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Sinus rhythm restoration with electrical cardioversion: acute effect of shock configuration and subsequent modifications in peripheral flow and sleep.

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Abstract

Introduction: Atrial fibrillation (AF) is the most common sustained arrhythmia, and its incidence is increasing worldwide. It is associated with higher stroke risk and presence of sleep disorders and dementia. The choice between rhythm and rate control in AF patients remains a debated topic, and it should be tailored on specific patient clinical characteristics. In specific situations, electrical cardioversion (ECV) for rhythm control in AF patients represents the preferred choice; in particular, in patients affected by cardiopathy and/or heart failure. Because of relevant AF social costs, there is a growing interest in developing new devices for large-scale screening and monitoring programs in patients affected or at risk of AF, to reduce the incidence of disabling events.

Aim: To improve acute efficacy of ECV procedure and explore the feasibility of a multiparametric monitoring with wearables devices in AF patients undergoing ECV (photoplethysmographic and electroencephalographic signals' registration integrated with clinical and instrumental data) to evaluate autonomic and cognitive function, sleep pattern, and their relationship with clinical outcomes.

Methods:

All patients enrolled during the first part signed Informed Consent for inclusion in our observational prospective registry of AF patients. We compared two widespread strategies used for AF ECV [antero-apical pads (AAP) vs antero-posterior patches (APP)], and we elaborated a decision algorithm based on some biometrical parameters [i.e., body surface area (BSA), weight and height] to improve acute efficacy.

In the second part of the thesis, we reported our results on the feasibility of the use of new wearable devices for monitoring of candidates to AF ECV (specific Informed Consent). In particular, we analysed the effect of AF ECV on heart rate variability and vascular age parameters derived from PPG signals registered with Empatica (CE 1876/MDD 93/42/EEC), and on EEG pattern registered with Neurosteer (Israel).

Results:

From December 2005 to September 2019, we enrolled 492 patients, divided in two groups. In the first, we evaluated acute efficacy of AF ECV using AAP vs APP. and we elaborated a decision algorithm based on BSA, weight, and height. In the second, we validated the decision algorithm on ECV approach, which improved first shock efficacy (93.2% vs. 87.2%, p=0.025).

From 1st November 2021 to 1st April 2022, 24 patients were enrolled in the pilot study evaluating the feasibility of the use of Empatica and Neurosteer for monitoring of candidates to AF ECV. Considering vascular age parameters, it was observed a significant reduction in both TPR and a wave ($p<0.001$). Considering sleep patterns, a tendency to higher coherence was observed in registrations acquired during AF than in presence of sinus rhythm, or considering signals registered before and after ECV for each patient.

Conclusion: In this cohort of real-world candidates to AF ECV, we compared first shock efficacy using two widespread strategies, and we elaborated a decision algorithm, which improved acute efficacy tailoring ECV approach on biometrical parameters, and reduced costs associated with the use of adhesive patches. In the second part, we evaluated the feasibility of a new setting of patient monitoring using innovative wearable devices in candidates to AF ECV. Significant modifications were observed on vascular age parameters derived from PPG signals measured before and after ECV. Moreover, a possible AF effect on sleep pattern registered with Neurosteer was notice, but more data are necessary to confirm these preliminary results.

Short abstract

Atrial fibrillation (AF) is a widespread arrhythmia, associated with higher risk of stroke, sleep disorders and dementia. In some conditions, electrical cardioversion (ECV) represents the best choice for rhythm control. Nowadays, there is a growing interest in developing new devices for screening and monitoring of AF patients. We aimed to improve acute efficacy of ECV procedure and to explore the feasibility of the use of new wearable devices for monitoring in candidates to AF ECV. We compared antero-apical pads vs antero-posterior patches approach for AF ECV, and we elaborated a decision algorithm to improve acute efficacy. After, we evaluated the feasibility of the use of new wearable devices for monitoring of candidates to AF ECV. In particular, we analysed the effect of AF ECV on heart rate variability and vascular age parameters derived from PPG signals registered with Empatica (CE 1876/MDD 93/42/EEC), and on EEG pattern registered with Neurosteer (Israel).

From December 2005 to September 2019, 492 patients were enrolled. We evaluated acute efficacy of the two approaches for AF ECV and we elaborated a decision algorithm based on body surface area, weight, and height. The decision algorithm improved first shock efficacy (93.2% vs. 87.2%, p=0.025). From 1st November 2021 to 1st April 2022, 24 patients were enrolled in PPEEG-AF pilot study. Considering vascular age parameters, a significant reduction in TPR and a wave was observed ($p<0.001$). Considering sleep patterns, a tendency to higher coherence was observed in registrations acquired during AF, or considering signals registered for each patient independently from AF.

The new decision algorithm improved acute efficacy and reduced costs associated with adhesive patches. Significant modifications were observed on vascular age parameters measured before and after ECV, and a possible AF effect on sleep pattern was noticed. More data are necessary to confirm these preliminary results.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia, and its incidence is increasing worldwide.[1] AF is associated with a growing risk of stroke, being involved in up to one third of the ischemic cerebrovascular events with a high risk of disability and death.[2] Notably, arrhythmia symptoms and persistence are not strictly related with clinical events, and prevalence of asymptomatic AF seems to be about double with respect to symptomatic AF. For this reason, there is a general claim for large-scale screening and monitoring programs in patients affected or at risk of AF, to reduce the incidence of disabling events.

The electrical cardioversion (ECV) for rhythm control in AF patients is used since a long time with the aim to restore atrial contribution to ventricular filling, regularize heart rate (HR) and reverse atrial remodelling. Despite the results of AFFIRM (A comparison of rate control and rhythm control in patients with atrial fibrillation)[3] and RACE (A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation),[4] that support the rate control strategy in AF patients; nowadays the rhythm control strategy represents a suitable option in patients at low risk of AF recurrence. The treatment of choice between rhythm and rate control in AF patients remains a debated topic, and the best choice is tailored on the specific clinical characteristics of patient, in particular arrhythmia recurrence risk and presence of cardiopathy or heart failure. Conversion of AF to sinus rhythm can itself be beneficial and remains an important therapeutic option,[5] especially with the development of antiarrhythmic drugs to help persistence of sinus rhythm.[6-9] Although in literature there are some data regarding possible predictors of AF recurrence after ECV,[6, 10-13] these primary concern with clinical and/or instrumental data (e.g. AF duration, left atrial dimension, diagnosis of rheumatic disease, and previous ECV).

Some patients that underwent ECV can develop heart failure during early follow up, because of atrial stunning can impact ventricular filling, despite sinus rhythm restoration. To prevent this clinical event, it can be relevant the possibility of home-monitor after ECV.

Another interesting field of research is the connection between sleep disorder and AF. The Sleep Heart Health Study (SHHS) trial showed a strong association between AF and obstructive sleep apnoea (4.8% AF prevalence in patients with sleep breathing disorders vs 0.9% in the remaining cohort, p= 0.003). Moreover, several studies showed that >50% AF patients can present some kind of sleep disorders.[14] Moreover, sleep apnoea seems to play a crucial role on AF progression and failure of treatments. However, we lack data on the effect of AF interruption on sleep disorders. The modification of cerebral flow induced by sinus rhythm restoration can theoretically impact on sleep function, but we need additional data. Multiple cardiovascular risk factors and vascular diseases concur to

development of cognitive deficit and dementia. Numerous studies showed a correlation between AF and dementia, both vascular and degenerative. Possible pathogenetic mechanisms are manifested or silent cerebral ischemic stroke, multiple cerebral mini-stroke, cerebral haemorrhage or reduced global cerebral perfusion; however, a better understanding about correlation between AF and dementia can improve clinical management of patients with an initial cognitive deficit.[15, 16]

There are few data about better strategy for ECV procedure, to improve acute efficacy. ECV specific mechanism is not yet well known, and published data derived generally from studies about defibrillation of ventricular arrhythmias. The aim of the first part of the thesis was to compare efficacy of ECV of AF patients using anterior-apical pads (AAP) vs anterior-posterior patches (APP), to create and algorithm to improve acute efficacy of ECV. Processed algorithm was validated in a control population.

In the second part of the thesis, we evaluated clinical outcomes in candidates to AF ECV, using a set-up for multi-parametric analysis. In particular, new technologies were exploited for photoplethysmographic (PPG) and electroencephalographic (EEG) signal registration, integrated with clinical and instrumental data, to study AF ECV outcomes and AF impact on sleep pattern and cognitive function.

CHAPTER 1

ATRIAL FIBRILLATION

Association between irregular artery pulse and mitral stenosis was described for the first time by Robert Adams in 1827. Around 1900, after the invention of electrocardiograph by William Einthoven, atrial fibrillation (AF) was registered for the first time by Sir Thomas Lewis at University College Hospital of London.[17] The interest regarding AF grew progressively because of its clinical relevance; in fact, AF symptoms can cause reduction of exercise tolerance and worsening in quality of life (QoL). AF is also associated with cardiovascular and cerebrovascular events, and a high mortality rate. Nowadays, AF prevalence reached epidemic proportion, and it is estimated that AF incidence will grow because of general population aging.[18] Considering social and economic field, AF influences health costs, directly and indirectly, with loss of work power and growing disability, pressing national health care systems.[19] AF clinical importance growth was followed by a large number of published studies, with knowledge advancements pathogenesis, risk factors and therapeutic strategies.[20]

Epidemiology

AF is the most frequent clinically relevant arrhythmia with an estimated prevalence of 2-4% in adult population.[7] In 2010 it was calculated that 33.5 million of patients were affected by AF worldwide; moreover, AF incidence is growing.[21] It was observed growing AF prevalence in both sexes, with a higher prevalence in males. This growth was higher in advanced countries, in particular in North America (40.1%), and lowest in Sub-Saharan countries (3.4%).[21] Worldwide, lowest AF incidence was registered in Asian Pacific countries in both sexes, and highest in North America.

Age is a major AF risk factor,[20] with double AF incidence in patients over 35 years old;[21] it is estimated that one third of patients will develop AF over 55 years old.[22] A Scottish study reported AF incidence considering classes of age: 50/100,000 in 45-54 years old patients, 110/100,000 in 55-64, 320/100,000 in 65-74, 620/100,000 in 75-84, and 770 in ≥85.[23] European population is aging, and European Statistical Agency "Eurostat" estimates that in European countries 29.5% subjects were at least 55 year old in 2010, and this percentage will grow to 41.0% within 2060. If AF prevalence estimation remains stable, the numbers of AF patients will grow from 8.8 (1.8%) in 2010 until 17.9 (3.5%) millions within 2060.[24] It is interesting to underline that most old females are affected by AF; in fact, albeit AF is more prevalent in males at every age, >75 years old women are double alive than men, of consequence 60% old AF patients are female.[25]

Nowadays, AF represents an import issue for health care system with high social costs. In United Kingdom in 2000 1% national budget was spent for AF management.[26] A study of Kim et al. compared

United States costs spent for AF patients vs patients not affected, and AF was associated with an increment in health care costs of about 6 billion.[27] Blomstorm et al.[19] published data regarding AF costs; in particular, they showed that most costs were related to hospitalizations (52%), followed by drug therapy (23%), medical consultations (9%), instrumental exams (8%) and clinical assistance (2%). Growing incidence and prevalence of AF give relevance to this arrhythmia, which is associated with high morbidity, mortality, and social costs. Identification of modifiable risk factors could be the way to reduce AF incidence and related mortality and health care costs.[18]

Pathogenesis

AF is a complex arrhythmia, characterized by fast and disorganized electrical activity, caused by different physiopathological processes. AF development needs a trigger that initiates the arrhythmia, and a substrate for the maintenance, which consists in electrophysiological, mechanical and anatomical factors that sustain AF.[28] Most supported hypothesis affirms that AF trigger is represented by rapid potentials, coming from single or multiple atrial ectopic foci. These potentials start multiple re-entrant wave fronts, that cause AF in a vulnerable atrial substrate.[20, 29] In 1998 Haissaguerre et al.[30] identified that AF triggers occur at pulmonary vein origins. This result is supported by the fact that pulmonary vein isolation with transcatheter ablation permits sins rhythm persistence in 70-80% cases.[28] It was observed that pulmonary vein origins, in presence of favouring conditions, have predisposition to triggered activity, an automatic oscillation of membrane polarization that can generate new action potentials.[31] In relation to time in which these potentials develop, they are called early or late post-potentials. Late post-potentials are generally the cause of AF from pulmonary vein origins. These potentials are characterized by a diastolic loss of Ca^{2+} from the sarcoplasmic reticulum, this phenomenon causes Ca^{2+} overload in cytoplasm, which activates Na^{+}/Ca^{2+} exchanger. This generates Na^{+} entrance in cardiomyocytes, that causes a spontaneous premature depolarization.[20, 31, 32]

Beside pulmonary vein foci, there are other possible sites of AF initiation; in particular, superior cava vein, coronary sinus, left atrial appendance, Marshal ligament, terminalis crista and free posterior left atrial wall. Alternative initiation sites are more frequent in long persistent AF, and in patients that already underwent transcatheter ablation.[28] Ganglionic plexuses, that are conglomerates of autonomic ganglia located near epicardium, can play a role in AF onset and maintenance. In particular, cholinergic activity seems to be principally involved in AF beginning, whilst an increase in sympathetic activity in AF maintenance.[29] Effect of AF triggers is influenced by modification in atrial substrate.[20] Triggers are fundamental for AF onset; however, an atrial substrate vulnerable to re-entry circuits is necessary. Re-entry mechanism is not completely understood; nowadays, there are two dominant hypotheses,

which can be integrated. The hypothesis of chaotic activation, theorized by Moe e Abildskov,[33] that identifies multiple simultaneous re-entrant wave fronts. The second theory conceives presence of rotors, whose wave fronts are curve or spiral, that can be founded in the atrium, often near pulmonary vein origins or in areas with heterogeneous tissue. Wave fronts spread and fragment from rotor center, inducing a chaotic activity in the atrium.[34] Circulating wave fronts have to propagate quite slowly, so that atrial tissue could be out of absolute refractory period and depolarizable. Short refractory periods, slow electrical conduction and anatomical conduction barriers are fundamental aspects that promote re-entry;[32] these elements contribute to AF maintenance, as results of electrical and structural remodelling caused by the arrhythmia.[35]

Atrial remodelling

Ventricular cardiomyopathies were extensively studied and classified in literature. However, only recently atrial structural and electrophysiological modifications, that characterized different clinical cardiopathies, are classified within a univocal definition.[36] In 2016 EHRA (European Heart Rhythm Association), HRS (Heart Rhythm Society), APHRS (Asian Pacific Heart Rhythm Society), and SOLAECE (Sociedad Latino-Americana de Estimulacion Cardiaca y Electrofisiologia) groups proposed this definition of atrial cardiomyopathy: "Any structural, architectural, contractile or electrophysiological changes involving atria with possible subsequent clinical relevant manifestations.[36] This definition includes atrial remodelling induced by AF; however, atrial cardiomyopathy can be present before AF development.[35] Atrial remodelling is a time-dependent response of cardiomyocytes in case of different stress agents; in particular, electrical, mechanical and metabolic.[37] Stress agents cause fibroblastic proliferation and extracellular matrix deposition with subsequent atrial enlargement, these structural and functional changes create the substrate for AF beginning.[37] Moreover, electrical imbalance caused by AF determinates pathological substrate modifications, that contribute to AF maintenance. Rapid depolarization of atrial myocytes causes intracellular Ca^{2+} accumulation, which triggers adaptive and inflammatory responses, that determine myocyte apoptosis and precipitate atrial remodelling and fibrosis, with subsequent persistence of the arrhythmia.[35] Atrial electrical remodelling creates an environment that facilitate re-entry circuits.[37] Anomalous Ca^{2+} release from sarcoplasmic reticulum and down-regulation of L-type Ca^{2+} current cause cytosolic overload of this ion.[32, 38] This phenomenon, associated with increase in rectified K_1 current, leads to a shortening in action potential duration and absolute refractory period, that promote and stabilize re-entry circuit.[38] Finally, gap-junctions' abnormalities, in particular connexin mutations, can reduce conduction velocity.[35]

Atrial remodelling is characterized by tissue changes that appear during AF progression; in particular, modification in atrial geometry and structure, including ultrastructural cardiomyocytes alterations.[32] Principal structure modification is atrial enlargement, that is correlated with tissue fibrosis.[28] Atrial enlargement favours arrhythmia maintenance, because re-entrant circuits necessitate of a critical mass to persist.[32] Moreover, atrial enlargement causes cardiomyocytes' stretching, that is associated with AF development, reducing conduction velocity and increasing anisotropy.[32] Atrial fibrosis is arrhythmogenic for different reasons:

- Fibrotic tissue separates muscular bundles, interrupting muscular continuity and creating physical barriers to conduction, which promote re-entry phenomenon.
- Atrial fibrosis is characterized by fibroblastic proliferation and myofibroblastic differentiation.

The interaction between atrial cardiomyocytes and myofibroblasts promotes spontaneous ectopic activity and re-entry. Finally, cardiomyocytes interact with fibroblasts, that are not excitable, but conduct currents, dissipating and delaying electrical conduction.[39] Ultrastructural cardiomyocyte alterations were observed; in particular, loss of sarcomeres and glycogen accumulation, an adaptive mechanism that reduces cellular contractility.[32]

During last years, more evidence were published regarding inflammation rule in promoting AF onset and maintenance.[28] In fact, systemic inflammation is characterized by endothelial and endocardial involvement. Different inflammatory mediators interact in electrical and structural atrial remodelling; in particular, tumour necrosis factor (TNF), l'interlechina-2 (IL-2), and platelet-derived growth factor (PDGF). These mediators regulate Ca^{2+} homeostasis and cause a shortening in action potential duration.[38] Inflammatory cells' migration and pro-inflammatory molecule release cause tissue damage with subsequent atrial fibrosis development. Leucocytes, infiltrating atrial tissue, secrete myeloperoxidase (MPO), which play a role in extracellular matrix alterations with subsequent tissue disarrangement and fibrosis.[40] Another inflammation mechanism is mediated by angiotensin II, that activates NADPH oxidase with production of reactive oxygen species (ROS). ROS excessive production determinates oxidative stress; moreover, these molecules play a role as mediators. In fact, they contribute with angiotensin II to Ca^{2+} intracellular overload in cardiomyocytes with subsequent atrial loss of contractility and activation of Ca^{2+}-dependent signalling.[40] This phenomenon induces oxidative stress, membrane dysfunction, energy depletion, cellular apoptosis and inflammation. Moreover, tachycardia associated with AF causes itself Ca^{2+} overload and subsequent inflammatory consequences. AF maintenance and atrial inflammation are concomitant processes, that sustain each other.[41]

Diagnosis and classification

AF is a supraventricular arrhythmia, characterized by irregular ventricular rate; the diagnosis is based on specific electrocardiographic findings:

- Irregular R-R intervals (particularly in case of normal atrioventricular conduction)
- Absence of distinct and repetitive P waves
- Irregular atrial activation

Following actual European guidelines on AF management, these characteristics founded in a 30-second electrocardiogram (EKG) are diagnostic.[7]

Generally, AF is classified in five categories, based on arrhythmia duration:[7]

- First episode: First AF diagnosis, independently of duration and/or symptoms
- Paroxysmal: episode terminated within 7 days
- Persistent: episode lasting more than 7 days
- Long persistent: episode lasting more than 1 year
- Permanent: when AF is accepted, and no more rhythm control attempts are undertaken

This simple classification standardized the nomenclature and presents correlations with atrial substrate extension. However, this arrhythmia is a complex and multifactorial disease, and this classification lacks precision since it considers only time dimension of the disease. 4S-AF Scheme was proposed for a more structured AF classification, it includes 4 domains:[42]

- Stroke risk: CHA_2DS_2-VASc Score recommended for thromboembolic risk stratification.
- Symptoms: EHRA Symptom Scale and QoL questionnaires.
- Severity of AF burden: episodes duration and frequency (anamnesis and follow up). The introduction of new technologies for patient monitoring, as wearable devices, could have an important role in the next future.[7]
- Substrate severity: it concerns cardiovascular risk factors, comorbidities, and atrial remodelling [determined by transthoracic or transoesophageal echocardiography (TTE or TEE), cardiac computed tomography (CT) or magnetic resonance (MR), and biomarkers].

This scheme provides useful suggestions for decision making in AF management, in particular regarding oral anticoagulation (OAC) indication, choice between rhythm and rate control strategy, and comorbidities' treatment.[42] However, this approach has not yet widely validated.

ESC guidelines[7] recommend EHRA Symptom Scale for symptoms' classification (see Table 1).

SCORE	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

Table 1. EHRA Symptom Scale.

Most frequent symptoms include palpitations, dyspnoea, asthenia, chest pain, dizziness, sleeping abnormalities and syncope.[7] Data from Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF)[43] showed a high percentage of symptomatic AF patients (61.8%); in particular, patients affected by paroxysmal form are more symptomatic than persistent AF patients (53.8% vs 45.3%, p<0.001). Another study confirmed this result; respectively, paroxysmal AF symptomatic patients were 80%, persistent 76%, and permanent 51% (p<0,0001).[44] Some data about QoL (AFEQT questionnaire) were published from ORBIT-AF Registry.[43] Patients in inferior QoL quartile presented more comorbidities; in particular, peripheral vasculopathy, congestive heart failure, chronic obstructive pulmonary disease (COPD), obesity and sleep apnoea. Finally, QoL was related to EHRA Symptom Scale.

In patients with new onset AF, it is important to evaluate hemodynamic status. In case of hemodynamic imbalance (i.e., syncope, acute pulmonary oedema, myocardial ischemia, symptomatic hypotension, or cardiogenic shock) ECV is recommended.[7] Finally, asymptomatic AF exists and can shows up primarily with complications (i.e. heart failure or cerebral ischemic stroke).[45]

Complications

AF is associated with high risk of cerebral transient ischemic attack (TIA) or stroke.[20] 15-20% of cerebral ischemic strokes affect AF patients and are associated with major severity and mortality.[46] Stroke risk is related to age and comorbidities; in fact, it is estimated 1.5% in patients between 50 and 59 years old, and >23% in over 80.[32] Even asymptomatic or subclinical AF is associated with higher stroke risk.[47]

AF and heart failure are interdependent conditions,[48] with similar risk factors (i.e., hypertension, diabetes, ischemic cardiopathy and valvular diseases).[20] Heart failure causes AF with different mechanisms: neurohormonal, structural and functional. Heart failure raises left atrial pressure, with

subsequent atrial dilatation, fibrosis, and conduction abnormalities. Furthermore, AF can cause or precipitate heart failure. In fact, loss of atrial systole, high ventricular rate and diastolic impairment determinate high atrial pressure, and decrease blood pressure and cardiac output.[48] The coexistence of these two clinical conditions is associated with high mortality rate (OR 1.26, 95% 95%CI 1.03-1.42; p=0.02).[49]

Over 60% AF patients present significantly compromised QoL and/or exercise tolerance, and 17% present disabling symptoms.[43] Development of anxiety disorders or depression, related to AF symptoms, mostly impairs QoL.[50] Generally, females are most symptomatic than males (85.0% vs 68.3%; p<0.001), and perceive more negatively their health condition.[44]

There are a lot of data regarding correlation between AF and cognitive impairment and dementia. Thromboembolic risk prevention plays a key role in the prevention of these conditions, thanks to adequate OAC. Moreover, even in absence of previous cerebral ischemic strokes, AF is associated with higher prevalence of dementia; and this fact can be related to silent strokes or mechanisms different from cardio-embolism. It was hypnotized that in AF patients systemic inflammation and reduction in cerebral blood flow can contribute to dementia development.[51]

AF is associated with high mortality rate (3.5 times). In particular, 1/10 deaths among AF patients is associated with cerebral ischemic stroke, while 7/10 are caused by cardiovascular conditions.[52] Nowadays, only OAC significantly reduces AF mortality; meanwhile, there are conflicting data regarding impact of rhythm control strategies on mortality.[32, 53]

Patient management: ABC approach

The simple Atrial Better Care (ABC) pathway is a proposed strategy to manage AF patients in a holistic and structured way:

- A: Avoid stroke
- B: Better control of symptoms
- C: Cardiovascular and comorbidity treatment[54]

This approach was associated with better outcomes (i.e., mortality, ischemic stroke, major bleeding, cardiovascular mortality and hospitalization).[7, 52]

Stroke preventions is generally mediated by OAC, that determines 24% reduction in mortality and 64% in stroke incidence.[55] Stroke risk is influenced by multiple risk factors, that are combined in CHA_2DS_2-VASc Score (Table 2), widely used in clinical practice.

SCORE	Risk factors	Points
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75 years old	2
D	Diabetes	1
S	TIA/Stroke	2
V	Vasculopathy	1
A	Age between 65 and 74 years old	1
Sc	Female	1

Table 2. CHA2DS2-VASc Score.

Following ESC guidelines,[7] males with CHA2DS2-VASc ≥2 and females ≥3 have OAC indication; meanwhile, patients with no risk factors (not considering gender) do not have indication, and patients with one risk factor are borderline. Patients at low risk of stroke should be revaluated during follow up.[56] Vitamin K antagonists (VKA) were for a long period the first choice for OAC in AF patients; however, VKA use is limited by necessity of INR monitoring to target dosage.[7] After approval, direct oral anticoagulants (DOAC) rapidly spread. All DOAC (apixaban, edoxaban, rivaroxaban and dabigatran) demonstrated a good safety/efficacy ratio.[57-60] In a published meta-analysis,[61] DOAC were associated with 19% reduction in stroke or thromboembolic events (OR 0.81, 95%CIC 0.73-0.91; p<0.001). Moreover, they reduced all-cause mortality (OR 0.90, 95%CI 0.85-0.95; p=0.003) and intracranial bleeding (OR 0.48, 95%IC 0.39-0.59; p<0-0001) but were associated with higher incidence of gastrointestinal bleeding (OR 1.25, 95%CI 1.01-1.55; p=0.040). Nowadays, DOAC are the first choice in case of OAC indication, except for patients with moderate or severe mitral stenosis, mechanical prosthetic valves or 5th degree renal failure, in which these drugs are contraindicated in favour of VKA.[7, 62]

For treatment of AF symptoms, two possible strategies are available: rhythm vs rate control. Rhythm control strategies aim to restore sinus rhythm in symptomatic AF patients.[7] At first step rhythm management consists in cardioversion, pharmacological or electrical (first choice in unstable patients), also thanks to antiarrhythmic drugs' development, that can help long term maintenance of sinus rhythm. Afterwards, interventional strategies, as transcatheter or surgical ablation, can be considered. ECV presents higher efficacy than pharmacological (about 90%) and is suggested in case of persistent AF. Pharmacological cardioversion is useful in stable paroxysmal or recent onset AF; it is a simple procedure, that does not need sedation.[7, 63] Moreover, some patients necessitate of antiarrhythmic therapy before undergoing ECV, to improve persistence of sinus rhythm restoration.[64] Different drugs

are used for sinus rhythm restoration. Flecainide and propafenone are useful in absence of ventricular systolic dysfunction, and can be orally administered in outpatients.[7, 65] Amiodarone is used with good efficacy in case of ventricular systolic dysfunction; however, chronic administration is associated with side effects.[66] Rate control strategy aims at reducing ventricular rate, principally with a pharmacologic approach:[7]

- Beta-blockers: First choice in case of normal or moderate impair ventricular function, with good efficacy both in acute and chronic conditions. Contraindicated in case of severe COPD or asthma.[7, 67, 68]
- Non-dihydropyridine calcium channel blockers: Diltiazem or verapamil is first choice in case of normal ventricular function. Compared to beta-blockers, they are associated with better exercise tolerance.[7, 69]
- Digoxin: Second/third line because of possible toxicity, mainly used in patients with ventricular dysfunction.[7, 29]
- Amiodarone: Generally used for rhythm control, last choice for rate control thanks to its negative chronotropic property. It can be used in acute phase in patients with hemodynamic instability.[7, 67]

While results from AFFIRM (The results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management)[3] and RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation)[4] trials reduced the appeal for sinus rhythm restoration, current evidences are in favour of rhythm control strategies, especially in heart failure patients[70] and/or in presence of recent onset AF[71]. DOAC availability, obviating VKA complex management, improved the road to sinus rhythm restoration through ECV. Moreover, the advent of transcatheter ablation for rhythm control demonstrated an improvement in ventricular systolic function and QoL in patients with heart failure.[7, 48, 52] The rhythm control strategy should be preferred in young patients with limited atrial remodelling and no relevant comorbidities.[7, 65]

Several risk factors are implicated in AF development and maintenance (see Table 3). A vicious lifestyle and/or presence of cardiovascular diseases can contribute to atrial remodelling, creating AF substrate. Different mechanisms can favourite the arrhythmia:[32, 41]

- Inflammation
- Structural remodelling
- Conduction abnormalities
- Intracellular Ca^{2+} overload
- High sympathetic tone

More evidences suggest the importance of a good lifestyle and management of comorbidities, to better treat AF patients (weight loss, diet, alcohol consumption limitation, stop smoking, glycaemia and blood pressure control).[7, 72]

AF risk factors	
Age	Sex
Genetic factors	Valvular heart disease
Hypertension	Diabetes
Heart failure	Coronary artery disease
Sleep apnoea	Previous heart attack
Obesity	Sedentary lifestyle
Renal failure	Alcohol abuse
Hyperthyroidism	Smoke

Table 3. AF risk factors.

ELECTRICAL CARDIOVERSION

After the advent of defibrillator for the treatment of ventricular fibrillation, in 1962 Lown et al. applied this technology for the treatment of AF patients;[73] the old procedure do not much differ from actual practice.[64] ECV is used for sinus rhythm restoration in case of different tachyarrhythmias, it consists in the delivery across the thorax of a direct current shock synchronized with QRS complex (a random shock could happen during T wave vulnerable period, causing ventricular fibrillation). Nowadays, direct current is used for ECV, because it was demonstrated that alternative current causes more myocardial damage, because of high flow and duration of delivered energy.[74] In the past, for ECV two types of defibrillator were used, able to deliver monophasic or biphasic shock wave. The first type delivers current only in one direction, in the second type the shock wave flows in both directions more times. During first phase, biphasic shock wave causes myocardium hyperpolarization, with recovery of Na^+-channel activity; so in the second phase it is more effective in myocardium depolarization, blocking the arrhythmia.[64] Evidences suggest the use of biphasic shock defibrillators, because they are characterized by better efficacy than monophasic at low energy levels and with a minor number of required shocks; these properties ensure less procedure side effects, as skin burns.[74, 75]

ECV is a fundamental procedure for rhythm control,[7, 76] it is the first choice in hemodynamic unstable AF patients.[77] ESC guidelines[7] suggest ECV in symptomatic patients, in particular in presence of these characteristics:

- Young age
- First/recent onset AF
- No/few comorbidities
- Absence of organic cardiopathy or presence of tachycardiomyopathy

ECV efficacy is estimated from 60% to 98%.[78-80] However, a relevant problem after effective ECV is the high incidence of AF recurrence, that is about 50-70% at one year.[78, 81] Patient opinion about possible strategies should be considered by clinicians, before choosing better patient tailored approach.

Electrophysiological mechanism

Nowadays, ECV mechanisms are not completely understood, and available knowledges principally derived from studies on defibrillator for the treatment of ventricular fibrillation. AF is characterized by multiple casual re-entrant wave fronts circulating through atria. Therefore, ECV aims to determinate coordinate action potential changes in a relevant area of atria, so that sinus rhythm can be restored.[64] Most theories were elaborated to explain the effect of electric shock on arrhythmia interruption. The hypothesis of refractory period prolongation affirms that shock prolongs cardiomyocytes' refractory

period, of consequence re-entrant wave fronts cannot propagate, because myocardial tissue is refractory; AF stops, and sinus node resumes normal activity.

Zipes et al.[82] elaborated the theory of critical mass: for an effective defibrillation a quite extensive area of myocardium must be depolarized. Electrical application can be itself pro-arrhythmic.[83] In fact, there are vulnerability energy limits for arrhythmia induction, inferior and superior; the last is comparable to shock threshold. From these observations arises the hypothesis of upper limit of vulnerability: for an effective defibrillation, the shock must block activation fronts, but also must not reinitiate arrhythmia circuits.[74]

ECV procedure

Before ECV procedures some recommendations should be considered: patient needs venous access and monitoring (EKG, pulse-oximetry, and pressure), and respiratory support equipment should be available. Patient must be sedate with a short-acting agent, such propofol or midazolam (the first is considered the best option, with a rapid recovery period and low rate of side effects); drug antagonists should be available.[84]

Shock delivery must be synchronized with QRS complex, and level of energy selected. Two strategies can be used for shock delivery:

- AAP: one pad is positioned in $4^{th}/5^{th}$ intercostal space on medium-axillary line, second is in $2^{nd}/3^{rd}$ intercostal space on right sternal margin.
- APP: one patch is positioned on right sternal margin, the second between inferior left shoulder blade limit and vertebral column.

Some recommendations must be considered to reduce thoracic impedance: conductive gel utilization, skin cleaning with alcohol solution, and hair shave. Pacemakers (PM) and implantable cardioverter defibrillator (ICD) must have a distance of at least 8 cm from ECV electrodes.[85]

The choice of initial shock energy is a debated issue. AF stops if an adequate myocardial mass is depolarized,[74] and current depends on thoracic impedance and quantity of delivered energy.[76] After the development of ECV technique, Lown et al.[86] implemented growing energy protocol; this consists in a first low energy shock, followed by growing energy shocks in case of unsuccess of the first. The aim of this approach was to minimize totally delivered energy and post-shock arrhythmic risk; in fact, high shock energy could damage myocardial tissue and trigger atrial and ventricular arrhythmias.[87] Another possible approach consists in high shock energy application from the beginning, to reduce total number of necessary shocks and subsequently procedure time (in particular sedation exposure).[74] Nowadays, scientific community does not suggest a specific approach for clinical practice.

Monophasic defibrillators needed higher shock energy than biphasic,[74] so 2001 guidelines suggested a first shock at 200 J.[88] With the advent of biphasic defibrillators, low shock energy levels were tested with good efficacy;[89-91106,107,108] Canadian guidelines recommend a first shock at 150 J.[65]

Patient management

The first step of AF patient management is the evaluation of hemodynamic status. In case of unstable AF patients, ECV can be the best choice to promptly restore sinus rhythm;[67] however, in case of long episodes (>48 hours) and inadequate anticoagulation a TEE should be performed. In stable subjects, the first issue is to verify adequate anticoagulation status, because AF cardioversion increases the risk of stroke and thromboembolic events.[78] If the patient takes adequate anticoagulation therapy, the choice is between cardioversion, pharmacological or electrical, vs wait and see approach (in particular in patients affected by recent onset AF).[7, 92] In patients not under adequate anticoagulation, AF duration must be verify. In case of <48 hours' AF episodes, anticoagulation must be started promptly, and ECV can be performed immediately with a low thromboembolic risk.[93] If AF episodes last >48 hours, anticoagulation therapy must be administered for at least 3-4 weeks, before proceeding to ECV.[94] If ECV is immediately necessary in patients affected by >48 hours' episodes, a TEE must be performed to exclude presence of atrial thrombus; otherwise, oral anticoagulation must be administered for at least 3-4 weeks before ECV procedure.[95] After ECV, all patients must take oral anticoagulant therapy for at least 4 weeks, after this period chronic indication to oral anticoagulation must follow thromboembolic risk (CHA_2DS_2-VASc score ≥ 1 in men, ≥ 2 in women).[7]

Complications

Incidence of thromboembolic events after ECV of >48 hours' AF episodes is estimated about 1-2% within 10 days after procedure, and adequate OAC for 3-4 weeks before ECV reduces risk of thromboembolic events at 0.28-0.33%.[96, 97] A lot of factors contribute to thrombus formation before and after ECV (i.e., alterations in blood flow, activation of inflammation and coagulation response, atrial remodelling and stunning).[98] Sinus rhythm restoration can cause embolization of preformed thrombus.[78] Moreover, atrial stunning after ECV (atrial contractile depression) can favourite thrombus formation; it is maximal immediately after ECV, and needs time to regress (from few minutes to 4-6 weeks in relation to AF episode duration, atrial dimension and presence of cardiopathy).[99] European AF guidelines actually recommends OAC for 4 weeks after ECV in case of episodes lasting >48 hours;[7] instead, patients with <48 hours' AF episodes have a low risk of thromboembolic events (excluding patients with high CHA_2DS_2-VASc score).[78] Regarding OAC, DOAC progressively

replaced VKA; in fact, VKA use needs time to reach INR target and frequent laboratory samples.[100] DOAC safety in patients undergoing ECV was validated in numerous studies.[101, 102] Nowadays, DOAC represent the first choice for thromboembolic risk prevention in candidates to AF ECV; however, VKA use remains important in case of contraindications to DOAC.[62] Thromboembolic and haemorrhagic events after ECV are rare, and generally caused by wrong management of OAC.[80]

Other possible complications of ECV are ventricular fibrillation (caused by sedation or loss of synchronization between shock and QRS complex), non-sustain ventricular tachycardia, atrial arrhythmias, bradycardia, atrioventricular block, left bundle branch block, myocardial ischemia, cardiac dysfunction, hypotension, pulmonary oedema, skin burn and pain.[76, 78]

Efficacy

ECV is characterized by high efficacy rate; however, 50-70% of patients present AF recurrence at 1 year.[78, 81, 103, 104] AF recurrence can occur at different time, about 10% of patients present an early recurrence, and most AF recurrences happen during the first month after ECV procedure.[78, 105] ECV efficacy is influenced by clinical, structural and technical factors.[106] Paroxysmal AF is generally associated with triggers, while AF risk factors are more represented in persistent or permanent forms.[107] A lot of studies try to identify risk factors associated with acute and long term efficacy, in order to optimize ECV procedure and duration (sedation time, total delivered energy with possible complications),[86, 108] and sinus rhythm maintenance after procedure with improvement in QoL.[109131] These risk factors can be related to patient or to procedure.[106]

Thoracic impedance

When a defibrillator delivers a shock, the quantity of delivered energy is measured in J. The delivered energy is characterized by current intensity, measured in Ampere (A), and electric voltage, in Volt (V). Current density, which is influenced by crossed materials, determinates defibrillation efficacy. Thoracic impedance, measured in Ohm (Ω), reflects tissue resistance to current flow. Crossed tissues influence current flow, reducing current density that reaches the myocardium.[110] Thoracic impedance is determined by numerous factors:

- Procedure related factors: effective delivered energy, electrode dimension and composition, interface between skin and electrode, respiratory period, pressure and distance between electrodes, effect of single shock and time between.[76, 110]
- Tissue composition between electrodes and heart.[64]

A specific current density is necessary to cardiovert myocardium, and it is estimated that only 4% of delivered current reaches the myocardium, so reducing thoracic impedance is fundament for ECV efficacy.[111] Electrode dimensions influence current density; in particular, bigger electrodes reduce impedance (too big electrodes reduce current density, too small concentrate energy with possible myocardium damage).[110] Air reduces conductivity, so conductive material and/or pressure must be apply between electrodes and skin.[112] Modern defibrillators are able to balance thoracic impedance, adjusting delivered energy during biphasic shocks.[74] A study of Sadek et al. analysed 1055 biphasic shocks performed in 703 patients, and demonstrated that thoracic impedance is a predictor of total number of deliver shocks, of total delivered energy and of procedure efficacy.[111] Even with modern defibrillators, thoracic impedance remains an important factor able to influence ECV efficacy.

Electrode positioning is an important factor influencing thoracic impedance,[113] and numerous studies tried to find the better strategy; however, ESC guidelines do not report significantly differences in term of outcomes between the two strategies (AAP vs APP).[7] Vector generated in case of right APP positioning (Figure 1A) involves both atria. It useful in case of AF; however, electrodes are distant, and some pulmonary tissue can be involved. Left APP positioning (Figure 1B) determinates less distance and pulmonary tissue between the two electrodes. Finally, AAP (also called antero-lateral, see Figure 1C) is the best choice in case of ventricular fibrillation, but it is sometimes used for atrial arrhythmias.[110]

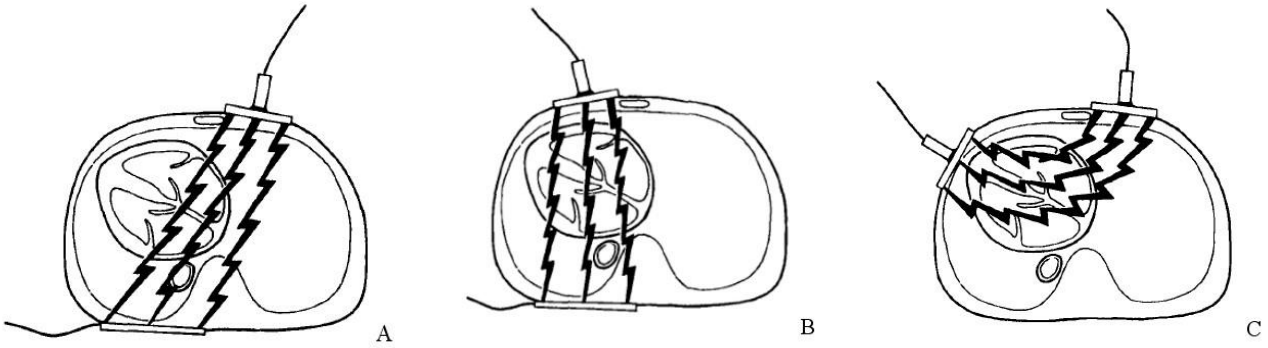


Figure 1. Possible electrode positioning: (Panel A) right APP, (Panel B) left APP, and (Panel C) AAP (modified by Ewy).[59] AAP, anterior-apical pads; APP, anterior-posterior patches.

Instead of choosing absolute better ECV approach, it is interested that some studies identify subgroup of patients in which a specific electrode positioning can be preferred. The study of Voskoboinik et al. suggests the AAP approach in obese subjects, because thoracic impedance can be reduce with pressure.[114] Regarding electrode materials, some considerations have to be outlined. Adhesive patches have the advantage of causing less skin burn and personnel necessity; however, they have to be change each patients with high costs.[115] After initial cost for purchasing, pads have minor daily costs, but they

need good cleaning after use.[116] Pads' use permits to reduce thoracic impedance exerting pressure on the skin.[113, 114]

Patient related factors

Minor duration of AF episodes are associated with better acute and long term ECV efficacy.[106, 117]Since AF itself favours atrial remodelling and persisting of arrhythmia circuits, it is reasonable that AF persistence creates an irreversible substrate that sustained the arrhythmia.[35]

Obesity is a relevant risk factor for AF development;[118] moreover, it is associated with worse ECV efficacy.[10, 106, 119-121] High body weight is associated with high thoracic impedance. Studies on tissue bioimpedance showed that adipose tissue is characterized by high electrical resistance, because of low vascularization and water content.[122] Moreover, high thoracic diameter, characteristic in obese subjects, increased thoracic impedance.[112, 114] To improve ECV efficacy in obese patients, it is better to start with high energy level, preferably using AAP to exert more pressure on skin.[114] Hypertension is associated to minor ECV efficacy.[123] High blood pressure is a risk factor for AF development, and favours ventricular hypertrophy and atrial enlargement.[124]

Diabetes is associated to AF recurrence with different mechanisms: cardiomyocytes apoptosis induced by hyperglycaemia, renin-angiotensin-aldosterone system hyperactivation, neuropathy and inflammation.[117] COPD reduces acute ECV efficacy, and favours recurrence.[125] Reduced acute efficacy can be due to major thoracic impedance caused by high thoracic diameter. Instead, AF recurrence can be related to physiopathological changes, such as high pulmonary pressures that causes atrial stretching and remodelling.[106] Sleep apnoea increased long term risk of AF recurrence,[126] and adequate treated patients have less AF recurrence than not treated.[127] Renal failure is associated with increased AF recurrence after ECV.[79] Moreover, patients with renal dysfunction, who maintain sinus rhythm after ECV, presented a significantly improvement in glomerular filtration rate. This can be due to an increase in cardiac output, and subsequently in renal perfusion.[128] Hyperthyroidism can cause AF, and sinus rhythm restoration is generally reached only with normalization of thyroid hormone levels, and subsequent normalization of atrial refractory period.[129] Presence of cardiopathies increases AF recurrence; however, in some case ECV can be useful to restore sinus rhythm and improve hemodynamic.[7]

Atrial dimension is a relevant predictor of AF recurrence, probably because atrial remodelling is the macroscopic result of interaction of different risk factors.[103, 130] In the AFFIRM trial, a >4.5 cm atrial diameter was identified as a predictor of AF recurrence, whilst other studies identity a cut-off of 5 cm.[131] A study of Marchese et al. founded that indexed left atrial volume is a good predictor of long term recurrence, in particular in case of indexed left atrial volume >33.5 mL/m^2;[130] whilst, another

study identities a cut-off of 30 ml/m^2.[132] Atrial enlargement is not a contraindication to ECV, but some actions should be undertaken after procedure to favour sinus rhythm maintenance.[106]

CHA_2DS_2-VASc score is a fundamental instrument for thromboembolic risk stratification in AF patients;[7] however, some authors evaluated its role as a predictor of atrial arrhythmias' development.[133, 134] A study of Rovaris et al., that enrolled ICD patients without previous AF diagnosis, evidenced a correlation between high CHA_2DS_2-VASc score and atrial high rate episodes.[133] Regarding CHA_2DS_2-VASc score as a predictor of AF recurrence after ECV, in 2019 a systematic review was published.[107] It confirmed that the score is an independent predictor of AF recurrence after cardioversion, pharmacological or electrical; in particular, for CHA_2DS_2-VASc ≥ 2 the risk of AF recurrence was 37%. Age,[106, 125, 130] heart failure,[135] hypertension,[124] diabetes,[117] sex,[136] and vasculopathy[79] are all risk factors for AF recurrence after cardioversion. CHA2DS2-VASc score includes all these factors, and can indirectly reflect the complex pathophysiological substrate of AF.[107]

Antiarrhythmic therapy

A lot of trials investigated the role of antiarrhythmic therapy to maintain sinus rhythm after ECV, and a metanalysis demonstrated that antiarrhythmic therapy reduced AF recurrence.[137] However, this effect decreases progressively with 47-67% risk of AF recurrence after 1 year. Moreover, it was demonstrated no effect on mortality and stroke risk.

The choice of antiarrhythmic therapy after ECV is based on the importance to maintain sinus rhythm after procedure to reduce symptoms and improve cardiac function, balancing possible side effects.[8] Nowadays, different antiarrhythmic molecule are available, and the choice of best drug depends on some patient characteristics (i.e., ventricular function, basal electrocardiographic abnormalities, drug interactions and comorbidities).[7]

Class I antiarrhythmic drugs

Flecainide and propafenone, administered before ECV, improve acute efficacy with less risk of AF recurrence.[138, 139] They are not recommended in patients with ventricular systolic dysfunction or ischemic cardiopathy.[7]

Class II antiarrhythmic drugs

Use of beta-blockers before ECV was associated with sinus rhythm maintenance after 1 month.[10]

Class III antiarrhythmic drugs

Sotalol is generally contraindicated in patients with relevant ventricular dysfunction, hypertrophy or long QTc; it can be considered in ischemic cardiopathy (under strict monitoring).[7] Amiodarone, administered before ECV, improves acute efficacy and sinus rhythm maintenance;[140] moreover, it is the most effective in long term sinus rhythm maintenance (47% AF recurrence at 1 year).[137] Because

of possible side effects, especially in case of chronic amiodarone assumption, it is indicated only in selected patients, in particular if affected by cardiac dysfunction and heart failure.[7] Pharmacological effect of dronedarone is similar to amiodarone, but with less extra-cardiac side effects. If administered before ECV, it reduces AF recurrence,[106] hospitalization and mortality in paroxysmal/persistent AF patients; however, it is associated to higher mortality in patients affected by severe heart failure or permanent AF.[7, 141]

Class IV antiarrhythmic drugs

Verapamil and diltiazem improve exercise tolerance compared to beta-blockers, but should not be administer in patients with ventricular systolic dysfunction.[106] Co-administration of verapamil with flecainide or amiodarone before cardioversion, seems to reduce AF recurrence.[142]

Other drugs

Digoxin has no role in sinus rhythm maintenance after ECV.[143]

Renin-angiotensin-aldosterone system is upregulated in AF patients, and contributes to atrial remodelling.[144] Considering this assumption, some studies were done about association between ACE-inhibitors or Angiotensin II Receptor Blockers and antiarrhythmic therapy; this combination was associated to better sinus rhythm maintenance than only antiarrhythmic therapy.[145, 146] Aldosterone plays a role in AF development and maintenance,[147] and mineralocorticoid receptor antagonists (i.e., spironolactone and eplerenone) are useful in AF prevention in heart failure patients.[148]

CHAPTER 2

External electrical cardioversion of atrial arrhythmias with biphasic shock wave: determinants of acute efficacy

The aim of this study was to identify the best approach for performing ECV with current external defibrillators using biphasic shocks with either AAP or APP.

MATERIALS AND METHODS

To compare AAP and APP approaches for ECV, we adopted a quasi-experimental study design, which was developed in two different temporal stages (see Figure 2).

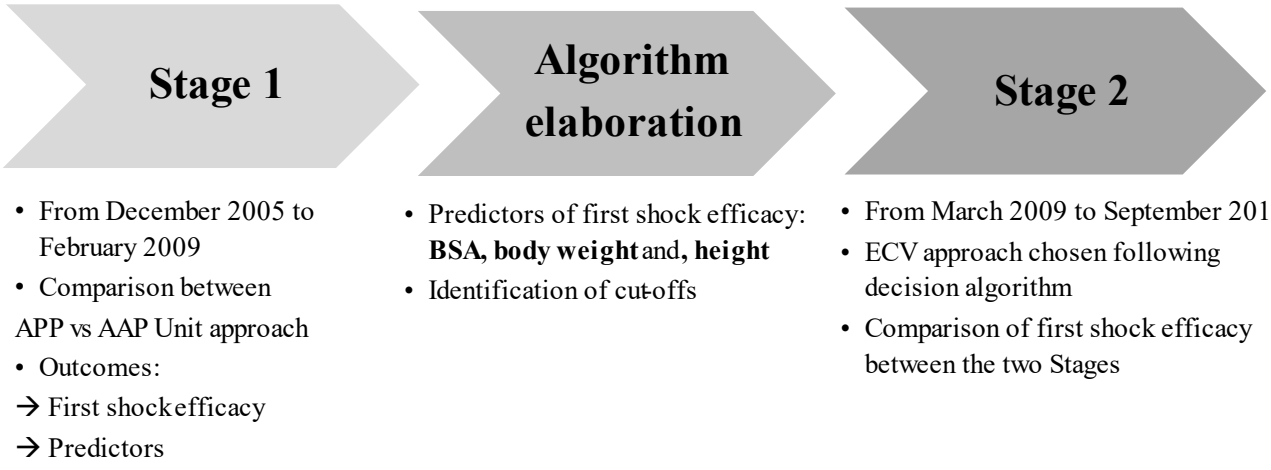


Figure 2. Study design. BSA, body surface area.

All patients signed Informed Consent for inclusion in our observational prospective registry of patients with AF diagnosis, as previously reported.[149] In the first stage, we tested the hypothesis of APP approach superiority as follows. Two different Units, belonging to Cardiology Department of S.Orsola-Malpighi University Hospital of Bologna, were involved; this choice was made on the basis of the difference in standard approach adopted by each Unit. AAP Unit used to perform ECV with paddles positioned in the typical antero-apical configuration, to decrease trans-thoracic impedance through external pressure during expiration phase. APP Unit adopted adhesive patches positioned in the antero-posterior configuration, aimed at reducing energy dispersion in view of shorter distance and increased skin adherence. Both groups adopted a step-up protocol, that increases shock energy starting at 120 Joule (J), followed by two additional shocks at 200 J in case of ineffective sinus rhythm restoration. All patients, referred to the two Units for elective ECV from December 2005 to February 2009, were considered for enrolment. After preliminary analyses, we found no difference between

patients enrolled in AAP vs APP arm (see Result section). However, we found a significant influence of some anthropometric features, already reported in current literature [i.e., weight, height, body surface area (BSA), and specific cut-offs],[11-13, 64] in predicting ECV efficacy with one of the two approaches, leading to the development of a decision algorithm (see Figure 3). It was subsequently adopted to perform ECV by both Units, aimed at reducing shock number necessary for obtaining sinus rhythm restoration. To confirm algorithm utility, we planned the second stage of this project, creating a validation cohort, including all patients performing ECV in accordance with the novel algorithm by both Units from March 2009 to September 2019.

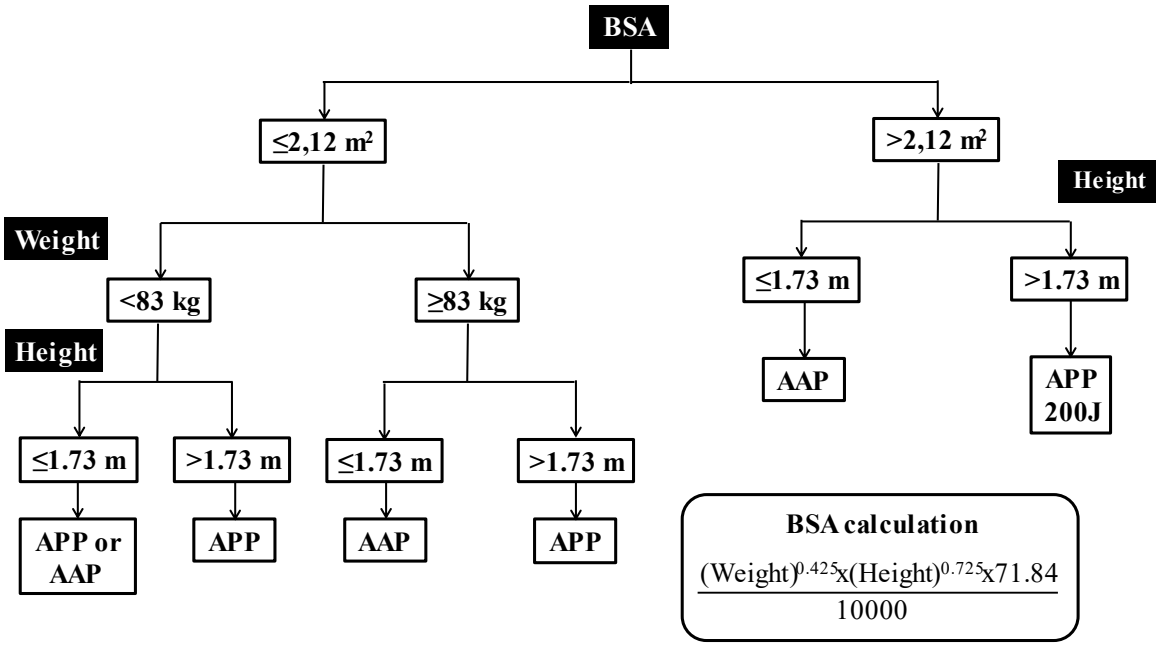


Figure 3. Algorithm for use of AAP vs APP. AAP, anterior-apical pads; APP, anterior-posterior patches; BSA, body surface area.

For each patient following data were collected before undergoing ECV:

- Anamnestic data, in particular comorbidities (i.e., hypertension, diabetes, presence of cardiopathy, previous cerebrovascular events)
- Pharmacological treatment, especially antiarrhythmic
- Biometrical parameters (in particular, weight, height, and BSA)
- Electrocardiographic, echocardiographic e laboratory data

Furthermore, specific procedure data were collected: delivered J, measured impedance, efficacy of first shock, and antiarrhythmic therapy after ECV.

ECV procedure

For ECV procedure an external defibrillator, able to deliver biphasic shocks was used. For shock delivery two strategy were possible:

1) APP: one electrode positioned in the middle of the chest on the left parasternal line and the second on the left part of infra-scapular line.
2) AAP: one electrode on left parasternal line under the clavicle and the second on anterior axillary line at 5th left intercostal space.

Delivered energy during subsequent shocks followed a step-up protocol with the first shock at 120 J; following the decision algorithm, only a subgroup of patients (BSA >2.12 m^2 and height >1.73 m) underwent the first shock at 200 J because of high body mass.

Before ECV, all patients underwent adequate anticoagulation period as recommended by European guidelines.[7] In particular, for oral anticoagulation the possible strategy were:

- Direct oral anticoagulants (DOAC) for 3-4 weeks before procedure
- K-vitamin antagonists with INR in range for 3-4 weeks before procedure

With the aim to reduce transthoracic impedance, all patients underwent adequate chest depilation and degreasing with denatured alcohol. Each patient was monitored with electrocardiogram, pulse-oximeter, and periodic blood pressure measurements, before and for at least 6 hours after procedure. During ECV, all patients underwent deep sedation with intravenous propofol or midazolam.

Statistical analysis

Normal distribution of variables was assessed with Shapiro-Wilk test, parametric/non-parametric statistic was adopted in accordance. Continuous variables with/without normal distribution are expressed as mean ± standard deviation or [median; interquartile range] in accordance. Categorical variables are expressed in terms of fraction and percentages. Comparisons between data were performed using the paired Student's t test or Wilcoxon test (when appropriate) and Fisher's exact test. Logistic regression analysis was performed to determine characteristics that were related to the outcome. Odds Ratio (OR) are reported with 95% Confidence Interval (CI). For continuous variables, ROC curves were considered to find cut-offs, better related with the outcome.

Statistical analysis was done using SPSS version 23.0 (Statistical Package for Social Sciences Inc.), p values<0,05 were considered significant.

RESULTS

Stage 1: comparison of APP vs AAP approach for ECV, and creation of decision algorithm

From December 2005 to February 2009, we enrolled 242 patients: 127 patients by APP Unit and 115 by AAP Unit. Patients from the two Units presented similar baseline clinical characteristics (see Table 4).

Variables analysed		APP (127)	AAP (115)	p
Age (years)		68±10	66±12	n.s.
Average duration of AF (days)		90 [59-175]	76 [48-112]	n.s.
Previous AF (%)	1	34 (26.8)	36 (31.3)	n.s.
	>1	25 (19.7)	16 (13.9)	n.s.
Previous CV (%)	1	29 (22.8)	31 (27.0)	n.s.
	>1	27 (21.3)	16 (13.9)	n.s.
Hypertension (%)		93 (73.2)	73 (63.5)	n.s.
Heart failure (%)		25 (19.7)	21 (18.3)	n.s.
Laboratory data				
Hb (g/dl)		14.3±1.6	14.3±4.2	n.s.
TSH (mU/l)		1.8 (1.2-3.9)	2.2 (1.3-3.6)	n.s.
FT3 (ng/l)		2.9±0.5	3.0±0.5	n.s.
FT4 (ng/l)		13.7±2.7	13.0±2.4	n.s.
PCR (mg/dL)		0.30 (0.14-0.45)	0,26 (0.12-0.52)	n.s.
Creatinine (mg/dl)		1.14 (1.05-1.29)	1.12 (0.97-1.28)	n.s.
K (mEq/l)		4.4±0.5	4.4±0.5	n.s.
NT-pro-BNP (pg/ml)		1079 (702-1695)	1151 (759-1821)	n.s.
Biometrical parameters				
Height (cm)		167±10	168±10	n.s.
Weight (Kg)		81±15	83±17	n.s.
HR (bpm)		81±19	81±21	n.s.
SBP (mmHg)		131±22	131±23	n.s.
DBP (mmHg)		81±13	81±11	n.s.
Drug history				
Amiodarone (%)		57 (44.9)	40 (34.8)	n.s.
Loop diuretics (%)		41 (32.3)	31 (27.0)	n.s.
K canrenoate (%)		12 (9.4)	17 (14.8)	n.s.
BB (%)		75 (59.1)	75 (65.2)	n.s.
Digoxin (%)		12 (9.4)	11 (9.6)	n.s.
Diltiazem/Verapamil (%)		28 (22.0)	17 (14.8)	n.s.
Dihydropyridine (%)		10 (7.9)	10 (8.7)	n.s.
ACE/ARB (%)		74 (58.3)	61 (53.0)	n.s.
Statin (%)		26 (20.5)	16 (13.9)	n.s.
Echocardiographic parameters				
LA (cm)		4.9±0.4	4.7±0.6	n.s.
LVEDV (ml)		107±37	111±45	n.s.
LVEF (%)		62±11	60±11	n.s.

Table 4. Basal characteristics of Stage 1 cohort. ACE, Angiotensin-converting enzyme inhibitors; AAP, antero-apical pads; AF, atrial fibrillation; APP, antero-posterior patches; ARB, Angiotensin receptor blockers; BB, beta-blockers; CV, cardioversion; DBP, diastolic blood pressure; ECV, electrical cardioversion; Hb, haemoglobin; HR, heart rate; K, potassium; LA, left atria; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; PCR, C-reactive protein; SBP, systolic blood pressure.

All patients underwent ECV following previous described procedure. Sinus rhythm was restored in 239 (98.8%) patients overall; however, 6 (2.5%) patients presented early AF recurrence. Sinus rhythm was restored in 211 (87.2%) patients at the first attempt, while 26 (10.7%) required an additional shock;

2 (0.8%) patients required two additional shocks with no sinus rhythm restoration. In no patients, intravenous antiarrhythmics were administered before shock delivery.

We explored possible predictors of sinus rhythm restoration with the first shock, evidencing only two significant predictors both at univariate and multivariate logistic regression analysis:

- Chronic treatment with amiodarone: OR 3.344, CI 1.204-9.288; p=0.021
- BSA: OR 0.030, CI 0.004-0.201; p<0.001

Subsequently, we compared APP vs AAP approach, evidencing only a non-significant superiority of the APP approach in terms of sinus rhythm restoration at first shock (87.4% vs 86.9%; p=0,661). Notably, use of amiodarone was not confirmed as a predictor of sinus rhythm restoration in the two subgroups, while BSA was confirmed at univariate analysis, but it was superseded by height and weight in AAP and APP groups respectively (see Figure 4). Analysing ROC curves, we identified a cut-off value for BSA (2,12 m^2) in stage 1 entire population, and two additional cut-off values in AAP and APP subgroups for height (1.73 m) and weight (83 kg), respectively.

Logistic regression analyses showed:

- In APP subgroup, patients with a body weight <83 kg presented a significant higher sinus rhythm restoration at first shock (OR 3.163, CI 1.012-9.884; p=0.048)
- In AAP subgroup, patients with a height ≤1.73 m presented a significant higher sinus rhythm restoration at first shock (OR 5.683, CI 1.857-17.381; p=0.002)
- In stage 1 entire population, BSA with cut-off ≤2,12 m^2 was the best predictor of ECV efficacy (OR 5.995, CI 2.636-13.635; p<0.001)

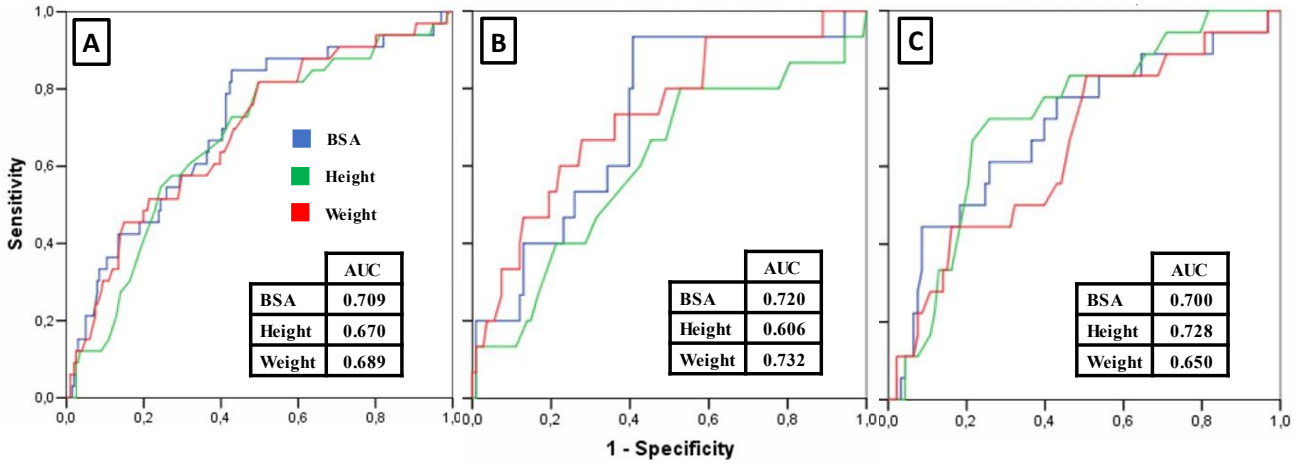


Figure 4. ROC curves of principal biometrical variables: (Panel A) entire population of group 1, (Panel B) APP subgroup, (Panel C) AAP subgroup. AUC, area under curve; BSA, body surface area.

These results were the basis to develop the proposed algorithm for choosing ECV configuration (Figure 3).

Stage 2: Algorithm validation

The elaborated algorithm was subsequently adopted by both Units to optimize shock delivery during ECV. To validate the algorithm, we enrolled a cohort of 250 patients undergoing ECV from March 2009 to September 2019. Comparison of basal characteristics between the two enrolled cohorts is shown in Table 5.

Medical history		**Stage 1 (242)**	**Stage 2 (250)**	**P**
Age (years)		67 ± 11	66 ± 12	n.s.
High Blood Pressure (%)		166 (68.6)	167 (66.8)	n.s.
Heart failure (%)		46 (19.0)	54 (21.6)	n.s.
Diabetes (%)		28 (11.6)	33 (13.2%)	n.s.
Prior TIA or stoke (%)		12 (5.0)	17 (6.8)	n.s.
Average duration of AF (days)		85 [50; 150]	109 ± 100	n.s.
Previous AF (%)	1	70 (28.9)	72 (48.8)	n.s.
	>1	41 (16.9)	55 (22.0)	
Previous CV (%)	1	60 (24.8)	66(26.4)	n.s.
	>1	43 (17.8)	47 (18.8)	
Pharmacological CV (%)		50 (20.7)	54 (21.6)	n.s.
ECV (%)		74 (30.6)	81 (32.4)	n.s.
Cardiovascular history				
Hypertensive cardiopathy (%)		66 (27.3)	51 (20.4)	n.s.
CAD (%)		38 (15.7)	32 (12.8)	n.s.
DCM (%)		12 (5.0)	18 (7.2)	n.s.
HCM (%)		4 (1.7)	9 (3.6)	n.s.
VHD (%)		38 (15.7%)	54 (21.6%)	n.s.
IPH (%)		6 (2.5%)	4 (1.6%)	n.s.
Physical examination				
SBP (mmHg)		131 ± 22	129 ± 22	n.s.
DBP (mmHg)		81 ± 12	80 ± 12	n.s.
HR (bpm)		82 ± 20	84 ± 18	n.s.
Weight (kg)		81.8 ± 16.5	79.1 ± 14.1	n.s.
Height (cm)		167 ± 10	168 ± 9	n.s.
BSA (m^2)		1.87 ± 0.33	1.89 ± 0.19	n.s.
Echocardiographic parameters				
LA (cm)		4.8 ± 0.7	4.7 ± 0.7	n.s.
LVEF (%)		61.2 ± 10.6	59.9 ± 10.5	n.s.
LVEDV (ml)		108 ± 41	103 ± 42	n.s.
LVEDD (cm)		5.0 ± 0.6	5.0 ± 0.7	n.s.
Lab parameters				
Hb (g/dL)		14.3 ± 1.5	13.8 ± 1.7	0.002
Hct (%)		42.2 ± 4.1	41.8 ± 4.1	n.s.
Plt (10^9/L)		238 ± 68	234 ± 108	n.s.
TSH (mU/L)		2.0 [1.2; 3.6]	2.0 [1.3; 3.3]	n.s.
PCR (mg/dL)		0.40 ± 0.45	0.35 ± 0.57	n.s.
Urea (mg/dL)		46 ± 20	43 ± 13	0.027
Creatinine (mg/dL)		1.23 ± 0.66	1.00 ± 0.25	<0.001
K (mEq/l)		4.4 ± 0.5	4.3 ± 0.4	n.s.
NT-pro-BNP (pg/mL)		1356 ± 942	1289 ± 1057	n.s.
Antiarrhythmic therapy		110 (45.5)	69 (27.6)	<0.001
Amiodarone (%)		97 (40.1)	52 (20.8)	<0.001
Flecainide (%)		9 (3.7)	9 (3.6)	n.s.
Propafenone (%)		1 (0.4)	3 (1.2)	n.s.
Sotalol (%)		3 (1.2)	3 (1.2)	n.s.
BB (%)		150 (62.0)	176 (70.4)	0.049
Diltiazem/Verapamil (%)		45 (18.6)	62 (24.8)	n.s.
Digoxin (%)		23 (9.5)	16 (6.4)	n.s.

Loop diuretics (%)	72 (29.8)	83 (33.2%)	n.s.
K canrenoate (%)	29 (12.0)	37 (14.8)	n.s.
Thiazide (%)	35 (14.5)	27 (10.8)	n.s.
VKA (%)	242 (100.0)	151 (60.4)	<0.001
DOAC (%)	0 (0.0)	99 (39.6)	<0.001
Antiplatelet (%)	19 (7.9)	21 (8.4)	n.s.
ACE/ARB (%)	135 (55.8)	125 (50.0)	n.s.
Oral antidiabetics (%)	16 (6.6)	20 (8.0)	n.s.

Table 5. Comparison between basal characteristics of the two cohorts. ACE, Angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, Angiotensin receptor blockers; BB, beta-blockers; BMI, body max index; BNP, B-type natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CV, cardioversion; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; DOAC, direct oral anticoagulant; ECV, electrical cardioversion; Hb, haemoglobin; Hct, haematocrit; HCM, hypertrophic cardiomyopathy; HR, heart rate; IPH, idiopathic pulmonary hypertension; K, potassium; LA, left atria; LVEDD, left ventricle end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; PCR, C-reactive protein; Plt, platelets; SBP, systolic blood pressure; TIA, transient ischemic attack; VHD, valvular heart disease; VKA, vitamin K antagonist.

Considering pharmacological therapy, more patients during stage 1 were under antiarrhythmic therapy before ECV than in validation cohort (45.5% vs 27.6%, p<0.001), mostly amiodarone (40.1% vs 20.8%, p<0.001).

Efficacy analysis evidenced a higher chance of acute restoration of sinus rhythm at first shock in case of ECV performed following the novel algorithm with respect to Stage 1 (93.2% vs. 87.2%, p=0.025). This result was coupled with a reduction in average thoracic impedance recorded during shock delivery in the validation cohort (70.8 ± 15.3 ohms vs. 81.8 ± 15.6 ohms, p<0.001).

DISCUSSION

Nowadays, the use of AAP vs APP approach in ECV procedures is still a matter of debate. ESC guidelines on AF[7] state that electrode position does not influence ECV efficacy, but they affirm that antero-posterior electrode position seems to present slightly better efficacy. However, available literature reports conflicting data derived from studies adopting different ECV approaches, in terms of biphasic vs monophasic shocks, number of delivered shocks, adopted energies, electrodes' position. In recently published RAFF2 trial,[150] the two different approaches had similar efficacy in sinus rhythm restoration (94% in antero-lateral group vs 92% in antero-posterior group, p=0.68). In this trial, patients received up to three consecutive biphasic shocks using adhesive pads in both groups, the first delivered at 200 J, followed by higher energy shocks in case of first shock inefficacy. Their adoption of only high energy shocks and adhesive pads in both groups permitted a scientifically correct comparison between the two configurations, but it did not consider the role of operator pressure in reducing impedance with antero-apical paddles, like in our study, which reflects common clinical practice. A meta-analysis of Zhang et al.[151] investigated the effect of antero-posterior electrode position on ECV efficacy, analysing 1281 patients from 10 clinical studies. It had no advantages in terms of ECV efficacy compared with anterior-lateral position (OR 1.02, CI 0.96-1.09; p=0.50). However, they

included data from studies using both monophasic and biphasic shocks. Similar results were reported by the systematic review of Kirkland et al.[152] including 13 studies: 7 using only monophasic shocks, 5 only biphasic shocks, and one adopting both. The authors reported that pad placement was not associated with an increased likelihood of restoring sinus rhythm with the first shock (OR 0.88, CI 0.73-1.06) and overall (OR 1.00, CI 0.95-1.05). In our study we decided to compare two approaches commonly used in clinical practice, also outside our university hospital (i.e., biphasic shocks, step-up protocol starting at 120 J, AAP approach with paddles) to provide good conversion results.[74, 75] Unsurprisingly, we found no difference between APP and AAP approaches in sinus rhythm restoration in stage 1 population (APP 87.4% vs AAP 86.9%; p=0,661). However, we found that BSA was a good predictor of first shock efficacy; in fact, patients with a BSA $\leq$2.12 m^2 presented a sixfold higher chance of being converted with a single 120 J shock (OR 5.995, CI 2.636-13.635; p<0.001). Similar finding was reported by the prospective multicenter REVERSE (Registry of Electrical Cardioversion in Spain) study,[153] identifying a slightly similar cut-off of 2.05 m^2; however, they used only monophasic shocks Considering the different vector characterizing AAP vs APP approach, we expanded our analysis to the two main components of BSA, weight and height, showing that these two variables differently affect ECV efficacy according to the specific electrode configuration. In APP subgroup, a weight <83 kg was a good predictor of first shock efficacy (OR 3.163, CI 1.012-9.884; p=0.048). This finding was confirmed by data from Frick et al.[10], that identified a cut-off of 80 kg for ECV using AAP approach, but they reported no data regarding shock type. On the contrary, we found that AAP approach is more affected by patient's height, probably because the more vertical heart axis of long-limbed subjects lengthens shock path, and part of atria can be not cross by shock vector. However, in the literature we have no specific data supporting this hypothesis. On these bases, we developed our ECV algorithm that determined an improvement in ECV efficacy with the first shock (93.2% vs 87.2%; p=0.025). The tailored electrode configuration approach following the developed algorithm, which considers patient body characteristics, was also associated to a decrease in thoracic impedance (70.8± 15.3 ohms vs 81.8± 15.6 ohms p<0.001). Sadek et al. analysed 1055 shocks with biphasic shock wave performed in 703 patients, and demonstrated that thoracic impedance is predictor of total number of delivered shocks, of total delivered energy and of procedure efficacy.[111] Lower thoracic impedance measured in our study using the developed algorithm can be related with an effective optimization of vectors, considering patient body measurements.

From a practical point of view, if we consider the entire study population, the number of patients being identified to specifically require APP configuration according to our algorithm is 156/492 (31.7%). Considering that this approach should produce an increase in the relative number of patients being converted with the first shock of 6%, we can estimate we require 5 patches for obtaining one positive

effect. This is a relevant observation considering healthcare system perspective, since the choice to adopt APP approach in all patients would significantly increase ECV costs (being the average cost of a set of patches about 50-100 euros each). A subset of patients that would require use of APP configuration is represented by subjects at risk of post-ECV bradyarrhythmia. However, in our population we experienced only two cases of relevant bradycardia after ECV, which resolved with intravenous atropine. In line with our finding, Gallagher et al. reported that sinus bradycardia or arrest complicated 0.95% of ECV attempts, but none required emergency pacing.[154]

CONCLUSION

In our cohort of real-world candidates to ECV, both APP and AAP configurations provided good conversion rates with use of biphasic shocks. In general, patients with higher BSA presented a lower change of sinus rhythm restoration with low energy. However, we found that weight and height differently affect ECV efficacy according to APP or AAP configuration use. Our novel decision algorithm to tailor ECV approach can optimize shock delivery while rationalizing the use of adhesive patches for AF ECV.

CHAPTER 3

PPEEG-AF pilot study (Prospective study on photopletysmographic and electroencephalographic signals for the monitoring of candidates to electrical cardioversion of atrial arrhythmias).

The aim of this study was to evaluate outcomes in candidates to AF ECV, using a set-up for multi-parametric analysis. In particular, new technologies were exploited for PPG and EEG signal registration, integrated with clinical and instrumental data, to study AF ECV outcomes and AF impact on sleep pattern and cognitive function.

Photoplethysmography

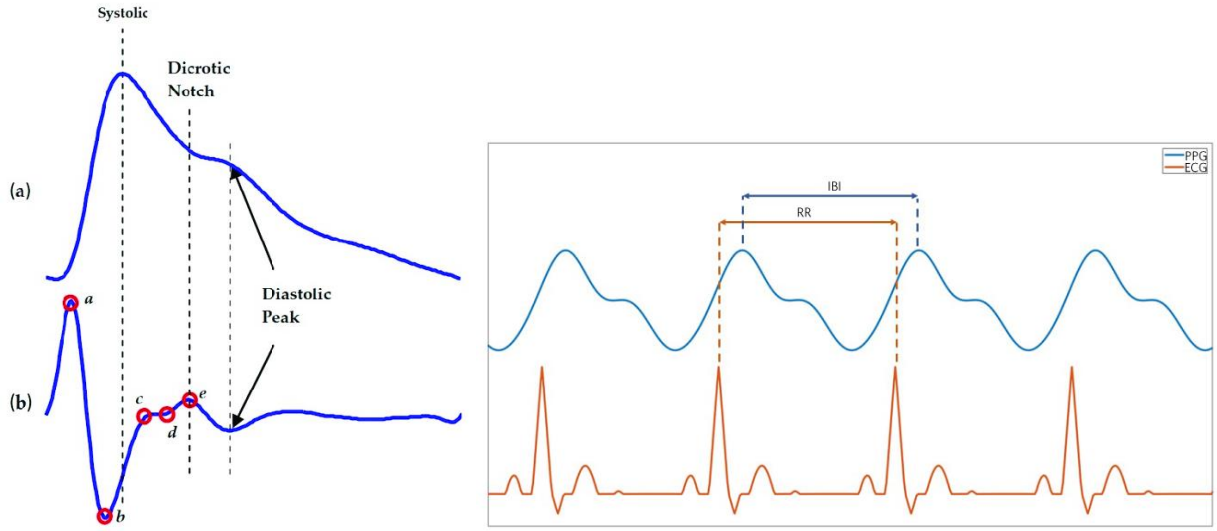
Photoplethysmography is a technique of optical measurement, which can be used to detect volume changes in small vessels. A device for PPG registration needs only two opto-electronic elements: a light source and a photodetector to measure intensity variance. It is a non-invasive approach, useful for the monitoring of many parameters. PPG sensors optically detect volume changes in small vessels, exploiting light reflection. PPG signals are principally influenced by blood flow and oxygen-distribution in capillaries. Body position of PPG sensors represents an important design issue, which determinates signal quality in case of movement artifacts. PPG signals are generally detected with devices positioned on finger, because in this location signals are higher. However, this place for PPG sensors is note applicable in daily life; for this reason, in the last years other locations were considered (i.e., annular, armlet, earlobe, front and wrist).[155-158]

Empatica E4 bracelet is a wrist wearable wireless medical device (CE 1876/MDD 93/42/EEC), see Figure 5. It continuously registers different physiological parameters derived from PPG signal. Collected data provide information regarding cardiovascular system (i.e., HR characteristics). PPG sensors of Empatica consist of 4 LED, 2 green and 2 red, and 2 photodiodes; covering a sensibility surface of 15.5 mm^2. The use of two different wave lengths permits a better quality of signal, free from movement and light artefacts.

A **B**

Figure 5. (Panel A) Empatica software interface, (Panel B) Empatica E4 bracelet.

Figure 6 shows a PPG signal and the second derivative.



A **B**

Figure 6. Panel A: (a) PPG signal, (b) second derivative. Panel B: PPG signals and electrocardiogram. IBI, Interbeat Interval.

The PPG signal is characterized by a systolic peak, a diastolic peak and a dicrotic notch.[159] Systolic peak is related to pressure wave generated by cardiac contraction that reaches distal vessels, diastolic peak reflects myocardium relaxation; wave amplitude correlates with peripheral vascular resistance. Dicrotic notch is determined by aortic valve closure, and it is more represented in case of compliant arteries.[160] Second derivative analysis was developed to better identify flex points and to permit an ease interpretation of PPG signals.[160]

Electroencephalography

Electroencephalography represents the registration of electrical cerebral activity, which reveals neuronal activity in microVolt (μV); it is registered by electrodes' application on head surface. Cerebral potentials can be registered in two different ways:

- monopolar derivation: registered with a receiving electrode connected to an indifferent electrode
- bipolar derivation: registered with a couple of receiving electrodes

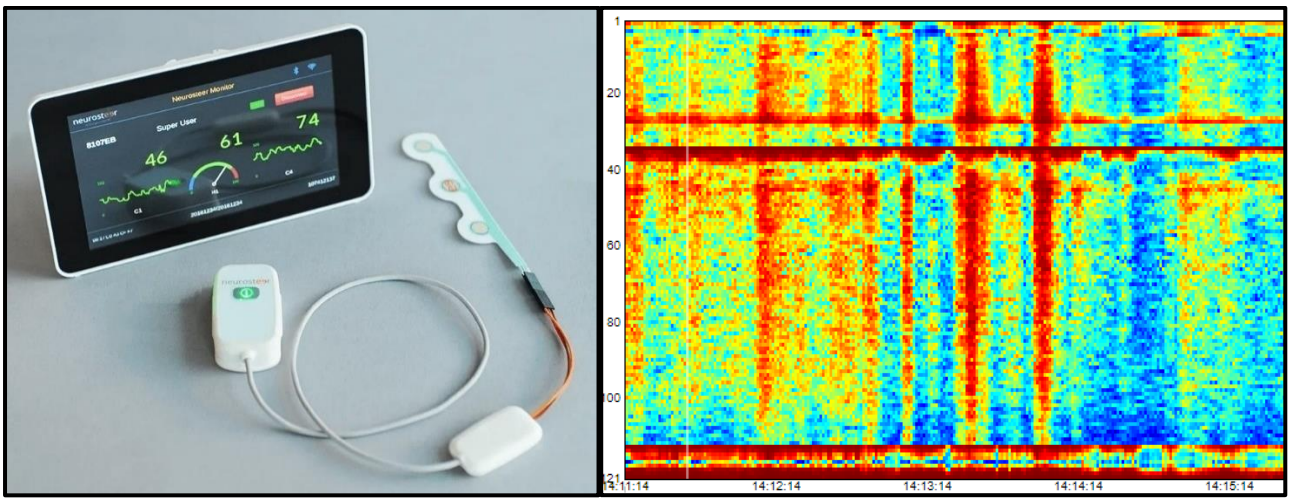
Standard registration needs 19 electrodes, positioned following conventional schemes; most used protocol is the "10-20". Electrode distance is 10 to 20% between predefined landmarks on head surface, and electrodes are coupled to cover most of cerebral areas. Nowadays, new systems are available, able to register EEG signals in a more simple and advance way. A routine registration lasts at least 30 minutes, the subject should close eyes and be relaxed. It is invited to open eyes at different time intervals to evaluate "stop reaction". Subsequently, two tests are usually administered: intermittent light stimulation and hyperpnea. Intermittent light stimulation can evoke epileptic seizures, mainly in patients affected by generalized photo-sensible epilepsy. Hyperpnea causes respiratory alkalosis with subsequent cerebral vasoconstriction, which favourites absence/petit mal seizures. EEG signal is characterized by following waves, organized in rhythms. Considering wave frequency, rhythms are classified in 4 classes:

- alfa: 8-13 Hertz (Hz)
- beta: >13 Hz
- theta: 4-7 Hz
- delta: <4 Hz

EEG signal amplitude is measured in μV, and it is generally inversely related to frequency. EEG of a normal subject is mostly influenced by two variables: age and vigilance. Younger age and/or low vigilance are characterized by slow rhythms. EEG during wakefulness of an adult subject is characterized by two rhythms: alfa predominates in posterior areas (temporo-parieto-occipital), beta in frontal areas; "stop reaction" blocks alfa rhythm. Older healthy subjects can present theta activity in anterior areas (frontal-temporal), mixed to alfa and beta rhythms. Abnormal EEG can be characterized by background activity alterations and/or paroxysmal activities. Abnormal background activity is generally characterized by an excessive slowness in relation to age (theta o delta), this alteration can involve all brain (widespread brain dysfunction) or only an area (focal dysfunction). However, no specific diseases can be diagnosed only with EEG registration. In case of pervasive encephalopathies, like dementia, EEG shows diffuse abnormalities. EEG use in patients affected by dementia was evaluated in numerous studies, aiming to characterize different types and severities of

the disease. Nowadays, visual analysis is the most used technique in clinical practice; however, digital signal processing has permitted quantitative analyses, fundamental to characterize cognitive impairments.

Neurosteer (Israel) developed a small thin sensor for real time monitoring of brain activity, it was approved by Food & Drug Administration (FDA). This sensor is composed of a plastic patch containing 3 EEG electrodes, it is positioned on forehead and connected via Bluetooth to a tablet implemented with an online software for real time signal analysis (Figure 7).



A **B**

Figure 7. (Panel A) Neurosteer sensor and tablet for online connection, (Panel B) Graphic presentation of real time signal registration.

This device provides information regarding brain activity, consciousness, emotional status, level of anaesthesia, sleep, and pain. Innovation offered by Neurosteer consists in its easy applicability coupled with the possibility of real time analysis of recorded signals to provide direct information to clinicians. Software, implemented by Neurosteer, uses a harmonic analysis based on time and frequencies, instead of classical spectral analysis; employed algorithms permit signal decomposition and connection to specific cerebral activities. The classification of different cerebral activities was developed using a specific packet of wave analyses, that integrate best available algorithms.[161]

Cognitive test

For the evaluation of presence of cognitive impairment, two specific tests were used. Mini Mental State Examination (MMSE) is a neuropsychological test that evaluates presence of cognitive impairment and dementia.[162] This test consists in 30 items, related to 7 cognitive areas (time, space, words, attention, calculation, memory, language, and constructive praxis); total score encounters between 0 and 30. A score ≤18 is associated to severe cognitive impairment, a score between 18 and

24 is related to mild/moderate cognitive impairment, and a score ≥26 is normal. However, the result of this test is influenced by age and schooling.

Montreal Cognitive Assessment (MoCA) is a widely used test for cognitive impairment screening.[163] This test consists in 30 items, a score ≥26 is considered normal. It evaluates different aspects of cognitive function: short-term memory, spatial visualization, executive activity, attention/concentration, language, elaboration, and space-time orientation. Cut-offs should be balanced in relation to schooling.

MATERIALS AND METHODS

All consecutive patients referred to Cardiology Department, S.Orsola-Malpighi Policlinic, University of Bologna, for a clinical evaluation before AF ECV from 1st November 2021 to 1st April 2022 were enrolled (age >18 years) after signature of Informed Consent. Study protocol was approved by local Ethics Committee.

All enrolled patients underwent PPG and EEG signals registration for 12-hours before and after ECV. Follow up after procedure were planned about three months after ECV. Registration exploited new wearable devices able to collect PPG ang EEG signals. Information collected with these new devices were integrated with clinical and instrumental data. For PPG signals, we used Empatica E4 bracelet, a medical device approved by European authority (CE No. 1876/MDD; 93/42/EEC). It is a wireless bracelet, able to collect different physiological parameters derived from PPG signal. For EEG signals we chose Neurosteer device, a thin plaster positioned on the front, to monitor cerebral activity in real time. This device was approved by Food & Drug Administration.

Before ECV, following data were collected for each patient:

- Anamnestic data, in particular comorbidities (i.e., hypertension, diabetes, presence of cardiopathy, previous cerebrovascular events, sleep disorders)
- Pharmacological treatment, especially antiarrhythmic
- Biometrical parameters (in particular, weight, height, and BSA)
- Electrocardiographic, echocardiographic e laboratory data

Furthermore, specific procedure data were collected: delivered J, measured impedance, efficacy of first shock, and administration of antiarrhythmic therapy.

PPG analyses

Registered PPG signals were analysed to evaluate ECV effect on HR Variability (HRV) and Vascular Age. PPG signals were processed using a 5th order band-pass filter (0.5-12 Hz), their quality was

checked by a new elaborated algorithm (submitted paper under revision); 15-minutes time frames were considered before and after ECV. Interbeat Intervals (IBI) were estimated and HRV data extracted; time domain, frequency domain and non-linear analyses were done.

The *time domain analysis* permits to evaluate heart cycle variability, considering following variables:

- RR interval (ms)
- Mean HR (bpm)
- SDNN (ms) = $\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(IBI_i - mean(IBI))}$ (standard deviation of RR intervals)
- RMSSD (ms) = $\sqrt{mean((IBI_{i+1} - IBI_i)^2)}$ (root mean square of successive differences)
- SDSD (ms), standard deviation of successive differences in RR intervals

The *frequency domain analysis* estimates the contribute of sympathetic (SNS) and parasympathetic nervous system (PNS) on HRV, considering following variables:

- LF: low-Frequency activity (0.04-0.15 Hz)
- HF: high-Frequency activity (0.15-0.4 Hz)
- LF/HF ratio

Non-linear analyses reflect the complexity and randomness of IBI, considering SD1, SD2 and their ratio (SD1//SD2). These parameters are calculated using a Poincaré plot (graphic representation of comparisons between each RR interval, X axis, with the subsequent, Y axis).

- SD1 (ms): standard deviation, perpendicular to identity line
- SD2 (ms): standard deviation, following identity line
- SD1/SD2 ratio: measurement of heart rhythm regularity

Even considering 15-minutes time frames, second derivative of PPG signals was elaborated, and following variables of vascular age were calculated:

- a wave: index of vascular elasticity
- Turning Point Ratio (TPR): number of extreme points divided total number of points in the signal, index of randomness

Comparisons between these variables were analysed considering:

1) All signal registration before and after ECV
2) 1-hour registration early and late after ECV
3) 3-hours registration during day and night before and after ECV

Neurosteer

Each patient underwent EEG registration before and after ECV using Neurosteer device. Because of connectivity problems, registered signals were selected considering quality and duration of collected signals. To evaluate the relation between EEG signals registered before and after ECV and possible correlation due to AF presence we compared coherence coefficients in following circumstances:

- EEG signals registered before and after ECV for each patient
- EEG signals during AF
- EEG during sinus rhythm

Statistical analysis

Normal distribution of variables was assessed with Shapiro-Wilk test, parametric/non-parametric statistic was adopted in accordance. Continuous variables with/without normal distribution are expressed as mean ± standard deviation or [median; interquartile range], in accordance; categorical variables are expressed in terms of fraction and percentages.

Comparisons among HRV and vascular age parameters were represented with box plots. Generalized Linear Mixed Effects Models (GLMM) were used for evaluating significant differences between HRV and vascular age parameters registered before and after ECV, marginal F test was used for hypotheses' verification. Wilcoxon signed rank test was used for comparisons between signals registered early and late after ECV, and during day and night before and after ECV.

Coherence coefficient was used to quantify phase synchrony between pairs of registered EEG signals collected in different time periods, its value ranges from 0 to 1; this analysis was represented using a Cartesian coordinate system.[164] We considered relevant a coherence coefficient >0.6.

Statistical analysis was done using SPSS version 23.0 (Statistical Package for Social Sciences Inc.), p values<0,05 were considered significant.

RESULTS

From 1st November 2021 to 1st April 2022, 24 candidates to AF ECV at Cardiology Department of S.Orsola-Malpighi Policlinic were enrolled, 5 patients were not included in PPG analyses for the following reasons:

- In 1 patients ECV was ineffective
- 2 patient presented AF early recurrence
- In 2 patient registered signals were insufficient

Table 6 shows clinical and instrumental data of enrolled population.

Tot Pop	**24**
Males (%)	18 (75)
Age (yr)	65.6 ± 8.5
BMI (kg/m^2)	28.0 ± 4.8
BSA (m^2)	2.02 ± 0.23
Ex-smoker/Smoker (%)	12 (50)/ 3 (12.5)
Hypertension (%)	16 (66.7)
Dyslipidemia (%)	18 (75)
DM (%)	3 (12.5)
Heart failure (%)	10 (41.7)
Renal failure (%)	8 (33.3)
CHA_2DS_2-VASc	2.1 ± 1.2
HAS-BLED	0.54 ± 0.51
Previous ECV/PCV (%)	7 (29.2)/1 (4.2)
CIC (%)	2 (8.3)
DCMP (%)	3 (12.5)
Hypertensive CMP (%)	4 (16.7)
Previous cardiac surgery (%)	5 (20.8)
LVEF (%)	52.8 ± 11,0
LVEDV (ml)	112,8 ± 35,6
PAPs (mmHg)	33.6 ± 8.0
LA dilatation (%)	21 (87.5)
RV dilatation (%)	2 (8.3)
HR (bpm)	91 ± 19
QRS (ms)	98 ± 10
LBBB/RBBB (%)	1 (4.2)/1 (4.2)
TSH (μU/ml)	1.9 [0.9– 2.5]
DOAC/VKA (%)	23 (95.8)/1 (4.2)
AAD (%)	7 (29.2)
BB/CCB (%)	20 (83.3)/4 (16.7)
MoCA	25 ± 4
MMSE	28 ± 2
6mwt (m)	462 ± 84
iv AAD (%)	9 (37.5)
Atrial stunning (%)	14 (60.9)
AAD post (%)	20 (83.3)
Diuretic post (%)	10 (41.7)

Table 6. Data of enrolled population. AAD, antiarrhythmic drug; BB, beta-blocker; BMI, body max index; BSA, body surface area; CCB, calcium channel blocker; DM, diabetes mellitus; HR, heart rate; iv, intravenous; LA, left atrium; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; PM, pacemaker; RBBB, right bundle branch block; RV, right ventricle; VKA, K-vitamin antagonist.

ECV was effective in sinus rhythm restoration in 23 (95.8%) patients, in 14 (60.9%) at first attempt. Intravenous antiarrhythmic administration was necessary in 9 (37.5%) patients: 3 (12.5%) patients received amiodarone and 6 (25.0%) flecainide.

PPG analyses

HRV analyses considering 15-minutes time frames registered before and after ECV showed a significant reduction of most variables: mean HR, SDNN, RMSSD, SDSD, SD1, SD2, SD1/SD2, LF and HF (see Table 7). Only LF/HF ratio did not differ significantly.

	Pre		Post		p-value
	Estimate	SE	Estimate	SE	
Mean HR	81,399	1,8429	70,517	0,67595	**<0.001**
SDNN	227,77	18,01	154,905	4,9905	**<0.001**
RMSSD	298,22	24,335	192,2	6,0163	**<0.001**
SDSD	299,99	24,409	193,55	6,0826	**<0.001**
SD1	210,69	17,169	135,548	4,1979	**<0.001**
SD2	238,31	18,455	165,149	5,0812	**<0.001**
SD1/SD2	0,91161	0,021669	0,80977	0,010928	**<0.001**
LF	63127	13667	36663	4308	**<0.001**
HF	10697	1461,4	4648,7	429,3	**<0.001**
LF/HF	105,28	26,645	106,6558	35,594	n.s.

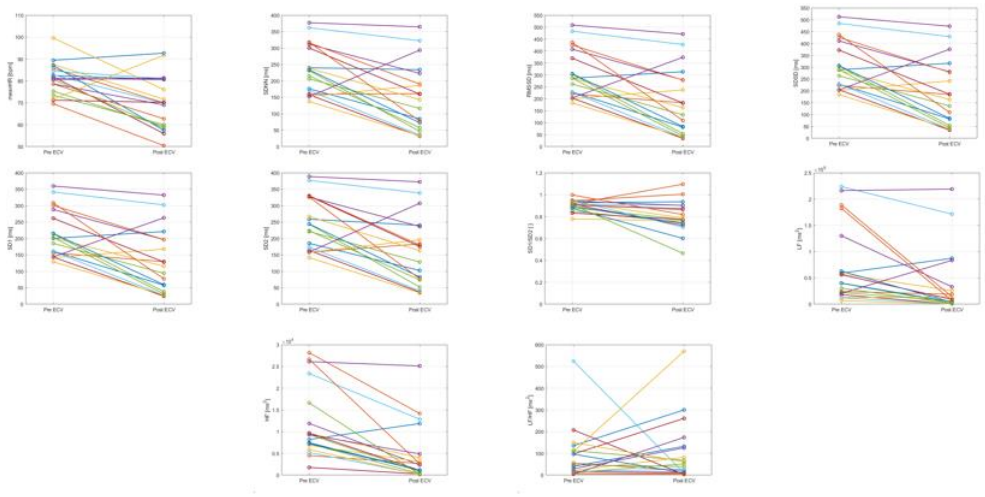
Table 7. HRV analyses considering 15-minutes time frames before and after ECV.

Considering same time frames, it was observed a significant reduction in both vascular age parameters (Table 8).

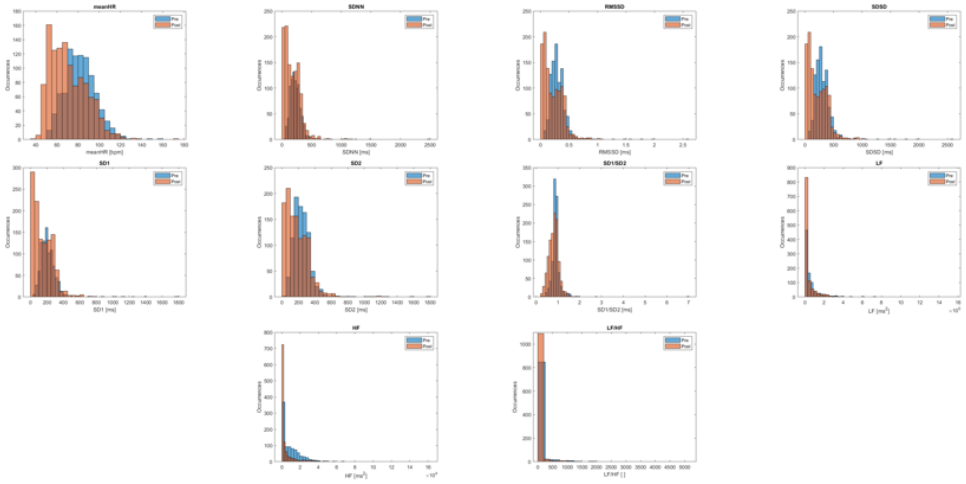
	Pre		Post		p-value
	Estimate	SE	Estimate	SE	
a wave	178,15	12,947	148,093	4,5905	**<0.001**
TPR	64,579	0,59957	62,1461	0,20064	**<0.001**

Table 8. Vascular age parameters analyses.

Figure 8 shows the results of HRV analyses considering 15-minutes time frames registered before and after ECV.



A



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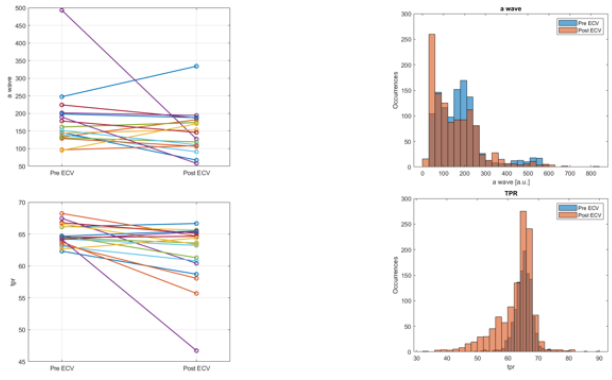

C

Figure 8. (Panel A) Mean values of all HRV parameters registered before and after ECV for each subject. (Panel B) Histograms of HRV parameters. (Panel C) Mean values and histograms of vascular age parameters registered before and after ECV.

Comparing PPG signals registered for 1-hour early and late after ECV, no HRV parameters showed significant differences (Figure 9).

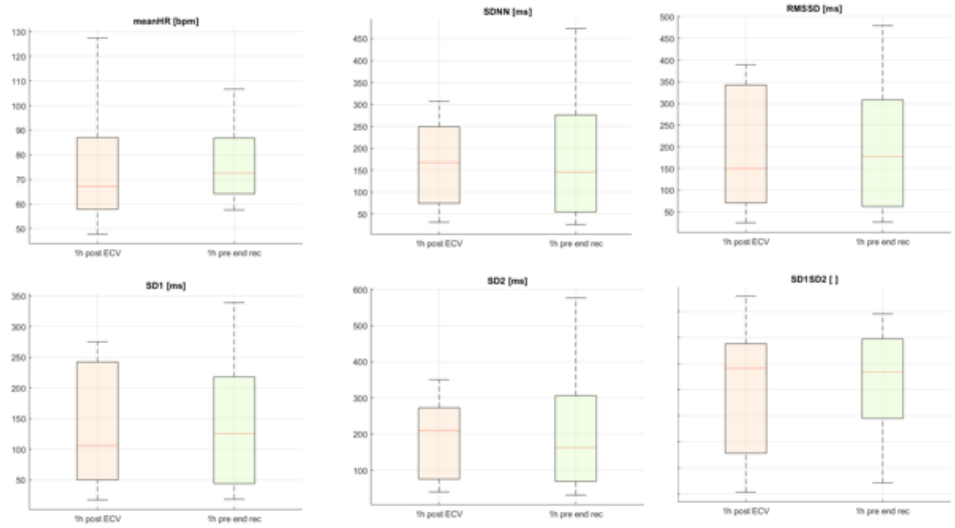

Figure 9. Box plots of HRV parameters considering 1-hour early and late after ECV.

Considering HRV parameters, comparisons between PPG signals registered during day or night before and after ECV showed a significant difference in SD1/SD2 ratio and HF (see Table 9 and Figure 10).

	Pre ECV			Post ECV			Wilcoxon (p-value)
	Day	Night	Diff (Day-Night)	Day	Night	Diff (Day-Night)	
meanHR	87,03 (7,32)	76,15 (9,80)	10,88 (14,83)	76,59 (14,83)	62,95 (13,64)	13,64 (11,50)	n.s.
SDNN	238,18 (57,07)	235,05 (98,99)	62,95 (7,79)	170,10 (112,01)	155,34 (118,73)	62,95 (7,80)	n.s.
RMSSD	298,44 (73,67)	304,87 (121,57)	-6,43 (69,27)	202,70 (144,06)	177,37 (162,82)	25,33 (85,35)	n.s.
SDSD	298,92 (73,65)	304,97 (121,668)	-6,05 (69,46)	203,08 (144,31)	177,55 (163,14)	25,53 (85,95)	n.s.
SD1	211,03 (52,09)	215,57 (85,96)	-4,55 (48,98)	143,33 (101,87)	125,42 (115,13)	17,91 (60,35)	n.s.
SD2	259,82 (63,51)	252,40 (111,39)	7,42 (84,04)	190,69 (122,17)	177,95 (124,77)	12,74 (88,42)	n.s.
SD1/SD2	0,83 (0,07)	0,87 (0,08)	-0,04 (0,11)	0,73 (0,13)	0,66 (0,16)	0,07 (0,13)	**0.04**
LF	76330,02 (100763,2)	71792,05 (100763,2)	71792,05 (118080)	4537,97 (99634,27)	32489,42 (52125,03)	12069,70 (27392,96)	n.s.
HF	4780,45 (5050,58)	13749,52 (6216,35)	-8969,08 (8212,302)	4619,06 (9042,37)	2883,99 (3930,93)	1735,07 (7538,67)	**0.002**
LF/HF	94,62 (198,85)	5,28 (6,24)	89,34 (199,80)	41,54 (75,54)	10,40 (15,10)	31,13 (79,27)	n.s.

Table 9. Comparisons of HRV parameters registered during day or night before and after ECV.

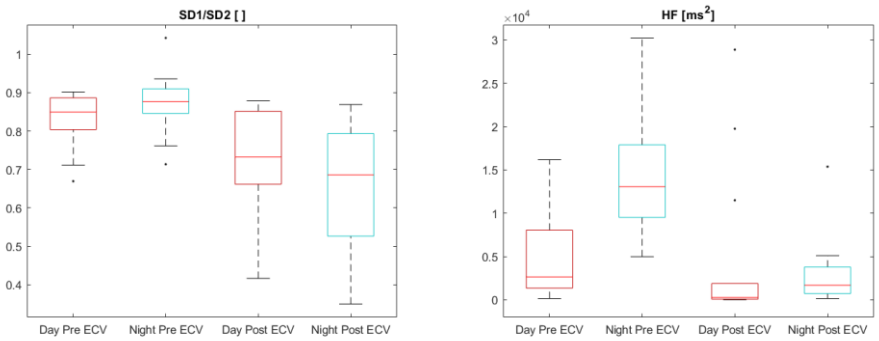

Figure 10. Box plots of SD1/SD2 e HF registered during day or night before and after ECV.

Considering results from cognitive tests, we observed that patients with MMSE≤28 presented higher values of TPR (65.9±1.6 vs 64.2±1.4, p=0.035) and CHA_2DS_2-VASc (2.9±0.9 vs 1.7±1.2, p=0.022), see Figure 11.

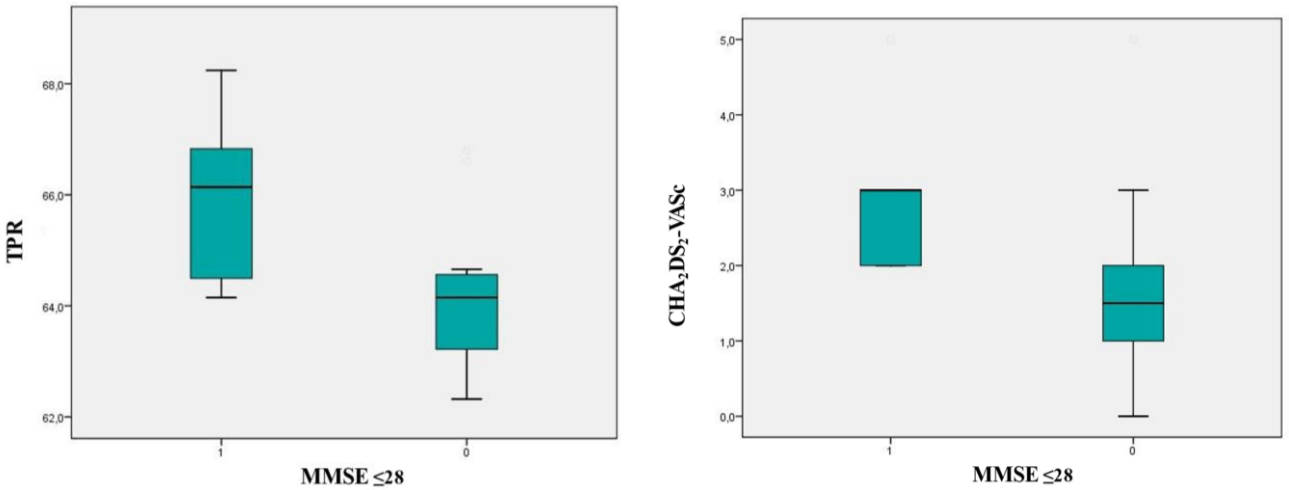

Figure 11. Box plots of TPR and CHA_2DS_2-VASc considering MMSE≤28.

Neurosteer

Considering EEG signals, 25 tracks were selected for quantification of phase synchrony (see Figure 12).

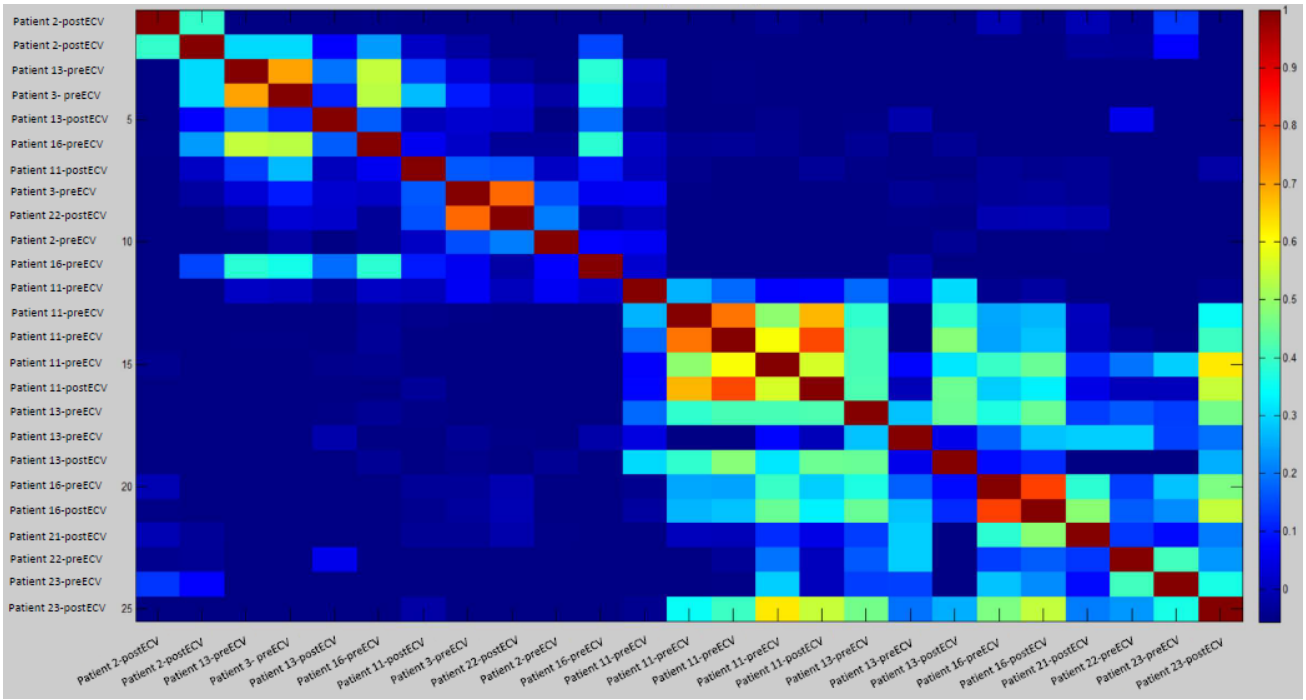

Figure 12. Coherence coefficient for quantification of phase synchrony between pairs of registered EEG signals collected in different time periods.

Comparison of EEG tracks registered before ECV showed some correlations in 3 subjects (patient 3, 13 and 16). Moreover, patient 3 pre-ECV EEG presented some correlation with patient 22 post-ECV registration, and patient 23 post-ECV with patient 11 pre-ECV and patient 16 post-ECV.

Considering correlations between EEG signals registered with Neurosteer, Figure 13 shows coherence coefficients between signals registered before and after ECV procedure for each patient, and between signals registered during AF or sinus rhythm. In particular, we observed that signals' coherence was higher between EEG signals registered during AF vs signals registered before and after ECV for each patient, and vs signals registered during sinus rhythm.

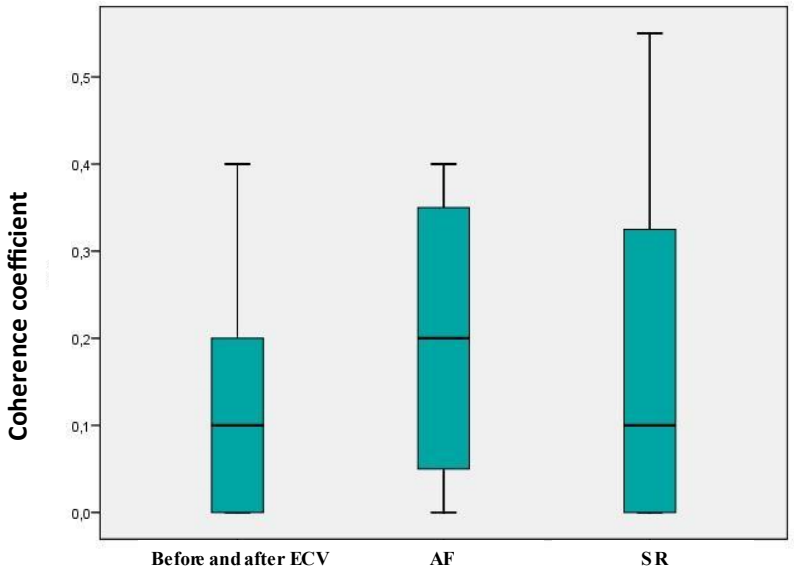

Figure 13. Box plots of coherence coefficients between EEG signals registered before and after ECV, and during AF or sinus rhythm. AF, atrial fibrillation; ECV, electrical cardioversion; SR, sinus rhythm.

DISCUSSION

This study evaluated the feasibility of a new setting of patient monitoring using innovative wearable devices for non-invasive registration of PPG and EEG signals in candidates to ECV of atrial arrhythmias. Available data permitted the comparison of HRV and vascular age parameters measured before and after ECV, even considering different time periods during day and night. In the next future, data derived from follow up registrations could provide information regarding possible predictors of AF recurrence, heart failure and cognitive impairment development.

AF is a common arrhythmia, even in "healthy" subjects (lone AF), and early diagnosis and treatment are fundamental for patient safety and quality of life. Nowadays, new wearable devices (i.e., bracelets or watches) were developed for PPG signal registration, and the interest in these technologies is growing, because of the possible utilization of these devices for early automated diagnosis of cardiac

arrhythmias.[165] PPG signal devices could represent in the next future an alternative to ECG monitoring.[166]

Prognostic role of HRV in sinus rhythm subjects was widely discussed in literature,[158, 167] while few studies on HRV considering AF patients were published.[159, 168, 169] Our study revealed a statistically significant reduction in most HRV parameters considering 15-minutes time frames registered before and after ECV. These parameters reflect the variations between RR intervals, and their reduction can be related to heart rhythm regularization after AF ECV. SDNN and RMSSD reflect the effect of autonomic nervous system (ANS) on HR; in particular, SDNN is influenced by both SNS and PNS, while RMSSD mainly reflects PNS.[170] The heart rhythm is regulated by an internal ANS, and through sympathetic nervous fibres coming from stellate, cervical or thoracic ganglia, and parasympathetic fibres from vagal nerve. Internal ANS is constituted by ganglion plexuses, located in fat pads near pulmonary veins.[171] Khan et al.[172] demonstrated that AF patients are characterized by higher values of SDNN and RMSSD compared to sinus rhythm subjects, and this result was explained by an higher parasympathetic activity in AF patients. ANS plays a fundamental role in AF onset and maintenance: parasympathetic activity induces a miscellaneous reduction of activation potential duration and of refractory period, while sympathetic activity induces Ca^{2+} accumulation in cardiomyocytes' cytoplasm, promoting ectopic firing.[173] Progression from paroxysmal to persistent forms of AF is associated with neural/autonomic remodelling, besides electrical and structural; however, specific mechanisms are still matter of debate.[174] Autonomic dysfunction plays a relevant role in AF pathogenesis, and studies on HRV in AF patients could provide interesting results.[171]

Our analyses showed a significant reduction of SD1, SD2 and of their ratio. SD1 represents short variations between RR intervals, and it is related to HF and RMSSD; instead, SD2 represents long variations, and it is related to LF.[170] SD1/SD2 ratio represents an index of randomness of RR intervals.[170] Poincaré plot provides information on RR variability, and could be related to cardiac dysfunction. It was demonstrated that SD1/SD2 ratio is increased in case of premature ventricular complexes, AF, sick sinus syndrome and ventricular fibrillation, due to increased variability between RR intervals; whilst, it decreases under low normal level in patients affected by cardiomyopathies or complete atrioventricular block, because of slow variation between heart cycles.[175]

Both LF and HF decreased after ECV, which reflect mainly SNS and PNS activity, respectively; however, some author outlined a parasympathetic influence on LF. [171, 176] LF/HF ratio, that would reflect sympathovagal balance,[175] did not vary significantly after ECV. Nowadays, the interpretation of LF/HF ratio is a matter of debate; Pagani et al. affirmed that this parameter could be an index of sympathovagal effect on heart activity.[176] Considering this hypothesis, observed reduction in LF and

HF and no modification in LF/HF ratio could reflect a proportional reduction in sympathetic and parasympathetic activity after ECV.

For the first time, Van den Berg et al.[174] applied time and frequency domain analyses in AF patients, demonstrating that HRV parameters reflect vagal tone even in this class of patients. Blocking sympathetic activity with propranolol, they observed an incrementation of HRV parameter (in particular HF) in both arrhythmic and control group.[174] However, in AF patients HRV is not only related to parasympathetic activity.[172] Our study demonstrated higher values of almost all HRV parameters in AF subjects comparing signals registered before and after ECV. On the contrary, HRV parameters considering signals registered 1-hour early and late after ECV did not show any statistically significant difference. In the next future, follow up data will be collected, that could provide more information about predictive role of HRV parameters on clinical outcomes. Lombardi et al. demonstrated that increased sympathetic and reduced vagal modulation of sinus node characterize patients with early AF recurrence, suggesting that an abnormal autonomic control may contribute to electrical remodelling in AF subjects.[177] After ECV, it was observed a significant reduction in difference between diurnal and nocturnal value of SD1/SD2 ratio and HF. These results would be compared with follow up data analyses, to evaluate real effect of sympathovagal balance during day and night in relation to AF presence or sinus rhythm maintenance.

Analyses about vascular age parameters showed a significant reduction in a wave and TPR measured after ECV. Vascular aging, which is not necessarily related to biological age, is associated with higher arterial stiffness. It can be revealed analysing PPG signals; in particular, considering velocity of PPG wave propagation and changing in wave form (loss of dicrotic notch in case of reduction of vascular compliance).[178] A wave and TPR, calculated from second derivative of PPG signal, showed a relevant correlation with aging, respectively positive and negative.[179] The a wave amplitude quantifies the acceleration due to systolic arterial flow, and it is related to vascular elasticity; the TPR is an index of randomness. The reduction of TPR after ECV is related to sinus rhythm restorations; in fact, it was demonstrated that AF patients are characterized by higher TPR values.[180] Data published by Dall'Olio et al.,[179] showed that minor TPR values or major a wave amplitude are predictive of healthy vascular aging. In this study, TPR reduction measured after ECV can be associated with a better vascular performance after sinus rhythm restoration. Instead, the reduction observed in a wave amplitude can be determined by regularization in heart contractions after sinus rhythm restoration. Moreover, higher TPR values registered in patients with MMSE $\leq$28 can be related to vascular damage that could be present in case of initial cognitive impairment. Patients with MMSE $\leq$28 presented even significantly higher CHA_2DS_2-Vasc score, this result can be explained by the fact that factors considered in

CHA_2DS_2-Vasc score are also risk factors for cognitive impairment and dementia (i.e., age, hypertension, diabetes, and previous cerebral events).[181-184]

Results on Neurosteer signals' coherence showed a major correlation between signals registered during AF vs sinus rhythm, or vs EEG signals registered before and after ECV for each patient. There is a tendency of AF to impact on EEG registered during night, and future data could confirm this consideration.

CONCLUSION

This study is validating the feasibility of the use of new wearable devices for monitoring of AF patients undergoing ECV. Our results showed a significant effect of AF on vascular age parameters derived from PPG registrations; in particular, in patients with initial cognitive impairment. Comparing EEG registrations, it was observed that AF could influence sleep pattern; however, more data are necessary to confirm this observation.

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