronic renal failure have a significant association with atherosclerosis.[8] Pulse wave velocity, a measure of arterial stiffness (AS), starts to increase after 50 years of age following a cubic trend.[9] Contrasting evidence exists about the interaction between vascular properties and AF development and maintenance. During a follow-up lasting 12 years, the Framingham Heart Study demonstrated that the incidence of AF progressively grew from 5.6 to 23.3% mirroring the increase of basal pulse pressure from $\leq$40 to >61 mmHg.[10] Also in the hypertensive patients enrolled in the LIFE (the Losartan Intervention For Endpoint reduction in hypertension) study, new cases of arrhythmia were more frequently observed in those with higher pulse pressure values.[11] In the ARAPACIS (the Atrial Fibrillation Registry for Ankle-Brachial Index Prevalence Assessment Collaborative Italian

*Corresponding author. Tel: +39 055 2758135, Fax: +39 055 7946297, Email: fumadue@tin.it

Study) study the prevalence of subjects with ankle-brachial index (ABI) values <0.90 increased from 18 to 24% with the progressive growth of arrhythmia burden (i.e. from paroxysmal to permanent forms of AF).[12] However, more recently, the parallel analysis of data from the ARIC (Atherosclerosis Risk in Communities), the MESA (Multi-Ethnic Study of Atherosclerosis) and the Rotterdam studies revealed that carotid intima-media thickness and AS predict AF development, albeit with only a modest statistical power.[13]

On this basis, we conducted two consecutive studies.[14,15] The first was aimed at determining the clinical factors correlated to AS in a population of patients who underwent external cardioversion (ECV) of the persistent forms of the arrhythmia. Then, we verified if an association exists between AS, left atrial and left ventricular dimensions. The existence of this link could justify the incidence of relapses after sinus rhythm restoration.[14] With the second study, we aimed at evaluating in a new population of aged patients if AS can be related to sinus rhythm maintenance after ECV.[15] For this purpose, we took into consideration also interleukin-6 (IL-6) concentration, which revealed itself to be associated with both AS and AF relapses.[15,16]

Methods

We enrolled all consecutive patients who underwent ECV of persistent AF between January and June 2013 in the first study, and between March and December 2015 in the second study. The procedure was electively performed in the morning, in a day-hospital setting according to current guidelines.[6] In particular, after at least 3 weeks of oral anticoagulation, all patients in fasting conditions received i.v. propofol at a dose of about 1 mg/Kg of body weight to induce general anesthesia. To restore sinus rhythm, a Multipulse Biowave® synchronized biphasic shock was delivered through adhesive pads placed in antero-posterior or antero-lateral position with progressively increasing energies in case of failure of the preceding attempt (starting value: 150 J).[17] ECV was interrupted after three consecutive ineffective shocks. In this case, based on individual clinical conditions, a decision was taken about scheduling a new procedure after adjustment of anti-arrhythmic treatment or pursuing a rate-control strategy.[6]

A trans-thoracic echocardiogram using MyLab™30Gold Cardiovascular (ESAOTE SpA, Florence, Italy) was obtained and digitally recorded after sinus rhythm restoration in all patients immediately before the discharge from the day-hospital, at 5 h from ECV. At the same time, the 'cardio-ankle vascular stiffness index' (CAVI), an index of AS, independent of actual arterial blood pressure values, was determined using a dedicated device (VaSera VS-1500N, Fukuda Denshi, Japan).[18] Patients had to be lying down for at least 20 min before CAVI was measured.

During the continuous recording of EKG and heart sounds, right and left upper and lower extremity arterial pressure was obtained with the oscillometric method. Pulse wave velocity (PWV) was calculated dividing the distance from the aortic valve to the ankle by the sum of two time intervals [(1) aortic valve closing sound–notch of the brachial pulse wave; (2) rise of the brachial pulse wave–rise of the ankle pulse wave]. CAVI was then computed using the following equation:

$$\mathrm{CAVI} = \mathrm{a} \times [(2\rho/\Delta P) \times \ln(Ps/Pd) \times \mathrm{PWV}^2] + \mathrm{b}$$

where Ps/Pd are systolic/diastolic pressures, ΔP is 'Ps-Pd', ρ is blood density, and a/b are constants.[18]

We decided to evaluate CAVI after ECV to avoid any possible bias associated to irregular RR intervals. The complex mechanisms of atrial reverse remodelling should have not significantly changed left atrium properties after such a short period from sinus rhythm restoration. No exclusion criteria were defined.

At baseline, before ECV, a venous blood sample was drawn in 27 out of 31 (87.1%) patients enrolled in the second study to determine IL-6 concentration with commercially available ELISA kits (R&D Systems, Inc.; Minneapolis, MN, USA).

At the follow-up (mean length: 179 days, 33th-66th percentile: 104–252 days) evaluation, we had no dropouts; arterial blood pressure, EKG and main clinical events were recorded for all subjects.

In addition, to verify the existence of a specific arrhythmia-related behaviour, echocardiographic, and CAVI data of a healthy control population–patients from our outpatient clinic–were compared with those with AF enrolled in the first study.

Statistical analysis

Continuous variables are expressed as mean values (± standard deviation) and categorical variables as raw data and percentages. Student's *t*-test and analysis of variance, with related non-parametric tests in the case of a not normal distribution, were used to verify the existence of differences in continuous variables between groups of patients. Chi-square test and associated tests assessed the differences in distribution of discrete variables. Multivariate linear regression analysis models and multivariate logistic regression analysis models were used to define the predictors of CAVI and AF relapses, respectively. Two-tailed P values <0.05 were considered to indicate statistical significance. For all the analyses, we used SPSS for Windows, version 22 and 23.

Results

First study population

In the first study, aimed at exploring the relationship between AF and AS,[14] we enrolled 33 patients. Mean age was 73 ± 12 years; 85% were men, body mass index (BMI) was 27.0 ± 5.0 Kg/m^2. Prevalence of hypertension, coronary artery disease and HF were 67, 18, and 33%, respectively. The most frequently observed valvular disease was mitral regurgitation (51%). Diabetic subjects were 12% of the whole population. Upstream therapy of AF was widely adopted (ACE-I/ARB: 82%; beta-blockers: 76%). The values of systolic/diastolic arterial pressure were 140 ± 16/85 ± 11 mmHg. Left atrial diameter (LAD), interventricular septum, and left ventricular end-diastolic diameter (LVDD)

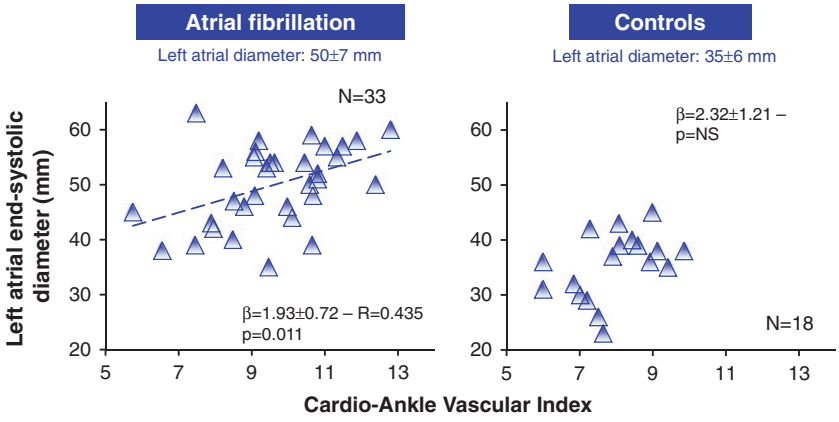

Figure 1 Correlation between 'cardio-ankle vascular stiffness index' (CAVI) and left atrial end-systolic diameter in atrial fibrillation patients (left) and in a control population (right).

were 50 ± 7 mm, 10 ± 1 mm, and 56 ± 9 mm, respectively; left ventricular ejection fraction (LVEF) was 56 ± 14%. The ABI values were normal, with no differences between right and left side measures (right: 1.10 ± 0.15 vs. left: 1.07 ± 0.12, $P = 0.222$). Also CAVI did not differ by side of evaluation (right: 9.6 ± 1.6 vs. left: 9.6 ± 1.6, $P = 0.777$).

CAVI predictors in AF patients

When carrying out univariate analysis, CAVI was significantly associated with age ($P = 0.025$), BMI ($\beta = -0.1 \pm 0.1$, $P = 0.037$), AF length ≤3 months (yes: 10.1 ± 1.5 vs. no: 8.9 ± 1.5, $P = 0.031$), and mitral regurgitation (yes: 10.3 ± 1.4 vs. no: 8.9 ± 1.6, $P = 0.012$). The presence of diabetes, hypertension, coronary artery disease and HF did not correlate at all with AS; CAVI values did not differ by AF causes ($P = 0.657$). Moreover, AS was not associated with interventricular septum thickness, LVDD, and LVEF. However, a direct correlation existed between CAVI and LAD ($P = 0.011$) (*Figure 1*). In multivariate analysis (overall $R = 0.538$, $P = 0.006$), age, with a 0.5 index increase every 10 years of age ($\beta = 0.5 \pm 0.2$, $P = 0.018$), and an AF length ≤3 months ($\beta = 1.2 \pm 0.5$, $P = 0.018$) predicted CAVI.

LAD predictors in AF patients

In our series of patients, apart from CAVI, LAD was directly correlated only with interventricular septum thickness ($P = 0.030$). No association existed with age, gender, BMI, comorbid conditions, and drug therapy. A multivariate model ($R = 0.574$, $P = 0.002$) confirmed that both CAVI ($\beta = 1.9 \pm 0.7$, $P = 0.007$) and interventricular septum thickness ($\beta = 1.8 \pm 0.7$, $P = 0.018$) were determinants of LAD.

Control patients

Our control population was represented by 18 subjects younger than AF patients (51 ± 14 years; men: 37%; both *P*-values <0.001 vs. AF population). CAVI was significantly lower than that observed in arrhythmic patients (7.7 ± 1.2, $P < 0.001$). Also in this case, a direct association existed between age and AS ($\beta = 0.6 \pm 0.1$ per 10 years of age, $P < 0.001$). Importantly, no correlation existed between CAVI and LAD (*Figure 1*).

Second study population

In the second study, we assessed the effects of AS on AF relapse after ECV,[15] enrolling 31 patients (mean age: 78 ± 7 years), of which 67.7% were men. The prevalence of hypertension was high (87%), with a proportion of coronary artery disease, chronic heart failure and diabetes (29.1, 48.4, and 25.8%, respectively) greater than that observed in the previous study. CHA_2DS_2-VASc score (mean: 4.1 ± 1.6) and CAVI were high (mean: 9.9 ± 1.6). Left ventricular systolic performance was preserved (LVEF: 61 ± 9%) and LAD higher than normal (mean: 52 ± 4 mm). Also in this case, upstream therapy was widely adopted (ACE-I/ARB: 87%; beta-blockers: 71%). Amiodarone was the most frequently prescribed anti-arrhythmic agent (45%). In 48% of cases, AF had a length ≤2 months.

Efficacy of ECV and clinical predictors of AF at follow-up

ECV restored sinus rhythm in 28 patients (90%). At follow-up AF was observed in 48% of cases.

In univariate analysis, patients with AF were older (81 ± 4 vs. 74 ± 8, $P = 0.005$), with a higher prevalence of diabetes (47 vs. 6%, $P = 0.015$), higher baseline systolic arterial pressure (141 ± 20 vs. 127 ± 20, $P = 0.036$) and greater CHA_2DS_2-VASc score (5.0 ± 1.4 vs. 3.3 ± 1.4, $P = 0.003$). Also AS, as measured by CAVI, was significantly increased (*Figure 2*). The prevalence of an AF length ≥2 months was more frequently found in those with arrhythmia (80 vs. 25%, $P = 0.004$). Interestingly, at least in the medium term, amiodarone exerted a protective role on AF relapse (Amiodarone use-AF: 20% vs. sinus rhythm: 69%, $P = 0.011$). Increasing IL-6 concentrations corresponded to increasing values of CAVI (*Figure 2*) and CHA_2DS_2-VASc score, and to higher proportions of patients with AF at follow-up (*Figure 3*).

A multivariate logistic regression analysis model (overall predictivity: 83.7%) showed that, at follow-up, AF was directly associated to CHA_2DS_2-VASc score ($OR_{\text{per 1 point difference}} = 2.65$, 95%CI = 1.01–6.94; $P = 0.048$) and to CAVI

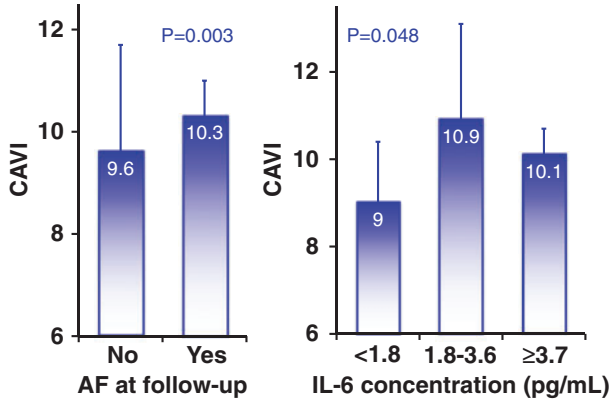

Figure 2 Cardio-ankle vascular stiffness index (CAVI) in patients with and without atrial fibrillation at follow-up (left) and by Interleukin-6 (IL-6) concentration (right). CAVI is higher in the two groups of subjects with higher IL-6 levels.

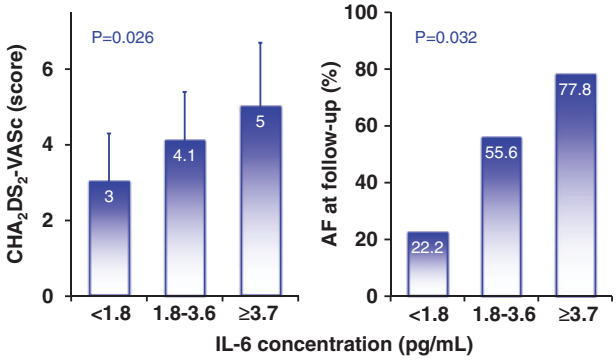

Figure 3 CHA_2DS_2-VASc score (left) and proportion of patients with atrial fibrillation (AF) at follow-up (right) by Interleukin-6 (IL-6) concentration. In both cases, a direct relation is evident.

($OR_{\text{per 1 unit difference}} = 2.31$, 95%CI = 1.01-5.25; $P = 0.046$). Amiodarone use was found to be inversely related to AF relapse ($OR_{\text{Yes vs. No}} = 0.05$, 95%CI = 0.01-0.70; $P = 0.027$).

Discussion

AS, evaluated with CAVI, is directly associated with age also in cases of persistent AF. Interestingly, in our patients, CAVI, together with interventricular septum thickness, is an independent predictor of left atrial dimensions. This correlation was not found in a population of control subjects.

As previously mentioned, in a large cohort of patients with non valvular AF, the prevalence of vascular disease, condition assigned for ABI values ≤ 0.90, was high and equal to 21%.[12] Our experience extends this result, demonstrating that AS can exert a significant influence on LAD. A possible explanation of this link could be the synergy between left atrium and left ventricle, with the degree of atrial dilation expressing the severity of ventricular diastolic dysfunction.[19] However, in our multivariate model, CAVI remained an independent predictor of LAD even after adjustment for interventricular septum thickness, an expression of impaired ventricular relaxation.[20] The presence of mitral regurgitation could represent a possible explanation of the association between AS and atrial dimensions. Recently, it was found that the loss of arterial distensibility could stimulate inflammation and vascular smooth muscle cell contraction in atrial tissues.[21] More in detail, it was observed that several comorbid conditions could induce an inflammatory-mediated coronary micro-vascular dysfunction, able to accelerate the processes leading to myocardial stiffness development.[22] In particular, the endothelial induced production of Transforming Growth Factor-β, with the consequent fibroblast-dependent collagen release, and the increased hypertrophy and resting tension of cardiomyocytes, secondary to the reduced activity of protein kinase G, could play a significant part in the process linking AS, left ventricular diastolic dysfunction and left atrial dimensions.[22] A key-role in the promotion of this cascade of events could be exerted by several mediators, among which one of the most important is IL-6.[22] In this regard, the close link between AF burden and the degree of systemic inflammation is well known.[23] Furthermore, in the series of patients enrolled in our second study we showed the existence of a linear relationship between IL-6 concentrations and the CHA_2DS_2-VASc score and, importantly, the proportion of AF at follow-up. These considerations help to explain the direct relationship between AS and the presence of arrhythmia at follow-up, which is arguably our most interesting result. For each one-unit increase of CAVI, our measure of AS, the risk of finding AF at the control visit was 2.31 times higher. These results are the first to demonstrate that in an elderly population undergoing ECV the presence of AF at follow-up is directly related to vascular properties. In our patients, the CHA_2DS_2-VASc score itself proved a multivariate predictor of the presence of arrhythmia after ECV. As in previous experiments, the score was significantly associated with early and late recurrences of AF,[24,25] revealing itself as a useful tool to identify those patients with a global, higher, risk of events. Indeed, in elderly subjects, during a 2-year follow-up, scoring 9, when compared to 0, was associated with a three times greater probability to be admitted into hospital for cardiovascular causes.[26]

Study limitations

Our experience originated in a single centre and it was conducted in two small series of patients. Moreover, it was possible to measure IL-6 concentration in only 27 of the 31 subjects (87.1%) enrolled in the second study. However, our results seem to be biologically and clinically consistent, and they could represent a basis for further, larger, experiences.

Conclusions

Through CAVI, an index of AS, easily measured at the bedside, we showed the existence of a physio-pathological link between AS, atrial dimensions and arrhythmia relapse in patients with persistent AF. As already mentioned, patients were assessed only a few hours after sinus rhythm restoration, a time interval too short to overcome the alterations that characterize the atrial remodelling process.[27]

Interestingly, this correlation between vascular properties and LAD was not found in a control population and it is possibly mediated by both mechanical and circulating factors. Our findings emphasize the importance of the 'atrial-ventricular-arterial association' in promoting the development and the maintenance of the arrhythmia and its frequent relapses. If these data are confirmed, AS evaluation will become a key component in the medical assessment of older, comorbid, AF patients.

Acknowledgements

We thank Mrs. Yumiko Kato of Fukuda Denshi, Japan, Mr. Simon Martin of Fukuda Denshi, UK, Dr. Mitsuya Maruyama of Fukuda Denshi, Japan, and Mr. Angelo Sortezza, EE, of ESAOTE SpA, Italy, for their technical assistance and their unconditional and passionate support.

Conflict of interest: none declared.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics-2016 update: A report from the American heart association. *Circulation* 2016;**133**:e38–e360.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;**114**:119–125.
3. Collerton J, Davies K, Jagger C, Kingston A, Bond J, Eccles MP, Robinson LA, Martin-Ruiz C, von Zglinicki T, James OF, Kirkwood TB. Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. *BMJ* 2009;**339**:b4904. doi: 10.1136/bmj.b4904.:b4904.
4. Coyne KS, Paramore C, Grandy S, Mercader M, Reynolds M, Zimetbaum P. Assessing the direct costs of treating nonvalvular atrial fibrillation in the United States. *Value Health* 2006;**9**:348–356.
5. Fumagalli S, Tarantini F, Guarducci L, Pozzi C, Pepe G, Boncinelli L, Valoti P, Baldasseroni S, Masotti G, Marchionni N. Atrial fibrillation is a possible marker of frailty in hospitalized patients: results of the GIFA Study. *Aging Clin Exp Res* 2010;**22**:129–133.
6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). *Eur Heart J* 2016;**37**:2893–2962.
7. Thacker EL, McKnight B, Psaty BM, Longstreth WT Jr, Sitlani CM, Dublin S, Arnold AM, Fitzpatrick AL, Gottesman RF, Heckbert SR. Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology* 2013;**81**:119–125.
8. Boyd AC, Richards DA, Marwick T, Thomas L. Atrial strain rate is a sensitive measure of alterations in atrial phasic function in healthy ageing. *Heart* 2011;**97**:1513–1519.
9. Cavalcante JL, Lima JA, Redheuil A, Al Mallah MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011;**57**:1511–1522.
10. Mitchell GF, Vasan RS, Keyes MJ, Parise H, Wang TJ, Larson MG, D'agostino RB Sr, Kannel WB, Levy D, Benjamin EJ. Pulse pressure and risk of new-onset atrial fibrillation. *JAMA* 2007;**297**:709–715.
11. Larstorp AC, Ariansen I, Gjesdal K, Olsen MH, Ibsen H, Devereux RB, Okin PM, Dahlof B, Kjeldsen SE, Wachtell K. Association of pulse pressure with new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study. *Hypertension* 2012;**60**:347–353.
12. Violi F, Davi G, Hiatt W, Lip GY, Corazza GR, Perticone F, Proietti M, Pignatelli P, Vestri AR, Basili S. Prevalence of peripheral artery disease by abnormal ankle-brachial index in atrial fibrillation: implications for risk and therapy. *J Am Coll Cardiol* 2013;**62**:2255–2256.
13. Chen LY, Leening MJ, Norby FL, Roetker NS, Hofman A, Franco OH, Pan W, Polak JF, Witteman JC, Kronmal RA, Folsom AR, Nazarian S, Stricker BH, Heckbert SR, Alonso A. Carotid intima-media thickness and arterial stiffness and the risk of atrial fibrillation: the atherosclerosis risk in communities (ARIC) study, multi-ethnic study of atherosclerosis (MESA), and the Rotterdam study. *J Am Heart Assoc* 2016;**5**:e002907.
14. Fumagalli S, Gabbai D, Nreu B, Roberts AT, Boni S, Ceccofiglio A, Fracchia S, Baldasseroni S, Tarantini F, Marchionni N. Age, left atrial dimension and arterial stiffness after external cardioversion of atrial fibrillation. A vascular component in arrhythmia maintenance? Results from a preliminary study. *Aging Clin Exp Res* 2014;**26**:327–330.
15. Fumagalli S, Giannini I, Pupo S, Agostini F, Boni S, Roberts AT, Gabbai D, Di Serio C, Gabbani L, Tarantini F, Marchionni N. Atrial fibrillation after electrical cardioversion in elderly patients: a role for arterial stiffness? Results from a preliminary study. *Aging Clin Exp Res* 2016;**28**:1273–1277.
16. Smit MD, Maass AH, De Jong AM, Muller Kobold AC, Van Veldhuisen DJ, Van Gelder IC. Role of inflammation in early atrial fibrillation recurrence. *Europace* 2012;**14**:810–817.
17. Fumagalli S, Boni N, Padeletti M, Gori F, Boncinelli L, Valoti P, Baldasseroni S, Di Bari M, Masotti G, Padeletti L, Barold S, Marchionni N. Determinants of thoracic electrical impedance in external electrical cardioversion of atrial fibrillation. *Am J Cardiol* 2006;**98**:82–87.
18. Shirai K, Hiruta N, Song M, Kurosu T, Suzuki J, Tomaru T, Miyashita Y, Saiki A, Takahashi M, Suzuki K, Takata M. Cardio-ankle vascular index (CAVI) as a novel indicator of arterial stiffness: theory, evidence and perspectives. *J Atheroscler Thromb* 2011;**18**:924–938.
19. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol* 2002;**90**:1284–1289.
20. De Marchi SF, Allemann Y, Seiler C. Relaxation in hypertrophic cardiomyopathy and hypertensive heart disease: relations between hypertrophy and diastolic function. *Heart* 2000;**83**:678–684.
21. Luft FC. Molecular mechanisms of arterial stiffness: new insights. *J Am Soc Hypertens* 2012;**6**:436–438.
22. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–271.
23. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;**104**:2886–2891.
24. Falsetti L, Viticchi G, Tarquinio N, Silvestrini M, Capeci W, Balloni A, Catozzo V, Gentile A, Pellegrini F. CHA2DS2-VASc in the prediction of early atrial fibrillation relapses after electrical or pharmacological cardioversion. *J Cardiovasc Med (Hagerstown)* 2014;**15**:636–641.
25. Kornej J, Hindricks G, Kosiuk J, Arya A, Sommer P, Husser D, Rolf S, Richter S, Huo Y, Piorkowski C, Bollmann A. Comparison of CHADS2, R2CHADS2, and CHA2DS2-VASc scores for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation: the Leipzig Heart Center AF Ablation Registry. *Circ Arrhythm Electrophysiol* 2014;**7**:281–287.
26. Naccarelli GV, Panaccio MP, Cummins G, Tu N. CHADS2 and CHA2DS2-VASc risk factors to predict first cardiovascular hospitalization among atrial fibrillation/atrial flutter patients. *Am J Cardiol* 2012;**109**:1526–1533.
27. Kumar S, Teh AW, Medi C, Kistler PM, Morton JB, Kalman JM. Atrial remodeling in varying clinical substrates within beating human hearts: relevance to atrial fibrillation. *Prog Biophys Mol Biol* 2012;**110**:278–294.