HEART RHYTHM DISORDERS AND PACEMAKERS

Effects of blood pressure on the prothrombotic risk in 1235 patients with non-valvular atrial fibrillation

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Background: Increased levels of plasma von Willebrand factor (vWf, an index of endothelial damage/dysfunction) and soluble P-selectin (sP-sel, an index of platelet activation) concentrations have been reported as indices of the prothrombotic state in both non-valvular atrial fibrillation and hypertension separately. However, the effect of hypertension on the levels of these indices in the setting of atrial fibrillation, and whether increasing severity of hypertension presents an additive prothrombotic risk, is unclear.
Methods: Plasma concentrations of vWf and sP-sel were measured by ELISA in 1235 patients with atrial fibrillation, and levels related to a history of hypertension and rising quartiles of systolic, diastolic and pulse pressure in those with and without diabetes mellitus and prior vascular events.
Results: Mean plasma vWf was higher among patients with atrial fibrillation with a history of hypertension (149 vs 145 IU/dl, p = 0.005). Also, an increase in the levels of vWf with increasing quartiles of pulse pressure (p = 0.042) was noticed. However, on multivariate analysis, after adjusting for potential confounders, the effects of both hypertension and pulse pressure became non-significant (p = 0.261 and p = 0.5, respectively). Levels of sP-sel were unaffected by a history of hypertension and rising quartiles of systolic and diastolic blood pressure, or pulse pressure.
Conclusion: Among patients with atrial fibrillation, patients with hypertension have higher vWf levels, indicating endothelial damage/dysfunction, which is associated with increasing pulse pressure. However, these associations are probably owing to the presence of other associated cardiovascular disease, rather than hypertension itself. Furthermore, platelet activation (sP-sel) was unrelated to hypertension or blood pressure in this atrial fibrillation cohort. Hypertension or blood pressure levels do not seem to have an independent additive affect on the prothrombotic state in atrial fibrillation.

Hypertension is a well-recognised risk factor for coronary artery disease, atherosclerosis and cerebrovascular disease. In hypertension, the arterial walls are exposed to the surge of blood under high pressures; yet, the complications of hypertension, such as myocardial infarction or stroke, are paradoxically thrombotic rather than haemorrhagic—the so-called ''thrombotic paradox of hypertension''.[1] Indeed, hypertension fulfils the components of the Virchow's triad,[2] which includes abnormalities of the vessel wall (which we now recognise as endothelial damage/dysfunction), abnormal blood constituents (with abnormal levels of haemostatic, fibrinolytic and platelet factors) and abnormalities of blood flow.[3]

Non-valvular atrial fibrillation is the most common sustained arrhythmia, and is also recognised to increase the risk of stroke by fivefold.[4] However, the exact mechanisms of thromboembolism in the setting of atrial fibrillation remain incompletely understood.[5] Abnormal plasma markers of coagulation, endothelial function and platelet activation have been described in the setting of atrial fibrillation, in comparison with healthy controls.[6] For example, increased plasma levels of von Willebrand factor (vWf, a marker of endothelial damage/dysfunction) have been shown to be prognostically significant in atrial fibrillation,[7] whereas increased plasma levels of soluble P-selectin (sP-sel, a marker of platelet activation) have been related to risk factors for atherosclerosis in patients with atrial fibrillation.[8] However, many common clinical features can also influence the risk of stroke and thromboembolism in atrial fibrillation.[4] Of note, atrial fibrillation is common among patients with hypertension and constitutes part of the spectrum of hypertensive heart disease, and a combination of presence of the atrial fibrillation and hypertension would raise the thrombotic risk of stroke in this population.

Indeed, hypertension itself is manifest with an array of aberrant inflammatory[9] and metabolic factors[10] that may underline the prothrombotic risk associated with atrial fibrillation. We have previously shown that vWf levels increase with additional risk factors contributing to the metabolic syndrome in hypertension,[10] implying a relationship of increasing vWf levels with a greater cardiovascular risk ''burden''. Thus, we hypothesised that the presence of coexistent hypertension and increasing severity of blood pressure (and pulse pressure) would have an additive and independent effect on the prothrombotic risk in atrial fibrillation. We therefore examined the effects of blood pressure on the prothrombotic risk, as reflected by levels of vWf and sP-sel, in a large cohort of patients with non-valvular atrial fibrillation.

PATIENTS AND METHODS

We studied 1235 consecutive patients with non-valvular atrial fibrillation who were participants in the 3rd Stroke Prevention in Atrial Fibrillation study (SPAF-III). We included all SPAF patients in this analysis, irrespective of antithrombotic treatment use, as warfarin or aspirin did not considerably influence vWf or sP-sel levels in this cohort[8] or in other studies.[11] Patients with documented congestive heart failure were excluded from the study, as congestive heart failure has already been reported to increase prothrombotic risk in atrial fibrillation.[12] The remaining patients with atrial fibrillation were divided into two groups: those with hypertension (defined as untreated systolic blood pressure (SBP) >160 mm Hg and diastolic blood pressure (DBP) >90 mm Hg, or a history of hypertension

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; sP-sel, soluble P-selectin; vWf, plasma von Willebrand factor

Table 1 Baseline clinical characteristics of 1235 patients with non-valvular atrial fibrillation

	No history of hypertension, n = 555	History of hypertension, n = 680	p Value
Mean age (SD), years	69.03 (9.18)	69.8 (9.03)	0.139
Body mass index (SD), kg/m^2	27.13 (5.18)	29.04 (5.13)	<0.001
Sex, male (%)	420 (75.4%)	488 (71.8%)	0.150
Medical history			
Prior stroke	67 (12%)	149 (22%)	<0.001
Diabetes mellitus	52 (9.3%)	132 (19.4%)	<0.001
Peripheral vascular disease	32 (5.7%)	58 (8.5%)	0.062
Prior MI	52 (9.3%)	98 (14.4%)	0.007
Angina	58 (10.4%)	104 (15.3%)	0.014
CABG	59 (10.6%)	90 (13.2%)	0.161
Mean (SD), cholesterol mmol/l	5.13 (0.97)	5.2 (0.95)	0.256
Warfarin use (at the time of blood sample)	103 (18.5%)	188 (28%)	<0.001
Aspirin use (at the time of blood sample)	229 (41.1%)	219 (32.2%)	0.003
Smoking history (earlier and now)	339 (61%)	411 (60.45)	0.907
Alcohol use (earlier and now)	102 (18.3%)	120 (18%)	0.553
Mean SBP (SD), mm Hg	128.26 (16.74)	142.96 (18.05)	>0.001
Mean DBP (SD), mm Hg	75.34 (9.24)	80.47 (9.45)	>0.001
Mean pulse pressure (SD), mm Hg	52.92 (15.30)	62.49 (15.08)	>0.001
vWf (IQR), IU/dl	145 (124–166)	149 (130–169)	0.005
Soluble P-selectin (IQR), ng/ml	33 (26–41)	33 (25–41)	0.526

CABG, coronary artery bypass graft; DBP, diastolic blood pressure; IQR, interquartile range; MI, myocardial infarction SBP, systolic blood pressure; vWf, von Willebrand factor.

requiring antihypertensive drug treatment) and those without hypertension.

Blood collection and laboratory analysis

Blood for vWf and sP-sel assays was drawn into 3.8% sodium citrate tubes (Becton Dickinson, BD Biosciences, Oxford, UK), immediately mixed by gentle inversion, stored on melting ice, centrifuged at 4°C for 30 000 *g*-min within 1 h of phlebotomy, and plasma was separated for vWf and sP-sel assays.

Measurements of sP-sel and vWf were performed using ELISA with reagents from R&D Systems (Abington, UK) and Dako-Patts (Ely, UK), respectively. The unit for vWf is IU/dl and was standardised by reference vWf from the National Institute for Biological Standards and Controls, Blanche Lane, South Mimms, Potters Bar, Hertfordshire, UK. Intraassay coefficients of variation for all ELISA assays were <5%, inter-assay variances were <10%.

Data analysis

We initially compared the cohorts on the basis of the presence or absence of hypertension. As prior existence of vascular disease entails the presence of damage/endothelial dysfunction, we performed additional analyses after excluding patients with prior stroke, coronary artery bypass surgery, peripheral vascular disease, diabetes, myocardial infarction and angina, and diabetes mellitus. Finally, we divided this cohort into quartiles of systolic, diastolic and pulse pressure to explore a relationship between rising quartiles and either vWf or sP-sel levels, if any.

Normally distributed data are expressed as mean (standard deviation (SD)). Differences in distribution of variables between groups were evaluated using two-sample t tests and one-way analysis of variance, as appropriate, with Tukey's post hoc test for intergroup comparisons. The non-parametric distribution of vWf and sP-sel in this population was determined using normality testing and expressed as median (interquartile range). Differences in non-parametric variables were evaluated with the Mann Whitney U test and Kruskal Wallis test. Forward and backward stepwise linear regression analyses were used in multivariate analysis. Statistical significance was accepted at the 0.05 level (two-sided). Statistical analyses were undertaken using SPSS software.

RESULTS

In the whole cohort (n = 1235), vWf levels were significantly higher (p = 0.005), but sP-sel was not significantly different (p = 0.526), when patients with hypertension were compared with those without hypertension (table 1). As expected, significant differences were found between the two groups with respect to the presence of vascular disease.

When the patients were divided into quartiles on the basis of mean SBP, DBP and pulse pressure, no significant ordinal relationships were seen between vWf and sP-sel levels and rising quartiles of mean SBP and DBP (table 2). However, vWf (p = 0.042), but not sP-sel (p = 0.45), was found to be significantly associated with rising quartiles of pulse pressure in the whole cohort (table 2).

After excluding patients with diabetes or prior vascular events, vWf and sP-sel levels were not significantly related to blood pressure levels (table 3). On a similar analysis of quartiles of SBP, DBP and pulse pressure, no significant ordinal relationships were seen between vWf and sP-sel levels and rising quartiles of SBP, DBP or pulse pressure (table 4). Thus, after adjusting for potential confounders, the effect of both hypertension and pulse pressure on vWf became non-significant.

DISCUSSION

Hypertension is a strong clinical risk factor for stroke and atrial fibrillation, although many hypertensives often have comorbidities (eg, diabetes, vascular disease, etc) which are themselves associated with stroke and atrial fibrillation, and may confound any relationship. In our cohort of patients with non-valvular atrial fibrillation, although blood pressure seemed to influence vWf levels, consistent with current thrombotic risk stratification regimens,[4] subanalyses of groups after excluding those with diabetes or prior vascular disease showed that the relationship with vWf was not significant.

vWf is one of several endothelium-derived haemostatic mediators, with key roles in platelet aggregation and stabilisation of circulating clotting factors.[13] Large quantities of vWf are stored in the Weibel–Palade bodies of endothelial cells and can be mobilised rapidly after endothelial cell activation[13] to result in transient elevations of plasma vWf.[14] In experimental models at least, endothelial dysfunction promotes thrombosis, vasospasm and vessel occlusion.[15] Thus, persistently raised levels of vWf and endothelial damage/dysfunction may pose a real risk to thrombosis. Moreover, raised vWf has been linked to the presence of left atrial appendage thrombus (as detected by transoesophageal echocardiography),[16] and indeed there are reports showing a significant correlation between the degree of endocardial expression of vWf and the degree of platelet adhesion/thrombus formation in the atrial appendage.[17] Of note, raised plasma vWf has also been shown to be present in patients with damaged atrial appendage endocardium, and also mitral valve disease, many of whom had atrial fibrillation.[18] vWf has also been found to be a significant independent predictor of target organ damage in hypertension[19] and to

Table 2 Relationship of plasma von Willebrand factor and soluble P-selectin levels of quartiles of systolic, diastolic and pulse pressure (n = 1235)

Systolic blood pressure	1st Quartile (<122 mm Hg)	2nd Quartile (≥122 and <136 mm Hg)	3rd Quartile (≥136 and <150 mm Hg)	4th Quartile (≥150 mm Hg)	p Value
Number of patients (n)	301	299	315	320	
Age, mean (SD), years	67.03 (9.39)	69.72 (8.83)	69.85 (8.11)	71.03 (7.33)	<0.001
Men (%)	235 (78.1)	231 (77.3)	225 (71.2)	216 (61.5)	0.007
Body mass index, mean (SD), kg/m^2	27.40 (6.01)	28.28 (5.52)	28.65 (5.83)	28.36 (5.06)	0.04
Serum cholesterol, mean (SD), mmol/l	5.08 (1.03)	5.09 (0.99)	5.18 (1)	5.29 (1)	0.03
vWf (IQR) IU/dl	146 (122–166)	148 (127–168)	149 (130–171)	147 (128–166)	0.563
Soluble P-selectin (IQR) ng/ml	33 (27–41)	33 (25–410	32 (25–40)	33 (25–41)	0.314

Diastolic blood pressure	1st Quartile (<70 mm Hg)	2nd Quartile (≥70 and <80 mm Hg)	3rd Quartile (≥80 and <84 mm Hg)	4th Quartile (≥84 mm Hg)	p Value
Number of patients (n)	192	372	304	367	
Age, mean (SD), years	70.83 (8.46)	69.54 (8.94)	69.30 (8.28)	68.72 (8.34)	0.051
Men (%)	131 (68.2)	275 (73.9)	219 (71.8)	282 (76.8)	0.064
Body mass index, mean (SD), kg/m^2	27.50 (5.29)	28.05 (5.97)	27.90 (5.38)	28.91 (5.58)	0.019
Serum cholesterol, mean (SD), mmol/l	5.11 (1.04)	5.10 (1)	5.24 (1.03)	5.20 (1)	0.21
vWf (IQR), IU/dl	151 (131–172)	147 (125–168)	147 (125–167)	146 (128–166)	0.146
Soluble P-selectin (IQR), ng/ml	33 (26–41)	32 (26–40)	33 (25–42)	33 (25–40)	0.872

Pulse pressure	1st Quartile (<46 mm Hg)	2nd Quartile (≥46 and <56 mm Hg)	3rd Quartile (≥56 and <70 mm Hg)	4th Quartile (≥70 mm Hg)	p Value
Number of patients (n)	295	277	339	324	
Age, mean (SD), years	66.31 (9.3)	68.99 (8.82)	69.96 (7.95)	72.12 (7.15)	<0.001
Men (%)	240 (81.4)	214 (77.3)	249 (73.2)	204 (63.0)	<0.001
Body mass index, mean (SD), kg/m^2	28.13 (6.15)	27.87 (5.71)	28.56 (5.35)	28.09 (5.32)	0.491
Serum cholesterol, mean (SD), mmol/l	5.05 (0.97)	5.08 (1)	5.24 (1.05)	5.26 (1)	0.014
vWf (IQR), IU/dl	144 (122–166)	146 (128–168)	148 (127–166)	150 (131–170)	0.042
Soluble P-selectin (IQR), ng/ml	34 (27–41)	32 (25–40)	32 (25–41)	33 (25–41)	0.45

IQR, interquartile range; vWf, von Willebrand factor.

correlate well with Framingham risk-factor prediction scores.[20] In this study, mean plasma vWf was significantly higher among patients with atrial fibrillation with a history of hypertension and with increasing quartiles of pulse pressure. The increasing quartiles of pulse pressure can be related to vascular dysfunction, hypertensive target organ damage and prognosis.[21 22] Interestingly, after adjusting for potential confounders, the effects of both hypertension and pulse pressure became non-significant, suggesting that hypertension or blood pressure levels may not have an independent additive affect on the prothrombotic state in atrial fibrillation. Indeed, the prothrombotic state in atrial fibrillation may be more driven by concomitant comorbidities and vascular disease, and well-controlled hypertension may perhaps represent less of a risk factor for stroke and vascular events in atrial fibrillation.[23]

Table 3 Baseline clinical characteristics of 664 patients with non-valvular atrial fibrillation but no diabetes or prior vascular events

	No history of hypertension, n = 358	History of hypertension, n = 306	p Value
Mean age (SD), years	67.90 (9.01)	68.58 (8.98)	0.329
Body mass index (SD), kg/m^2	27.27 (5.22)	28.99 (5.18)	<0.001
Sex, male (%)	267 (74.6%)	210 (68.6%)	0.053
Mean cholesterol (SD) mmol/l	5.15 (1.02)	5.24 (0.97)	0.251
Mean SBP (SD), mm Hg	127.24 (16.02)	141.61 (18.18)	<0.001
Mean DBP (SD), mm Hg	75.79 (9.01)	81.36 (9.27)	<0.001
Mean pulse pressure (SD), mm Hg	51.45 (15.08)	60.25 (15.03)	<0.001
vWf (IQR), IU/dl	141 (120–160)	144 (125–163)	0.261
Soluble P-selectin (IQR), ng/ml	33 (25–41)	32 (24–39)	0.081

DBP, diastolic blood pressure; IQR, interquartile range; MI, myocardial infarction SBP, systolic blood pressure; vWf, von Willebrand factor.

Of note, sP-sel were unaffected by a history of hypertension and rising quartiles of SBP and DBP, or pulse pressure, in this analysis. P-selectin is a component of platelet α-granules that is expressed on the platelet surface membrane and shed into the plasma (as sP-sel) on platelet activation.[24] P-selectin is also found in Weibel–Palade bodies of endothelial cells, but the bulk of circulating sP-sel seems to be platelet derived.[25 26] Although vWf is similarly found in platelet α-granules and endothelial cell Weibel–Palade bodies, most of the circulating vWf seems to be derived from the endothelium.[14] The lack of relationship of sP-sel and hypertension severity is consistent with observations that platelet activation—although present in atrial fibrillation—is more related to associated comorbidities, rather than to atrial fibrillation in itself, where coagulation factor-related abnormalities predominate in contributing to the prothrombotic state.[27] This is evident by the lack of

Table 4 Relationship of plasma von Willebrand factor and soluble P-selectin levels with quartiles of systolic, diastolic and pulse pressure (n = 664)

Systolic blood pressure	1st Quartile (<122 mm Hg)	2nd Quartile (≥122 and <136 mm Hg)	3rd Quartile (≥136 & <150 mm Hg)	4th Quartile (≥150 mm Hg)	P value
Number of patients (n)	187	162	177	138	
Age, mean (SD), years	65.40 (10.15)	69.19 (8.96)	68.66 (8.23)	70.36 (7.06)	<0.001
Male (%)	142 (75.9)	128 (79)	119 (67.6)	87 (63)	0.006
Body mass index, mean (SD), kg/m^2	27.66 (6.31)	28.17 (5.16)	28.61 (5.88)	27.82 (5.05)	0.431
Serum cholesterol, mean (SD), mmol/l	5.19 (1.02)	5.09 (0.89)	5.19 (0.96)	5.31 (1.03)	0.297
vWf (IQR), IU/dl	142 (117–160)	142 (127–160)	145 (125–166)	139 (122–160)	0.564
Soluble P-selectin (IQR), ng/ml	32 (26–40)	31 (24–40)	33 (25–41)	31 (24–40)	0.621

Diastolic blood pressure	1st Quartile (<70 mm Hg)	2nd Quartile (≥70 and <80 mm Hg)	3rd Quartile (≥80 and <84 mm Hg)	4th Quartile (≥84 mm Hg)	p Value
Number of patients (n)	97	202	171	194	
Age, mean (SD) years	69.86 (9.54)	68.29 (9.20)	68.21 (8.98)	67.36 (8.32)	0.167
Male (%)	65 (67.7)	139 (68.8)	125 (73.1)	147 (75.8)	0.342
Body mass index, mean (SD) kg/m^2	27.23 (5.04)	28.20 (6.38)	27.70 (5.5)	28.68 (5.28)	0.150
Serum cholesterol, mean (SD) mmol/l	5.15 (1.04)	5.09 (0.96)	5.22 (0.92)	5.29 (1)	0.223
vWf (IQR) IU/dl	142 (125–171)	144 (120–158)	138 (121–159)	142 (125–163)	0.436
Soluble P-selectin (IQR) ng/ml	31 (26–40)	31 (25–40)	33 (25–41)	33 (24–41)	0.884

Pulse pressure	1st Quartile (<46 mm Hg)	2nd Quartile (≥46 and <56 mm Hg)	3rd Quartile (≥56 and <70 mm Hg)	4th Quartile (≥70 mm Hg)	p Value
Number of patients (n)	183	167	181	133	
Age, mean (SD), years	64.80 (9.65)	68.16 (9.54)	69.19 (7.88)	71.71 (6.71)	<0.001
Male (%)	148 (80.9)	125 (74.9)	128 (71.1)	75 (56.4)	<0.001
Body mass index, mean (SD), kg/m^2	28.03 (6.24)	28.38 (5.63)	28.36 (5.26)	27.34 (5.44)	0.381
Serum cholesterol, mean (SD), mmol/l	5.09 (0.94)	5.18 (1)	5.29 (0.97)	5.19 (1.01)	0.334
vWf (IQR), IU/dl	141 (115–160)	142 (126–166)	142 (124–158)	142 (124–167)	0.500
Soluble P-selectin (IQR), ng/ml	34 (26–41)	31 (24–40)	32 (25–41)	31 (24–40)	0.370

IQR, interquartile range; vWf, von Willebrand factor.

relationship of sP-sel with prognosis,[7] stroke risk stratification,[8] and the superior benefits of warfarin over antiplatelet treatment.[28]

This study is limited by its cross-sectional design. Furthermore, we have limited information on concomitant drug treatments, and some antihypertensive drugs (eg, angiotensin-converting enzyme inhibitors) may affect the endothelium and platelets. Also, a recent small study suggests that digoxin may influence flow cytometric assessments of platelet and endothelial activation,[28] but we are unaware of digoxin affecting vWf and sP-sel levels. Some patients were also taking warfarin and aspirin at baseline, but previous work does not suggest a significant influence on vWf and sP-sel levels.[8 11 29 30]

Although abnormally high levels of circulating markers of endothelial function and platelet activation have been described in patients with non-valvular atrial fibrillation,[6] this study shows the lack of an independent effect of blood pressure on these markers in the same setting. This is in keeping with our earlier observations from a smaller cohort of patients with atrial fibrillation[31] as well as a multivariate analysis, where neither hypertension nor SBP exceeding 160 mm Hg were found to be independently correlated with increased plasma concentration of either vWF or sP-sel.[8] This may perhaps be explained by the fact that concentrations of vWf may depend more strongly on other factors in the hypertensive microenvironment (eg, inflammation, angiogenesis, etc) rather than on the absolute level of blood pressure in itself.[9 32 33] Thus, hypertension or the severity of blood pressure elevation may not have an independent additive affect on the prothrombotic state in atrial fibrillation beyond that seen with concomitant vascular disease and comorbidities associated with atrial fibrillation.

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Non-thrombotic heart disease can kill suddenly

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Non-atherosclerotic heart disease should be looked for when coronary disease is suspected or when death is sudden and apparently unexplained, say doctors in Italy who uncovered four such cases in routine necropsies. This is particularly important for forensic pathologists and to avoid underestimating coronary causes of sudden death.

Death was attributed to arrhythmia secondary to myocardial ischaemia from non-atherosclerotic, non-thrombotic coronary disease after thorough histological examination and after excluding other causes of coronary vasculitis and other causes of sudden cardiac death.

Three cases were in previously healthy men aged 31-51 years whose deaths were sudden and unexpected. Medical histories afforded no clues, nor did gross pathological examinations of the heart and coronary vessels, except in one case. This man had mildly discoloured areas of anterolateral myocardium. Serial sections of his left descending anterolateral artery showed vasculitis through the vessel wall with a cellular infiltrate of CD8+ lymphocytes. In the second case, though the ventricles and coronary arteries on the heart surface appeared normal, serial sections of myocardium and coronary arteries showed a cellular infiltrate of mostly CD4+ and CD8+ lymphocytes in the wall of the small myocardial vessels. In the third, prominent medial and fibrointimal thickening of arteries was evident within the heart. Finally, in a woman aged 45 with severe liver failure who died suddenly during her admission, necropsy showed spontaneous dissection of the left main coronary artery and left anterior descending and circumflex arteries. There was granulation tissue in the left main coronary artery but signs of acute haemorrhage in the other affected arteries, almost blocking the lumen.

Non-atherosclerotic heart disease is often overlooked as a cause of sudden death.

▲ De Giorgio F, *et al*. *Journal of Clinical Pathology* 2007;**60**:94–97.