Ankle-Brachial Index as a Predictor of Cardiovascular Risk in Atrial Fibrillation

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Introduction

Atrial Fibrillation (AF) is the most frequent sustained arrhythmia, with a case record of a little less than 1% in general population, and with an incidence of 0.2% per year [1]. It is associated with a high rate of morbidity and mortality, requiring massive use of health resources. In particular, AF is a risk factor for death and non-deathly ischemic cardiovascular and cerebrovascular events [2,3] probably coming from thromboembolic and atherothrombotic processes [4].

Many traditional cardiovascular risk factors (such as arterial hypertension, diabetes mellitus, obesity and smoking) are connected, in fact, with AF [5]. Recently, other risk factors (such as the high concentration of inflammatory markers in blood) have been associated with AF [6]. We can assume that the background of high “global cardiovascular risk” in which AF emerges, could affect the clinical outcome of patients. It is less defined, instead, the “pro-atherosclerotic” role of arrhythmia itself.

The aim of our study is, first of all, to evaluate the prevalence of PAD in a sample of patients with AF. Furthermore, for each of them the global cardiovascular risk profile and the incidence of every risk factor has been evaluated.

The early conjecture is that the AF, by its variability in cardiac output, could constitute an “independent” risk factor for the acceleration of pluridistrictual atherosclerotic disease. From this perspective, time gains a crucial importance, in terms of length of the arrhythmia.

In the end, we have considered whether the association between AF and PAD in the sample of patients under analysis could represent or not a higher atherothrombotic risk (prevalence of an attendant chronic coronary and/or cerebrovascular disease) in front of AF and PAD considered apart.

Materials and Methods

Our study consists of observations conducted on patients arriving for a clinical examination in the Cardiology Division of “Paolo Giaccone” Polyclinic, in Palermo (Italy), between January and June 2011. We have included in the observation subjects older than 18, with and without AF. Fibrillating patients have been considered as affected by non-valvular AF, as they were not affected by an acquired or congenital valvular disease (such as stenosis, moderate or severe mithralic deficiency, valve substitution). Furthermore, we have excluded patients with AF and hyperthyroidism, subjects with EF (Ejection Fraction) <55% and patients with recent or ongoing ACS (Acute Coronary Syndrome).

We have sampled a population of 200 patients, divided into two groups: a “Cases” group, made of patients with AF and/or an ongoing AF, and a “Controls” group, made of subjects with normal Sinus rhythm.
Rhythm (SR), without AF and without any arrhythmic events in the ECG control during last 24 hours.

Afterwards, we have divided Cases and Controls according to the lack or presence of PAD, thus identifying four subgroups: Cases with PAD, Controls with PAD, Cases without PAD, Controls without PAD. In the end, according to the ESC 2010 guide-lines, we have stratified the presence of AF in paroxysmal, persistent and permanent [7].

The study was approved by the local ethics committee and all patients expressed their informed consent to the participation to the study. Then, we have submitted them to anamnesis, to estimate the eventual CVD familiarity and the presence of major CVD risk factors. We have carefully evaluated also body weight, height, arterial pressure and heart rate of all patients, and each of them has provided a blood sample for a blood chemistry test. The eventual CVD familiarity has been defined only in the presence of a coronary disease imputable to the subject’s father before the age of 55 and to the subject’s mother before the age of 65. The prevalence of preexistent cardiovascular or cerebrovascular events has been investigated according to the documentation shown at the moment of the admission to the hospital and according to the reported clinical history.

Arterial pressure was measured in the right arm, with the patient in the sitting position, using a standard sphygmomanometer, after 4 minutes of rest; 2 consecutive readings were taken and the average of the 2 used. Subjects with a systolic pressure ≥140 mmHg, or a diastolic pressure ≥90 mmHg, or currently taking medication, were considered hypertensive [8].

Height and weight were measured using a stadiometer and a weighing scale. Body Mass Index was calculated as the ratio between height and weight. Obesity was defined as having BMI ≥30 kg/m² [9].

In line with the ADA, subjects having regular hypoglycemic or insulin treatment were considered diabetic, as subjects exhibiting glycaemia >126 mg/dl [10].

Total Cholesterol (TC), HDL-cholesterol (HDL-C) and triglycerides (TG) were quantified using enzymatic-colorimetric methods, whilst LDL-cholesterol (LDL-C) was calculated using the Friedewald formula. Subjects with cholesterol ≥190 mg/dl, or receiving hypolipidaemic treatment were considered hypercholesterolemic [11].

Valuation of lower limb peripheral artery disease

The incidence of PAD was evaluated using ABI or the Winsor index. ABI measurement is simple and inexpensive, requiring the use of a standard sphygmomanometer and a portable Doppler unit with probe set at 8MHz. The ABI is the ratio between the systolic pressure measured on the lower limb and the systolic pressure measured on the arm. We have used the higher pressure between the pedalial anterior and tibial posterior arteries. The index was calculated from the ratio between the lower limb pressure and ipsilateral humeral pressure.

In normal conditions, the pressure measured in the calf is slightly higher than that measured in the arm; consequently, an ABI value close to 1 indicates a healthy vascular system.

Higher values (>1.30) could indicate the presence of less flexible arteries due to thickening or hardening of the artery wall – a common condition in diabetics. Also in asymptomatic patients, values < 0.90 are considered as a cut-off point to confirm a diagnosis of iliac-femoral-popliteal atherosclerosis [12].

In our study we have adopted the following interpretation:

- ABI >1.30 = non-squeezable artery
- ABI between 0.91 and 1.30 = normal
- ABI between 0.41 and 0.90 = light or moderate artery obstruction disease
- ABI between 0.00 and 0.40 = severe artery obstruction disease

Statistical analysis

This analysis was made using the Stratview program (Abacus Concepts Inc.). We have calculated the average and standard deviation for numerical variables and we have obtained the differences between the groups using the “T” test by Student or by variance analysis (ANOVA) where there were more than two groups to consider. Prevalence of several clinical and laboratory variables was calculated, and the difference between the groups obtained using the χ² statistical test. The statistical incidence is considered for values of p<0.05. To evaluate the variables independently associated with cerebrovascular and cardiovascular events, we have built a logistic regression model by applying uni-variant analysis to the significant results. The results of this model are expressed as Odds Ratio (OR) with 95% confidence.

Results

The principal clinical characteristics of the two groups are shown on table 1 (Cases vs. Controls). The ‘Cases’ group comprised a total of

| Variable                  | Cases (n = 100) | Controls (n = 100) | p value<0.05 |
|----------------------------|-----------------|--------------------|--------------|
| Age (n ± SD)               | 74.78 ± 9.23    | 72.83 ± 9.19       | 0.23         |
| Males                      | 53%             | 55%                | 0.89         |
| Females                    | 47%             | 45%                | 0.89         |
| Hypertension               | 91%             | 92%                | 0.99         |
| Diabetes mellitus          | 48%             | 40%                | 0.32         |
| Hypercholesterolemia       | 37%             | 35%                | 0.88         |
| Smoking                    | 34%             | 30%                | 0.65         |
| Obesity                    | 10%             | 14%                | 0.84         |
| Familiarity for CVD        | 19%             | 20%                | 0.99         |
| ABI (n ± DS)               | 0.95 ± 0.18     | 0.97 ± 0.14        | 0.37         |
| PAD                        | 42%             | 27%                | 0.037        |
| Coronary artery disease    | 49%             | 26%                | 0.0013       |
| Cerebrovascular disease    | 34%             | 16%                | 0.0055       |

CVD: Cardiovascular Disease; ABI: Ankle Brachial Index; PAD: Peripheral Artery Disease

Table 1: Clinical characteristics of “Cases” group (fibrillating patients) and “Controls” group (Sinusal Rhythm).
100 patients, 55 male and 45 female, with an average age of 72.8 (±9.2) years. The two groups were homogeneous for average age, distribution between sexes and the cardiovascular risks analyzed.

Within the entire test population, there was evidence of an incidence of PAD (defined as ABI < 0.9) of 34.5%. Although the average ABI value was largely applicable to both groups (0.95 ± 0.18 vs. 0.97 ± 0.14), the incidence of PAD appears significantly higher in the Cases group with respect to the Control group (42% vs 27%; p = 0.037).

### Table 2: Clinical characteristics of Cases and Controls groups stratified according to the lack or presence of PAD.

|                         | Cases with PAD (n = 42) | Controls with PAD (n = 27) | Cases without PAD (n = 58) | Controls without PAD (n = 73) | P value |
|-------------------------|------------------------|---------------------------|---------------------------|-------------------------------|---------|
| Age (n ± SD)            | 72.6 ± 9.73            | 74.22 ± 9.7              | 75.45 ± 8.75              | 72.1 ± 8.99                   | 0.18    |
| Males                   | 23 (54.76%)            | 15 (55.55%)              | 30 (51.72%)               | 40 (54.79%)                   | 0.98    |
| Females                 | 19 (45.24%)            | 12 (44.45%)              | 28 (49.12%)               | 33 (45.2%)                    | 0.98    |
| Hypertension            | 35 (83.33%)            | 25 (92.59%)              | 56 (96.55%)               | 67 (91.78%)                   | 0.13    |
| Diabetes mellitus       | 20 (47.61%)            | 21 (77.77%)              | 28 (48.27%)               | 19 (26.02%)                   | <0.0001 |
| Hypercholesterolemia    | 19 (45.23%)            | 22 (81.48%)              | 18 (31.03%)               | 31 (42.49%)                   | <0.0001 |
| Smoking                 | 15 (35.71%)            | 20 (74.07%)              | 19 (32.75%)               | 10 (13.69%)                   | <0.0001 |
| Obesity                 | 5 (11.90%)             | 7 (25.92%)               | 11 (16.96%)               | 7 (9.59%)                     | 0.15    |
| Familiarity for CVD     | 10 (2.38%)             | 5 (18.52%)               | 9 (15.52%)                | 15 (20.54%)                   | 0.0016  |
| Coronary artery disease | 28 (66.6%)             | 12 (44.44%)              | 21 (38.09%)               | 14 (19.18%)                   | <0.0001 |
| Cerebrovascular disease | 16 (38.09%)            | 9 (33.33%)               | 18 (31.03%)               | 7 (9.59%)                     | 0.0016  |

CVD: Cardiovascular Disease; ABI: Ankle Brachial Index; AF: Atrial Fibrillation; PAD: Peripheral Artery Disease; SR: Sinus Rhythm; AF + PAD: Presence of AF and PAD; AF – PAD: Presence of AF/absence of PAD; SR + PAD: Presence of PAD/absence of AF; SR – PAD: Absence of PAD and AF.

### Table 3: Clinical characteristics of the population stratified according to the lack or presence of cerebrovascular events in the clinical history.

|                        | Cerebrovascular events (n=50) | Not Cerebrovascular events (n=150) | p value<0.05 |
|------------------------|-------------------------------|-----------------------------------|--------------|
| Age (n ± SD)           | 74.40 ± 9.69                  | 73.15 ± 9.07                      | 0.41         |
| Males                  | 26 (52%)                      | 82 (54.6%)                        | 0.87         |
| Females                | 24 (48%)                      | 68 (45.3%)                        | 0.87         |
| Hypertension           | 47 (94%)                      | 136 (90.67%)                      | 0.66         |
| Diabetes mellitus      | 23 (46%)                      | 65 (43.33%)                       | 0.87         |
| Hypercholesterolemia   | 17 (34%)                      | 55 (36.67%)                       | 0.86         |
| Smoking                | 17 (34%)                      | 47 (31.33%)                       | 0.86         |
| Obesity                | 10 (20%)                      | 20 (13.33%)                       | 0.36         |
| Familiarity for CVD    | 11 (22%)                      | 28 (18.67%)                       | 0.76         |
| ABI (n ± SD)           | 0.91 ± 0.18                   | 0.96 ± 0.16                       | 0.047        |
| PAD + AF               | 16 (32%)                      | 26 (17.33%)                       | 0.045        |
| AF - PAD               | 18 (68%)                      | 40 (27%)                          | 0.28         |
| SR + PAD               | 9 (18%)                       | 18 (12%)                          | 0.40         |
| SR - PAD               | 7 (14%)                       | 66 (44%)                          | 0.0003       |
| Cardiovascular events  | 20 (40%)                      | 30 (20%)                          | 0.80         |

CVD: Cardiovascular Disease; ABI: Ankle Brachial Index; AF: Atrial Fibrillation; PAD: Peripheral Artery Disease; SR: Sinus Rhythm; AF + PAD: Presence of AF and PAD; AF – PAD: Presence of AF/absence of PAD; SR + PAD: Presence of PAD/absence of AF; SR – PAD: Absence of PAD and AF.

### Table 4: Clinical characteristics of the population stratified according to the lack or presence of cardiovascular events in the clinical history.

|                        | Cardiovascular events (n=75) | Not Cardiovascular events (n=125) | p value<0.05 |
|------------------------|------------------------------|----------------------------------|--------------|
| Age (n ± SD)           | 74.13 ± 9.02                 | 73.06 ± 9.35                     | 0.43         |
| Males                  | 41 (55%)                     | 67 (53.8%)                       | 0.1          |
| Females                | 34 (45.33%)                  | 58 (46.4%)                       | 0.1          |
| Hypertension           | 68 (90.67%)                  | 115 (92%)                        | 0.95         |
| Diabetes mellitus      | 33 (44%)                     | 55 (44%)                         | 0.88         |
| Hypercholesterolemia   | 37 (49.33%)                  | 35 (28%)                         | 0.004        |
| Smoking                | 24 (32%)                     | 40 (32%)                         | 0.87         |
| Obesity                | 8 (10.67%)                   | 22 (17.6%)                       | 0.26         |
| Familiarity for CVD    | 12 (16%)                     | 27 (21.6%)                       | 0.43         |
| ABI (n ± SD)           | 0.89 ± 0.14                  | 0.99 ± 0.18                      | <0.0001      |
| PAD + AF               | 28 (37.33%)                  | 14 (11.2%)                       | <0.0001      |
| AF - PAD               | 21 (28%)                     | 37 (29.6%)                       | 0.93         |
| SR + PAD               | 12 (16%)                     | 15 (12%)                         | 0.55         |
| SR - PAD               | 14 (18.67%)                  | 59 (47.2%)                       | 0.0001       |
| Cerebrovascular events | 20 (40%)                     | 55 (44%)                         | 0.8          |

CVD: Cardiovascular Disease; ABI: Ankle Brachial Index; AF: Atrial Fibrillation; PAD: Peripheral Artery Disease; SR: Sinus Rhythm; AF + PAD: Presence of AF and PAD; AF – PAD: Presence of AF/absence of PAD; SR + PAD: Presence of PAD/absence of AF; SR – PAD: Absence of PAD and AF.
Similarly, the prevalence of chronic coronary disease (49% vs 26%; \( p = 0.0013 \)), and chronic CVD (34% vs. 16%; \( p = 0.0055 \)) appears higher in patients with ongoing or recent AF.

On table 2 we have reported and compared clinical conditions of the sampled patients, divided into the following subgroups: cases with PAD (n=42), controls with PAD (n=27), Cases without PAD (n=58), Controls without PAD (n=73). From the results emerged a statistical incidence for diabetes mellitus (p<0.0001), hypercholesterolemia (p<0.0001), and smoking (p<0.0001) - risk factors definitely more represented in the “Controls with PAD” subgroup (Figure 1). We have to underline also an important statistical incidence in cerebrovascular and cardiovascular events (p=0.0016; p<0.0001), both of them mostly represented in the “Cases with PAD” subgroup (Figure 2). Again, to evaluate the variables independently associated with cerebrovascular and cardiovascular events, we have built a logistic regression model, using a uni-variant analysis system on the sample of patients, stratified in advance according to the lack or presence of cerebrovascular (Table 3) and cardiovascular (Table 4) adverse events, underlining variables with a statistical incidence. From this analysis emerged that the Sinusal Rhythm (OR = 0.20; 95% IC 0.09-0.48) constitutes a protective factor from cerebrovascular events (p=0.0003) (Table 5). Independent predictors of cardiovascular events seem to be, indeed, the coexistence of AF and PAD (p<0.0001; OR=4.67; 95% IC 2.22-9.82) and hypercholesterolemia (p=0.005; OR=2.47; 95% IC 1.31-4.64) (Table 6).

In the Cases group, patients were ordered according to the atrial fibrillation grade: paroxysmal (n = 12), persistent (n = 36) and permanent (n = 82). No statistical incidence emerged for almost all of the variables considered. PAD resulted slightly more frequent in patients with persistent AF (47.22% persistent vs. 40.38% permanent vs. 33.33% paroxystic). This trend hasn’t a statistical incidence, anyway. The prevalence of coronary and chronic cerebrovascular disease resulted, indeed, significantly higher in patients with permanent AF (respectively p=0.02 e p=0.01) (Table 7).

### Discussion

Many patients with AF show an increased risk of atherothrombosis due to various atherosclerosis factors that also increase the AF risk. In a recent prospective study, 14,598 middle-aged subjects, participants in the ‘Atherosclerosis Risk in Communities’ study (ARIC), were followed for 17 years. Of these, 56.5% of the ‘Cases of AF’ could be explained by the presence of multiple borderline or high risks. Among these, hyperension plays a dominant role \([5]\). Less clear, however, is the role played by AF as an independent factor in the development of atherosclerosis. In our study, even though the test population was fairly homogeneous with regard to the cardiovascular risks in the background, emerged a statistically important connection between AF and pluridistrictual atherosclerosis. Contrary to those patients with a sinusal rhythm, the group of fibrillating showed a greater prevalence of lower limb Obstructive Artery Disease and a greater prevalence of ischemic coronary and cerebrovascular disease in their clinical histories. It is interesting to note, focusing only on the group of patients with PAD (both fibrillating and non), how we can see a trend to higher prevalence of risk factors in non-fibrillating PAD patients. The association between AF and PAD seems to cause an increased atherothrombotic coronary risk compared to the individual risk from...
each of them: AF without PAD and PAD without AF. Other authors have confirmed the negative impact of such a connection in prognosis [13].

Unexpectedly, considering the variability in cardiac output as a possible cause of atherosclerosis independent of other risk factors, PAD results more representative in the sub-group of patients with persistent AF rather than in those with permanent AF. The scope of our study is however limited by the size of the patient group and therefore not suitable for validating physiopathological consequences. Additional evidence is required to clarify the existence of and the mechanisms for increased atherothrombotic risk from AF.

Conclusions

The results obtained show that patients with AF have an increased risk of cerebrovascular events, and patients with AF and PAD have an increased risk of coronary disease, thus suggesting that measuring ABI and diagnosis of, and research into, AF should be encouraged.

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Table 7: Clinical characteristics of Cases group stratified by AF grade.

| Age (n ± SD) | Paroxysmal (n = 12) | Persistent (n = 36) | Permanent (n = 52) | P value |
|-------------|---------------------|--------------------|-------------------|--------|
| Sex         |                     |                    |                   |        |
|             | M 6 (50%)           | M 19 (52.8%)       | M 26 (54.9%)      | 0.97   |
|             | F 8 (50%)           | F 17 (47.2%)       | F 24 (45.1%)      |        |
| Hypertension|                     |                    |                   |        |
|             | 12 (100%)           | 33 (91.7%)         | 46 (88.4%)        | 0.44   |
| Diabetes mellitus | 7 (58.3%)   | 16 (44.4%)         | 25 (48.08%)       | 0.70   |
| Hypercholesterolemia | 5 (41.7%)    | 13 (36.11%)        | 19 (36.54%)       | 0.93   |
| Smoking     | 3 (25%)             | 14 (38.9%)         | 17 (32.69%)       | 0.65   |
| Obesity     | 1 (8.3%)            | 5 (13.9%)          | 10 (19.23%)       | 0.59   |
| Family for CVD |                   |                    |                   |        |
|             | 0.89 ± 0.16         | 0.94 ± 0.18        | 0.95 ± 0.17       | 0.64   |
| PAD         | 4 (33.3%)           | 17 (47.22%)        | 21 (40.38%)       | 0.66   |
| ABI         | 12 (32.4%)          | 32 (61.53%)        | 18 (35.3%)        | 0.023  |
| Cerebrovascular disease | 4 (33.3%)  | 12 (32.4%)         |                   | 0.01   |

PAD: Peripheral Artery Disease; ABI: Ankle-Brachial-Index