Medical Research Archives

ESMED European Society of Medicine

OPEN ACCESS

Published: July 31, 2023

Citation: García Guerrero JJ, de la Concha Castañeda JF, et al., 2023. Avcs-Sonr Pilot Study: N-Terminal Pro-Brain Natriuretic Peptide Inversely Correlates with Sonr Signal in Patients with Dilated Cardiomyopathy and Reduced Left Ventricular Ejection Fraction, Medical Research Archives, [online] 11(7). https://doi.org/10.18103/mra.v11i7.2.4169

DOI
https://doi.org/10.18103/mra.v11i7.2.4169

ISSN: 2375-1924

RESEARCH ARTICLE

Avcs-Sonr Pilot Study: N-Terminal Pro-Brain Natriuretic Peptide Inversely Correlates with Sonr Signal in Patients with Dilated Cardiomyopathy and Reduced Left Ventricular Ejection Fraction

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ABSTRACT

Background. Chronic heart failure is a very important public health problem, and brain natriuretic peptide monitoring may help in its management but faces important logistical problems. A readily available surrogate of brain natriuretic peptide would be of value in this field. We hypothesized that SonR measurements might be this brain natriuretic peptide surrogate.

Methods. Patients with chronic heart failure, left ventricular ejection fraction ≤ 30% and implanted with a cardiac resynchronization therapy defibrillator able to provide SonR values underwent monthly assessment of brain natriuretic peptide levels for 1 year. The relationship between brain natriuretic peptide levels and paired SonR values was evaluated.

Results. An inverse and highly significant relationship between brain natriuretic peptide levels and paired SonR values was obtained.

Conclusions. We found an inverse and significant relationship between SonR values and brain natriuretic peptide levels. This finding might lead to the use of SonR values to monitor treatment and preclude hospital admissions in patients with chronic heart failure.

Keywords: decompensated heart failure, myocardial contractility, right atrial SonR sensor

Abbreviations. CHF: Chronic heart failure. ADHF: Acute decompensated heart failure. CPI: Cardiac power index. BNP: Brain natriuretic peptide. AICD: Automatic implantable cardiac defibrillator. NT-proBNP: N-terminal pro-brain natriuretic peptide

INTRODUCTION

Chronic heart failure (CHF) is a very important public health problem and is associated with poor outcomes and high rates of death and hospitalization. Acute and repeat episodes of decompensation lead to the progressive deterioration of cardiac performance and are also associated with a worse outcome and progressive multiorgan failure.1 Acute decompensated heart failure (ADHF) is a common disease observed in clinical practice. Its physiopathology is incompletely understood, and its treatment resources are limited.1 Moreover, ADHF remains the main reason for hospital stay in patients over 65 years old and is associated with high mortality and morbidity and mounting financial cost.2

Brain natriuretic peptides (BNP) are released by the ventricles as a response to increased pressure or fluid overload and have been recommended for CHF treatment.3

Cardiac power is an index of cardiac contractility, and the cardiac power index (CPI) is the product of simultaneously measured mean arterial blood pressure and cardiovascular flow; it decreases as pressure and fluid overload increase and has been demonstrated to be the strongest predictor of outcome in ADHF.4

SonR is a hemodynamic sensor able to detect the acceleration of the endocardial wall of the left ventricle. This sensor is encapsulated at the tip of the atrial pacing lead attached to the Platinium SonR CRTD 1841 cardiac resynchronization therapy defibrillator system (Microport CRM Clamart France). The SonR sensor transforms cardiac vibrations into an electric signal, and SonR signals have shown a high correlation with right and left ventricular dP/dT max. SonR is able to detect changes in myocardial contractility, unlike echocardiography.5

The aim of our study was to establish a correlation between SonR system signals and BNP levels in CHF patients with reduced ejection fraction. Increasing levels of BNP, reflecting elevations in pressure and fluid levels, could be matched with a simultaneous decrease in cardiac contractility properties measured by the SonR signal, allowing the use of SonR values as a guide to CHF treatment.

METHODS

The Added Value Changes in Signal SonR in Patients with left ventricular ejection fraction less or equal than 30% (AVCS-SONR) was a pilot, prospective, multicenter, nonrandomized, observational study.

Inclusion criteria: Patients were enrolled if they had ischemic or non-ischemic cardiomyopathy, a left ventricular ejection fraction (LVEF) less than or equal to 30%, and were candidates for a single or double chamber automatic implantable cardioverter defibrillator (AICD) for primary or secondary sudden cardiac death prevention. Implanted AICD had to be the Platinium SonR CRTD 1841 (Microport CRM Clamart) AICD, which was able to detect, measure and record the SonR signal with the left ventricular port unused since cardiac resynchronization therapy (CRT) was not allowed in the study. They should have had at least one hospital admission due to ADHF in the year prior to the inclusion date.

Exclusion criteria: The exclusion criteria included end-stage renal failure in hemodialysis, planned cardiac transplant or CRT, pregnancy, participation in other investigation protocols, and inability or unwillingness to follow the requirements of the protocol for any reason.

The follow-up period was 1 year after the implant, during which an N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement was performed monthly, and the SonR signal value registered on the date as close as possible to the NT-proBNP extraction was obtained from the AICD system. Hospital admission due to ADHF episodes was recorded.

The primary objective of the study was to evaluate the relationship between the SonR signals recorded by the AICD and the paired NT-proBNP values monthly for 1 year. The secondary objectives were to analyze the ADHF episodes and to establish whether the SonR values and NT-proBNP levels registered 1 month prior to the admission date could have an inverse relationship.

Statistical analysis. Continuous variables are presented as the mean ± SD. Discrete variables are presented as percentages. Associations were considered statistically significant when $p < 0.05$.

To explore the linear relationship between NT-proBNP and the paired measurement of SonR values, Spearman's rank correlation coefficient was used. Using the same approach, we explored the relationship between the natural logarithm of the NT-proBNP levels and SonR measurements. All analyses were performed using SPSS v. 23 (IBM Corp, Armonk, NY, USA).

Research ethics. The local Ethics Committee approved the study protocol, and all patients provided written informed consent to participate.

RESULTS

Patient characteristics

A total of 27 patients were enrolled in the study by 5 Spanish hospitals from April 2018 to July 2019. The indication for AICD was primary prevention in 92.6% of patients, and mean LVEF was 26.3%. Global baseline characteristics are shown in Table 1.

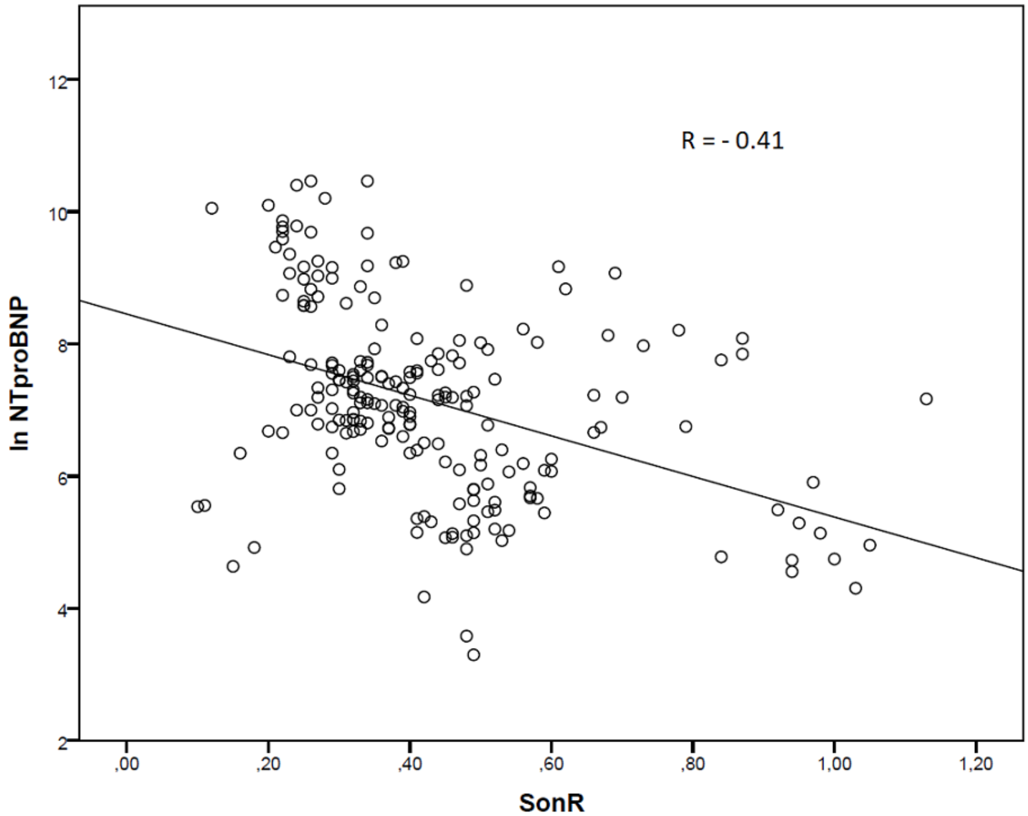
Table 1. Patient baseline characteristics n=27

General	
Sex (male)	25 (92.6%)
Age (years)	56±12
Medical history and medication	
Etiology	
Idiopathic	10 (37.0%)
Ischemic	17 (63.0%)
Atrial fibrillation	10 (37.0%)
Atrial regurgitation III/IV (%)	29.6/14.8
AICD 1° Prevention	25 (92.6%)
NYHA class	
II	7 (25.9%)
III	19 (70.4%)
LVEF (%)	26±3
Oral anticoagulation	10 (37%)
Oral antiplatelets	16 (59.3%)

NYHA: New York Heart Association. LVEF: Left ventricular ejection fraction. AICD: Automatic implantable cardiac defibrillator

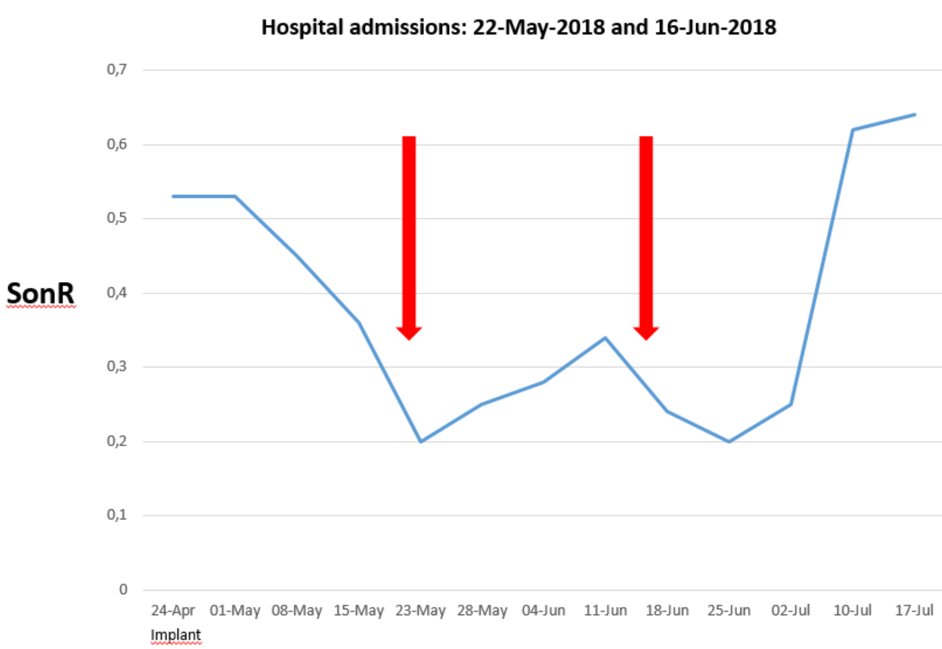
All 27 patients but one provided valid paired data to the global database. We obtained 203 NT-proBNP values and 212 SonR values (62% and 65%, respectively, of the total number of data expected). The missing data could not be retrieved mostly due to logistical and/or technical problems. In addition, two patients died a short time after the implant due to ACHF (one after 48 days and the other 78 days after), and no data could be retrieved from the first one, and only a few data pairs could be retrieved from the second one. There was no relationship between the cause of death and the previous implant procedure. All NT-proBNP levels obtained were collected with the SonR value obtained at the same time. Therefore, a total of 324 pairs or data points were expected, but only 203 (62%) could be retrieved and analyzed. In the data analysis, an inverse correlation between linear NT-proBNP levels and the SonR signals was obtained, R= -0,309 (p< 0.0001). Additionally, an inverse correlation between logarithmic NT pro-BNP levels and corresponding SonR signals was observed, R= -0,410 (p<0.000001). (Fig 1)

Fig 1



There were only 5 ADHF events in 4 patients, leading to death in two patients. One patient had 2 hospital admissions due to ADHF in a short period of time, and the evolution of the SonR values related to both admission dates is shown in Fig 2.

Fig 2



DISCUSSION

We demonstrated in this study that NT-proBNP levels (linear or logarithmic) were inversely correlated with SonR signal values, both with high statistical significance.

Congestion is considered the most important cause of hospitalization in patients with CHF and severe left ventricular dysfunction.2 Increases in intracardiac and pulmonary artery pressures are the cause of this congestion and occur several days or even weeks before signs and symptoms of decompensation occur, suggesting that intensifying the current treatment to reduce these pressures may reduce admission risk.6 In the CHAMPION study, the use of the CardioMEMS device enabled significantly less hospitalization in patients with CHF in New York Heart Association (NYHA) class III than usual care, as pressure information given to physicians in the active arm led to improved CHF management in the short (6 months) 7 and long (31 months) term.8 The use of CardioMEMS requires the invasive implant of an expensive device and the continuous collaboration of the patient, who must be trained before taking the measurements daily, under precise conditions and postures.

Other studies that aimed to provide a sensitive and accurate predictor of impending ADHF were published. The MultiSENSE study used a multiparameter-based algorithm (HeartLogic) to detect imminent decompensation and obtained a 70% sensitivity rate, with a very low positive predictive value (11.3%).9

Recent scientific evidence suggests that BNP-guided treatment is useful to reduce the hospitalization rate as a marker of increasing pressure and fluid overload. Once this marker indicates to the physician that the patient's condition is worsening, even when the symptoms of decompensation are not present, treatment may be adjusted, preventing hospital admission. In the STARS-BNP study, a BNP-based treatment strategy was able to reduce the risk of hospitalization-induced death and stay.10, and in the PROTECT study 11, the NT-proBNP-guided treatment strategy was superior to the standard of care, reducing the event rate, improving quality of life and demonstrating favorable effects on cardiac remodeling. Another study demonstrated an all-cause mortality reduction using BNP-guided treatment in patients aged younger than 75 years.12 Although some conflicting results were published in other studies,13 one systematic meta-analysis demonstrated a reduction in CHF hospitalization but not in total mortality,14 and another meta-analysis, which included the negative results of the GUIDE-IT study,13 found BNP-guided therapy beneficial in reducing CHF admissions and all-cause mortality.15 Based on this information, some guidelines regarding the clinical use of BNP consider that the combination of symptoms, weight gain and BNP concentration would be the best strategy to diagnose the early rise of pressures and fluid overload 16 or even suggest that NT-proBNP levels should be measured regularly in patients with CHF with reduced LVEF to decrease hospitalizations and potentially reduce mortality, mainly in individuals younger than 75 years old.3 This BNP-based treatment strategy requires continuous and regular BNP measurements and may involve disregarding BNP elevations not coincident with the schedule of the measurements, making it difficult to observe the decompensation warning in a timely manner, which is needed to adjust treatment and avoid hospitalization when pressures and fluid overload start to increase and symptoms are not present yet. While it is known that NT-proBNP levels are not linear in cases of ADHF 16 and instead show rapid changes as decompensation progresses or improves, we assessed the relationship between logarithmic NT-proBNP levels and SonR values, with even better results than the evaluation of linear NT-proBNP levels.

The SonR system is a hemodynamic sensor embedded in the tip of the right atrial lead attached to the Platinium SonR CRTD 1841 AICD. This sensor is a detector of left ventricle endocardial wall acceleration, and its signal has been demonstrated to closely correlate with left ventricular dP/dT max, which is currently considered the gold standard for the assessment of myocardial contractility.17 This system was able to show a close correlation with echocardiographic shortening fraction and noninvasive blood pressure and dP/dT max monitoring in patients with severely impaired LV ejection fraction who underwent an isometric stress test. The hemodynamic and echocardiographic parameters correlated very closely with the SonR signal both during rest and postexercise periods.5 Moreover, a clinical benefit in terms of NYHA class was demonstrated in the pilot CLEAR study,18 in which the system was used to automatically adjust the AV and VV delays in cardiac resynchronization pacemaker patients who were compared with a control group with usual adjustments. The SonR system was also used in the long-term follow-up RESPOND-CRT trial 19 with a similar design, in which a significant reduction in HF hospitalization was demonstrated in the SonR group.

In our study, we found an inverse and highly significant correlation between the SonR system signal, which can be used to assess the patient's myocardial performance, and the NT-proBNP levels measured monthly, which can be used to detect an early decompensation in the CHF patient. As there are evident logistic problems in continuously measuring NT-proBNP levels, it seems logical to identify another correlated measure that can be used to detect early HF decompensation and to allow the physician to intensively treat the patient before the situation worsens, leading to hospital admission. In patients implanted with an AICD featuring the SonR system, these measurements might be used as a surrogate for NT-proBNP measurements, providing a daily assessment of the status of myocardial contractility, which may play an important role in the management of these patients.

LIMITATIONS

This was a pilot study with a small number of patients. There was a significant inverse correlation between SonR signal values and NT-proBNP levels, showing that SonR signals might be considered a surrogate of NT-proBNP levels in CHF patient management, but this should be assessed in a future study with the appropriate design.

CONCLUSIONS

The SonR system values showed an inverse and statistically significant relationship with NT-proBNP levels during a 1-year period. This finding confirms our primary hypothesis that SonR values might be of value in CHF patient management.

Conflicts of Interest Statement: JJGG and JFCC have received fees for lectures and advice from St Jude Medical, Medtronic and Boston Scientific. IFL have received fees for lectures and advice from Abbot and Biotronik. JGF has received fees for lectures and advice from Biotronik, Medtronic and Boston Scientific

Funding Statement: The present study has no funding.

Acknowledgments: We would like to thank Arrhytnet Company for supporting this project with enthusiasm.

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