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ORIGINAL ARTICLE

Impact of low-dose Brain-Derived Neurotrophic Factor (BDNF) on atrial fibrillation recurrence

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ABSTRACT

BACKGROUND: Atrial fibrillation is the most common arrhythmia worldwide and is associated with significant morbidity and mortality. Despite the effectiveness of catheter-based ablation, periprocedural complication and recurrences remain a concern. In this context, we aim to appraise the potential impact of brain-derived neurotrophic factor (BDNF) on reducing episodes of paroxysmal atrial fibrillation (PAF).

METHODS: 22 patients with an established diagnosis of PAF and without structural heart disease were considered. Every patient received 20 drops of GUNA-BDNF administered in the morning. During the 24 months of follow-up, the arrhythmic burden was measured by the average monthly duration of PAF episodes.

RESULTS: At the end of the follow-up period (24 months), data from 22 patients, of whom 17 men and five women, were analyzed. The arrhythmic burden, measured in terms of average monthly duration of PAF episodes, was found significantly reduced after the administration of low dose BDNF (9.5 *vs.* 65.3 minutes per month, P<0.001). A total of 17 out of 22 patients saw their arrhythmic burden eliminated or consistently reduced, furthermore two patients underwent a drastic reduction of the average monthly duration of AF (more than 200 minutes compared to the baseline). Only four patients, despite the administration of BDNF, still experienced an arrhythmic burden of 20 minutes or more. Considering the age groups, the major reduction was observed in people aged 70 or more, who were also the most represented in the sample. These results are coherent with the poor literature currently available.

CONCLUSIONS: BDNF low dose therapy has shown to have an impacting role in reducing the arrhythmic burden and recurrences of AF, with a particular effectiveness in patients over 70 and without structural heart disease. We should welcome this work, despite it limitations. Further clinical and molecular studies are needed before-considering BDNF low dose as a tool against PAF.

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KEY WORDS: Atrial fibrillation; Brain-derived neurotrophic factor; Nerve growth factors.

Atrial fibrillation (AF) is the most common arrhythmia worldwide, especially in the elderly, and it is associated with significant morbidity and mortality.[1, 2] AF may be paroxysmal, persistent, or permanent. Paroxysmal AF (PAF), defined as episodes of AF that terminate spontaneously or with intervention within seven days of onset, has significant relevance in the AF pop-

ulation.[3] However, the real prevalence of PAF is likely to be underestimated since many episodes are asymptomatic or with very short duration.[4] Tue goal of therapy for patients with PAF is twofold: prevention of embolic thromboembolic episodes and prevention of AF recurrence and progression to persistent or permanent AF. Since AF burden is not directly proportional to stroke risk, the current guidelines are focused on the prevention of thromboembolic stroke and/or systemic embolism through oral anticoagulants, according to the patient's individual risk score and not linked with AF type, pattern, or burden.[3]

On the other hand, patients with frequent or highly symptomatic episodes of paroxysmal AF, especially if young, require pharmacologic or nonpharmacologic therapy to prevent AF recurrences.

Nowadays, there are two main therapeutic strategies to prevent future AF recurrence: antiarrhythmic drugs and/or catheter ablation.[5] Unfortunately, despite the available options there is still an unmet need for AF therapy due to the potential inefficacy and the side effects of current treatments. Antiarrhythmic drugs are associated with a potential for serious adverse effects, particularly the induction of pro-arrhythmias, limiting their use in clinical practice.[6] The use of flecainide and propafenone is limited to patients without structural heart disease; dronedarone and sotalol can be used in patients with coronary artery disease without heart failure, with amiodarone being the most prescribed drug available worldwide for patients with heart failure. However, it is fraught by many non-cardiovascular side effects.[7] Pulmonary vein isolation using catheter-based ablation is now becoming an effective therapeutic option, however, is still associated with a non-negligible risk of periprocedural major complications and a high rate of AF recurrence after successful ablation, commonly occurring within the first several weeks after the procedure.[5] Therefore, it is essential to look for further ways to treat these patients with novel strategies to intervene and mitigate the risk of AF recurrences.

Neurotrophins (NTs) are a group of proteins that play several functions in the nervous system.[8] Nevertheless, NTs and their receptors are essential in cardiovascular development during embryogenesis leading to heart and vessels formation, as well as after birth and in adulthood, where NTs play a crucial role in controlling endothelial cells, angiogenesis, and vasculogenesis.[8] The Brain-Derived Neurotrophic Factor (BDNF) is a member of NTs family that showed a variety of non-neuronal and cardiovascular functions, and it is essential for normal cardiac contraction and relaxation.[9, 10] BDNF and its receptor Tropomyosin receptor kinase B (TrkB) are involved in developing the heart's capillaries and cardiac endothelium formation. This signaling pathway is also implicated in the development of macrophages and atherosclerotic vessels.[9] Thus, data from several studies found a protective function of BDNF/TrkB signaling against coronary artery disease, acute coronary events, and stroke.[11-13] Therefore, it has been found that higher serum levels of BDNF are associated with lower mortality rates.[9, 14, 15] Furthermore, the BDNF/TrkB pathway has been shown to contribute significantly in physiological heart contraction and relaxation,[16] and there is evidence that lower levels of BDNF are associated with risk factors for AF, including age, alcoholism, male sex, tobacco use, and diabetes mellitus.[10, 14, 17-19]

However, it is still unclear if cardiovascular effects of BDNF could also act on the risk of AF, even if an analysis of the Framingham Heart Study failed to find a significant association between serum BDNF levels and risk of incident AF.[20] Notably, it is shown the mutual interaction between BDNF and TNF-α. Indeed, TNF-α. has a negative role towards BDNF expression, and it seems to be fundamental in remodeling the left atrium. On the other hand, BDNF appears to be effective in preventing the endothelial damage made by TNF-α. This interaction may be a physiological substrate of the potential role of B DNF/TrkB in preventing AF.[21-23]

In this context, the present study aims to appraise the potential impact of BDNF on reducing episodes of PAF.

Materials and methods

Study population

In this experimental study, 22 patients with an established diagnosis of PAF were considered.

TABLE I.—*Baseline features of the population.*

Patient	Sex	Age	Hyper-tension	Dys-lipid-emia	Type 1 dia-betes	Type 2 dia-betes	PAD	MI	PTCA	Drugs
P1	M	72	N	N	N	N	N	N	N	NOAC, amiodarone, bisoprolol
P2	M	84	N	N	N	N	N	N	Y	NOAC, amiodarone, ACE inhibitor
P3	M	90	N	N	Y	N	N	N	Y	NOAC, amiodarone, ACE inhibitor
P4	F	74	N	N	N	N	N	N	N	NOAC, bisoprolol
P5	M	87	Y	N	N	N	N	N	N	NOAC, amiodarone, amlodipine
P6	F	65	N	N	N	N	N	N	N	NOAC
P7	M	70	Y	Y	N	N	N	N	Y	NOAC, bisoprolol, amlodipine, statin
P8	M	80	Y	N	N	N	N	N	N	NOAC, ACE inhibitor, amlodipine
P9	M	83	Y	N	Y	N	N	N	N	NOAC, ACE inhibitor, amlodipine
P10	M	92	Y	Y	Y	N	N	N	N	Aspirin, bisoprolol, ACE inhibitor, insulin, statin
P11	M	71	Y	N	N	N	N	N	Y	NOAC, ACE inhibitor, bisoprolol
P12	M	60	N	N	N	N	N	N	N	NOAC
P13	M	53	N	N	N	N	N	N	N	Bisoprolol
P14	M	82	N	N	N	N	N	N	N	Dronedarone, clopidogrel
P15	M	79	N	N	N	N	N	N	N	NOAC, bisoprolol
P16	F	73	Y	N	N	N	N	N	N	Sartan, Aspirin
P17	M	71	N	N	N	N	N	N	N	NOAC, bisoprolol
P18	M	78	Y	Y	N	N	N	N	Y	NOAC, flecainide, ACE inhibitor, amlodipine, statin
P19	M	57	Y	N	N	N	N	N	N	NOAC, flecainide, Sartan
P20	F	70	Y	N	N	N	N	N	N	NOAC, Sartan, amlodipine
P21	F	70	Y	N	N	N	N	N	N	NOAC, Sartan, amlodipine
P22	M	86	Y	N	N	N	N	N	N	Aspirin, Sartan, sotalol

N: no; Y: yes; M: male; F: female; PAD: peripheral artery disease; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; NOAC: new oral anticoagulants.

None of them had structural heart disease. The study was conducted according to the rules of the Institutional Ethics Committee. All patients provided consent for intervention. Among the population, 17 were males, and five were females, the mean age was 74.86 years, and all had been treated with a stable pharmacological regimen for at least three months. The 22 patients belonged to a larger group (30 patients) evaluated with a symptom diary, dynamic ECG, Loop recorder, PM/ICD. Three of them had an ICD but were not taken into consideration for the analysis, as they suffered from heart failure. Two patients had Loop recorder implanted for syncopal episodes that proved to be of vasovagal origin without any structural heart disease. General features of the population are reported in Table I.

Intervention and follow-up

Every included patient received the experimental protocol consisting of 20 drops of GUNA-BDNF oral solution, drops (Guna S.p.a., Milan, Italy) administered in the morning.

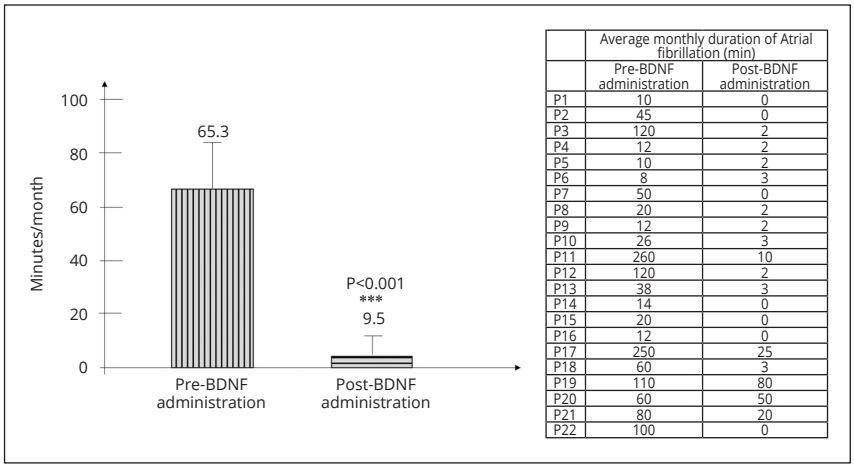
The entire population was treated, observed with regular appointments and followed up for 24 months. During the follow-up period, the arrhythmic burden was measured by the average monthly duration of PAF episodes, identified by the evaluation of symptoms, Holter dynamic ECG monitoring, Loop recorder, or analysis of pacemaker/implantable cardioverter defibrillator. The reference value of the arrhythmic burden was assessed three months before the administration of BDNF.

Statistical analysis

Student's *t*-test (paired two-tailed) was used for comparisons between groups. Values of P less than 0.05 were considered significant. The mean and standard deviation were used to describe quantitative variables. GraphPad Prism software (Graph-Pad) was used to perform the analysis.

Results

At the end of the follow-up period (24 months), data from 22 patients, of whom 17 men and five women, were analyzed. The arrhythmic burden,



	Average monthly duration of Atrial fibrillation (min)	
	Pre-BDNF administration	Post-BDNF administration
P1	10	0
P2	45	0
P3	120	2
P4	12	2
P5	10	2
P6	8	3
P7	50	0
P8	20	2
P9	12	2
P10	26	3
P11	260	10
P12	120	2
P13	38	3
P14	14	0
P15	20	0
P16	12	0
P17	250	25
P18	60	3
P19	110	80
P20	60	50
P21	80	20
P22	100	0

Figure 1.—Average monthly duration of atrial fibrillation and details of average monthly duration of atrial fibrillation for each single patient.

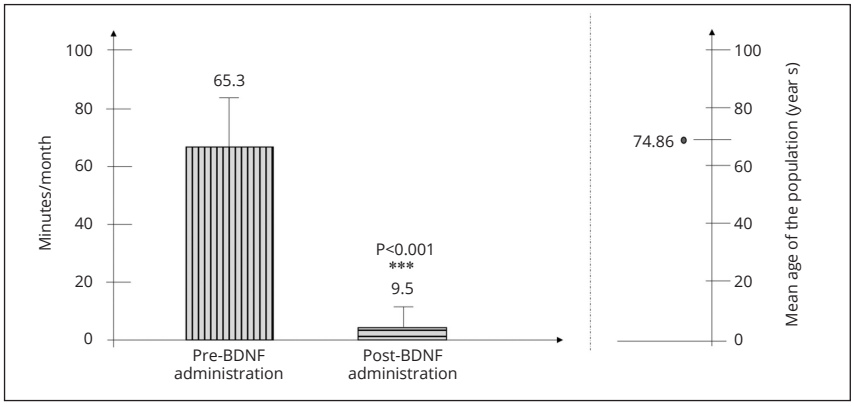


Figure 2.—Average monthly duration of atrial fibrillation and mean age of the population.

measured in terms of monthly average duration of episodes of PAF, was found significantly reduced after the administration of BDNF (65.3 minutes per month pre-BDNF administration, 9.5 minutes per month after-BDNF administration, P<0.001) (Figure 1). The mean age of the population was 74.86 years (Figure 2). In seven cases, patients no longer experienced episodes of AF, whereas in 10 other patients the duration of the episodes was reduced to three minutes or less per month. Thus, a total of 17 out of 22 patients saw their arrhythmic burden eliminated or consistently reduced. Despite the duration of AF episodes remaining considerable, two patients underwent a drastic reduction of their arrhythmic burden, of more than 200 minutes per month (from 260 to 10 minute per month and from 250 to 25 minutes per month). Only four patients, despite the administration of BDNF, still had an arrhythmic burden of 20 minutes or more. The lower reduction rate was observed in a patient who suffered from 8 min/month of AF and after BDNF 3 min/month. Considering the extent of the reduction of AF burden in relation to age groups, the one in which the greatest reduction was observed is from 90 to 100 years (70.5 min/month), but in patients aged 80-89 we should highlight that AF burden was almost set to zero (1 min of residual AF burden); however, in this last case, patients baseline arrhythmic burden was the lowest of the four groups (Figure 3). In the most represented subgroup of the sample, from 70 to 79 years, the reduction was satisfying as well as in the other groups (61.8 min/month) with 11 minutes of residual AF burden. Eventually, in patients between 50 and 69 years we observed a reduction of 47 minutes; we can state that BDNF low dose is particularly effective in patients aged 70 or more.

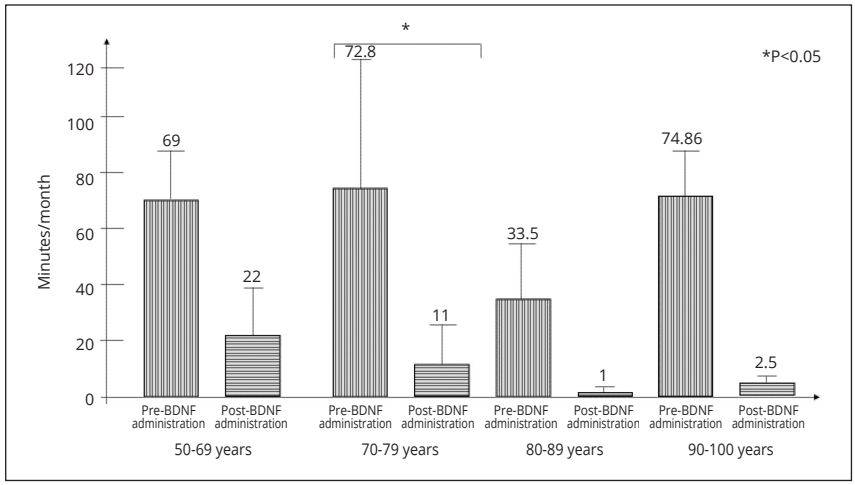


Figure 3.—Average monthly duration of atrial fibrillation in relation to age groups.

Discussion

Treatment and prevention of PAF, according to the latest guidelines, include a variety of therapeutic options mainly represented by antiarrhythmic drugs and catheter ablation.[3] Even though good results have been achieved with these tools, recurrence of PAF has not been completely tamed, still remaining a challenging clinical issue.[24] Among the numerous lines of research, researchers' efforts are focusing on the use of either less invasive procedures, such as radio-ablation, or drugs with fewer side effects compared to the currently available antiarrhythmics, such as endogenous peptides (*e.g.* BNP).[25, 26] In this context, because of several pathophysiological and biological! implications, we aimed at appraising the potential impact of BDNF in PAF. In fact, the well-known interplay between cardiovascular and central nervous system is clearly underlined by the many signal pathways and membrane channels shared, due to the need in both tissues of spreading action potentials.[27] Thus, our hypothesis is that BDNF may internet on these common pathways when AF occurs. While several studies have focused on the link between NTs and cardiovascular disease, limited if any research is available on the use of BDNF in preventing PAF recurrence or decreasing its arrhythmic burden.[28] A 2017 study by Rahman *et al.* was aimed at demonstrating a correlation between increased levels of serum BDNF and the risk of AF; results from this study, however, did not show a statistically significant association, suggesting that BDNF low dose administration in Atrial Fibrillation, first of all, should not be unsafe.[20] The main pathophysiological mechanisms related to the development of AF concern the electromechanical remodeling of the left atrium and the impaired activation of the autonomic nervous system;[29] during the years hypotheses have been gathered on the possible role of NTs, like nerve growth factor (NGF), but not of BDNF specifically, in stopping these processes.[28, 30] The role of the autonomic nervous system (ANS) in the onset of AF is well known, indeed many AF triggers (such as pneumonia and electrolyte disorders) impact directly on the ANS regulation;[29] notably this mechanism is thought to be impacting in the first 24 hours of AF episodes.[30] In their 2011 work, Rana *et al.* demonstrated that NGF and BDNF may boost NT-3-mediated acetylcholine upregulation after chronic High-Frequency Electric Stimulation (HFES) of the right inferior ganglionated plexus, stimulating cardiac parasympathetic tone.[31] Consequentially, it seems possible an involvement of NTs in the regulation of ANS, but further molecular studies are needed to gauge in detail the potential pathways by which BDNF could modulate the activity of ANS and cardiac conduction tissue (CCT). Furthermore, the greater effect of BDNF in the over 70 population suggests that it may act against the physi-

ological impairment of the two systems, ANS and CCT, that physiologically occurs with age. Moreover, circulating BDNF has been shown to be reduced in the case of acute ischemic stroke with worse long-term outcomes, therefore administering BDNF in patients with AF could convey clinical benefits also in the case of ischemic stroke, which is not impossible to occur even under optimal medical therapy for AF.[32] On the other hand, BDNF may enhance the reverse remodeling of the left atrium due to its positive action on the regeneration of cardiomyocytes, endothelial tissue and its anti-inflammatory action, as testified previously by many authors.[33] Results from the present study are coherent with the poor literature available the use of low dose BDNF, if proved safe and effective, may represent another weapon against AF: its main point of strength is represented by the fact that it is a natural compound.

Limitations of the study

Drawbacks of this work include selection bias, confounding, smallness of the sample size and non-uniformity in the assessment of the primary endpoint. It should be borne in mind that patients enrolled in this study did not have structural heart disease and were on Optimal Medical Treatment (OMT), defined according to current European Guidelines, for at least three months.[3]

Moreover, patients from the study were ideal candidates to receive potent antiarrhythmics such as flecainide and propafenone, contraindicated in patients with structural heart diseases.[3] Another critical issue is represented by the fact that the average monthly duration of atrial fibrillation episodes has been assessed with different tools (*e.g.* duration of symptoms, Loop Recorder or ICD) without uniformity in the estimation. In addition, the low number of patients enrolled in the study limits the conclusions: further studies with larger samples, and possibly randomized, are required, moreover it is worth to highlight the small presence of female subjects in the sample. Eventually, despite the limitations above, some interesting data are retrieved from the present study that should be viewed with caution and as exploratory only.

Conclusions

Despite ongoing efforts and several treatments available, the prevention of PAF episodes remains still a challenging issue in cardiovascular medicine. In this context, the administration of BDNF, a NT discovered in our Central Nervous System, could represent a promising and natural tool against PAF. This study shows that BDNF low dose may have an impacting role in reducing or eliminating the arrhythmic burden in patients with PAF. This holds true especially in patients aged 70 or more, without structural heart disease and under optimal medical treatment. However, this study presents several limitations, thus it should be considered mainly as hypothesis generating. Although presented results are encouraging, further data, retrieved from clinical and molecular studies, are required before routinely considering BDNF as a drug against PAF.

Key messages

- Atrial fibrillation is the most common arrhythmia worldwide and is associated with significant morbidity and mortality. In this context, we aim to appraise the potential impact of BDNF on reducing episodes of PAF.
- Despite the effectiveness of catheter-based ablation, periprocedural complication and recurrences remain a concern.
- BDNF low dose therapy has shown to have an impacting role in reducing the arrhythmic burden and recurrences of AF, with a particular effectiveness in patients over 70 and without structural heart disease. Further clinical and molecular studies are needed before considering BDNF low dose as a tool against PAF.

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Conflicts of interest
Giuseppe Biondi-Zoccai has been a consultant for Cardionovum, InnovHeart, Meditrial, Opsens Medical, and Replycare. All other authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Massimo Fioranelli has given substantial contributions to the conception and the design of the manuscript. Maria G. Roccia, Marco Del Buono, and Giulio Cacioli contributed to acquisition, analysis and interpretation of the data. All authors have participated to drafting the manuscript, in particular Luigi Spadafora, Marco Bernardi, and Giuseppe Biondi-Zoccai. Luigi Spadafora revised it critically. All authors read and approved the final version of the manuscript.

History
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