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TOWARDS AN INTEGRATED PERSONALIZED APPROACH FOR THE EARLY PREDICTION OF ATRIAL FIBRILLATION IN PATIENTS AT RISK

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1. Project summary

Atrial fibrillation (AF) is the most common cardiac arrhythmia, causing disability and major comorbidity although it may initially be asymptomatic in many patients. Consequently, diagnosis is often made when thromboembolic or heart failure related complications occur. Hypertension, the practice of resistance sports and heart valve disease have been associated as predisposing factors to AF.

The objective of the study is to identify and integrate biomarkers based on blood determinations, imaging and computational simulations as indicators of underlying atrial dysfunction that can predict the development of AF in high-risk population, in order to allow early detection of the arrhythmia.

Methodology: Patients at risk of AF have been studied, including three prospective cohorts of the population at risk of developing AF: systemic arterial hypertension, mitral regurgitation, and subjects who practice endurance sports. All of them have been studied with echocardiography and have had a blood test. Clinical variables related to AF and cardiovascular risk factors have been recorded. Biomarkers of renal function, myocardial damage, and stretching (cTnI, BNP) and fibrosis (MMP and TIMP) will be determined from blood samples. Atrial structure and function will be evaluated by standard, real-time 3D and speckle tracking echocardiography. Data will be integrated into a computational model that will simulate atrial performance and will be used to predict the incidence of AF. Patients will be followed up yearly by clinical interview and ECG recording. The results of the computational model will be validated with the clinical follow-up of the subjects for the detection of incidental AF or related thromboembolic complications.

2. Results

At the end of December 2019, 540 subjects had been included in the project, 276 were athletes, 225 were hypertensive and 40 with mitral insufficiency. Images of all of them had been obtained and 500 had had their blood drawn. Until then a total of 464 blood samples had been processed in which the different biomarkers were determined; it is expected that the rest of the samples will be analyzed during this semester. The

analysis of the images of all patients has also been completed, evaluating ventricular and atrial remodeling with bi-three-dimensional echocardiography techniques and with myocardial deformation imaging (speckle tracking).

A healthy control population was also included and the findings were compared with the group of patients with HBP. The thicknesses of the left ventricle wall and the interventricular septum were measured at the anterior basal septum level (in the parasternal plane long axis) and of the lower basal septum in the apical plane of 4 chambers as well as the size, geometry and atrial and left ventricular function. Myocardial work index (MWI), construction work (CW), wasted work (WW) and work efficiency (WE) between the mitral valve closing and opening were also calculated. Non-invasive pressure and strain relationships would offer the potential additional information on cardiac function in patients with HBP and mitral regurgitation with left ventricular ejection fractions and preserved longitudinal strain. The presence of localized basal septal hypertrophy (BSH) was also evaluated, a parameter that has been proposed as an increased after load marker.

The cohort was 56% men, median age 57 (52-61) years and median duration of hypertension 9 years (5-15). Compared to the control group, hypertensive patients had an enlarged atrium with more deterioration of reservoir function and conductive function, as well as a decreased mitral annular velocity (Loncaric et al., Euroecho 2018).

We continue working on the analysis of the relationship of atrial remodeling and blood biomarker levels and sending communications to scientific conferences. Two articles have been sent to two journals and are pending review while another is in preparation. The results have been presented to several congresses, in one case receiving the Best Young Researcher Award.

We have confirmed that there is left atrial remodeling in hypertensive patients and athletes. We see a certain degree of relationship between the levels of some biomarkers in blood (metalloproteinase) and atrial remodeling.

The electrocardiographic monitoring of patients continues; 72-hour electrocardiographic follow-up, clinical interview and analysis of 225 patients have

been carried out, and it is planned to complete shortly the one-year follow-up of all patients included until now. Only 1 patient has presented atrial fibrillation (AF) at follow-up. It is possible to think that it is a population still of low risk and that the development of AF is foreseen in the next 5 or more years.

The project has already had benefits and impact on our clinical and research practice. Among the benefits obtained so far we highlight that it has allowed creating a space in which academic, clinical and industrial researchers can share their experience and work as a team to improve the evaluation of cardiac function in the clinical and research environment, through new points of view / new products. During the development of the project, the team has been in continuous communication, allowing constructive feedback among different professionals.

Derived from this interaction, a Doctoral Thesis project (Filip Loncaric) has been developed.

The integration of the data obtained through computational tools has provided a simpler way to understand the physiopathology, integrating all the knowledge and being able to offer personalized monitoring and treatment to patients at risk of AF. With professionals from very divergent fields of knowledge working as a team (engineers with clinical researchers), and thanks to the continuous feedback between developers and users, it has proved possible for us to limit the development and innovation cycle and thus improve the clinical relevance of the computational tools that we can offer.

The first results of this work were presented at the ESC Congress in Paris 2019, winning the award for "Best moderated Poster" in the session “The Heart in Hypertensive” (Loncaric et al., ESC 2019).

The potential of the analysis of non-invasive myocardial work makes it possible to distinguish chronic and acute influences in the evaluation of myocardial deformation, which makes it possible to compare and explore the function in hypertensive hearts regardless of blood pressure. A gradient of apex-based work present in the left ventricle, unrelated changes in preload, demonstrates an abnormal redistribution of left ventricle work in hypertensive hearts. In addition, marked changes in the redistribution

of myocardial work reaffirm BSH as an echocardiographic parameter in hypertensive heart disease (Loncaric et al., submitted January 2020, Circ J).

We also compared non-invasive myocardial work between hypertensive patients and a cohort of patients with mitral insufficiency, a disease related to volume overload (Loncaric et al., Euroecho 2.019). In patients with mitral insufficiency, the assessment of left ventricular contractility is limited by the existence of volume overload, which magnifies and overestimates the ejection fraction of the left ventricle (parameter usually used as an indicator of ventricular contractility). This means that in some patients the left ventricular dysfunction is diagnosed late with the consequent prognostic implications of increased mortality in delaying the intervention and increasing the risk for surgical intervention. Therefore, a parameter that improves the evaluation of function (ventricular contractility) has a lot of clinical interest.

We have shown that the non-invasive measurement of strain pressures provides additional information on cardiac function in patients with hypertension and mitral regurgitation with preserved ejection fraction and longitudinal strain. As we observed, in hypertensive hearts myocardial work is elevated and redistributed with a gradient of base apex, which indicates an apical compensation of damage at the level of the basal myocardium due to an increase in afterload. Light and moderate mitral regurgitation was associated with a state of compensation for the normal global myocardial work index and its distribution. Even so, work per minute in hearts with severe insufficiency presents a global increase in the "workload", potentially predicting a process of remodeling the left ventricle in the future.

Work has also been done with the Pompeu Fabra University group on computational methodology (artificial intelligence) to develop tools that allow patients to be automatically classified into different subgroups (phenotypes) of cardiac output according to the integration of multiple parameters of echocardiography and biomarkers. While at one end of the spectrum all echocardiographic traces appear normal, the data at the other end describe a characteristic pattern of cardiac remodeling in response to pressure overload, with slightly reduced and delayed aortic output velocities, fused E and A waves. with a ratio <1, lower velocities of the mitral annulus, decrease in basal septal strain with post-systolic movement, prolonged relaxation to early diastole as seen by the traces of deformation and a change in atrial

deformation with increased left atrial contraction. These preliminary results show that the artificial intelligence-based analysis of complex echocardiographic data has the potential to recognize different patient profiles, related to the remodeling of the left ventricle in a hypertensive cohort with added diagnostic value beyond conventional clinical and echocardiographic parameters, by integrating multiple parameters and complex variables (Loncaric, Sanchez et al., Euroecho 2,019). This work has been recognized with the Young Investigator Award to the Euroecho Congress of the European Society of Cardiology recently held in Vienna (December 2019).

Finally, preliminary results show the association between the levels of some plasma biomarkers and left atrial function in patients with arterial hypertension. In this group of patients, the MMP-9 fibrosis marker showed a statistically significant inverse correlation with the parameters of atrial contractile function, assessed both by speckle tracking technique and 3D echocardiography: an increase in the marker was associated with a decrease in the peak negative of the left atrial strain (SaAI), a reduction in the strain wave rate SRa and a decrease in the active systolic volume of the LAr = -0.3; p = 0.006 vs. r = -0, 2; p = 0.049 vs. r = -0.3; p = 0.007 respectively) (Nunn et al., Euroecho 2018). The inflammation markers CXCL6 and OSM showed a significant inverse correlation with the total systolic volume of the LA and the index of the reservoir function of the LAr = -0.3; p = 0.014 and r = -0.3; p = 0.015 respectively). There was no statistically significant correlation between plasma biomarker levels and atrial volume, nor between atrial volume and years of HBP duration.

In conclusion, these preliminary data show that there is dysfunction of the left atrium in patients with HBP, which correlates with blood biomarker levels. These could potentially be used as indirect surrogates of atrial dysfunction and potential predictors of incidental AF

3. Relevance with possible future implications

The clinical implications of the findings mentioned in the previous section show that there is really a significant cardiac remodeling in hypertensive patients and athletes, both at the atrial and ventricular levels. This will give us a lot of information regarding the follow-up in the second phase, where we can see at 5 years what were the

characteristics of the patients who have developed atrial fibrillation. So, if in the future we find these parameters in clinical practice we will know that we will have to follow them more closely and personally. In fact, we know that both hypertensive subjects and athletes and patients with mitral insufficiency are a subset of risk for the development of atrial fibrillation, but we do not know why some of these subjects develop it and others do not. Thus, the knowledge that we intend to acquire with this study will allow us to identify factors that predict AF in these subgroups. We will identify clinical factors, plasma biomarkers and echocardiographic factors that will detect the most at-risk patients, allowing early diagnosis and treatment, to avoid such invalidating complications as stroke or heart failure. Our results, if positive for predicting the incidence of AF and avoiding complications, could be extrapolated to other risk populations such as patients with ischemic heart disease, heart failure or chronic lung disease (diseases also very prevalent in the population).

Thus, it is in the medium term that we will obtain more relevant data for real clinical practice. As previously mentioned, we plan to continue the follow-up of these patients since it is a very large cohort, very well characterized and a high quality prospective study source. However, we believe that the project has already had benefits and impact on our clinical and research practice. Among the benefits obtained so far from the project we highlight:

The project has created a space where academic, clinical and industrial researchers can share their experience and work as a team to improve the evaluation of cardiac function in the clinical and research environment through new points of view / new products. During the development of the project, the team has been in continuous communication, allowing constructive feedback among professionals of various kinds. Derived from this interaction, a Doctoral Thesis project (Filip Loncaric) has been developed.

The integration of the data obtained through computational tools has provided a simpler way to understand the physiopathology, integrating all the knowledge and being able to offer personalized monitoring and treatment to patients at risk of AF. With professionals from very divergent fields of knowledge working as a team (engineers with clinical researchers), and thanks to the continuous feedback between developers and users, it has proved possible for us to limit the development and

innovation cycle and thus improve the clinical relevance of the computational tools that we can offer.

Other relevant aspects to highlight are the following:

- Development of a computer platform, for other clinical scenarios, in which machine learning and help tools for clinical decision-making can be useful.
- Consolidation of a multidisciplinary approach to disease management and research.
- Provision of an adequate, collaborative and innovative environment for learning, research and development in the future.
- Empowerment of the patient allowing their participation in decision making by showing them how these integrative computational tools work.
- Driving disease management towards a preventive, predictive, personalized and participatory approach

4. Scientific output

Congress communications

Nunno L, Butakoff C, Mimbrero M, Loncaric F, Sanchis L, Montserrat S, Morales M, Bijnens B, Sitges M. Left atrial dysfunction is associated with high levels of fibrosis and inflammation biomarkers among patients with hypertension. European Heart Journal - Cardiovascular Imaging, Volume 20, Issue Supplement_1, January 2019, Pages i138–i254, https://doi.org/10.1093/ehjci/jey258

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Scientific articles

Loncaric F, Nunno L, Mimbrero M, Marciniak M, Fernandes JF, Tirapu L, Fabijanovic D, Sanchis L, Doltra A, Cikes M, Lamata P, Bijnens B, Sitges M. Basal septal hypertrophy – a marker of advanced cardiac impairment in arterial hypertension. American Journal of Cardiology 2020 (in press)

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