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Editorial

Is device-based prevention of heart failure decompensation rising like a phoenix from the ashes?

Prevención de las descompensaciones de la insuficiencia cardiaca mediante dispositivos. ¿Está resurgiendo de las cenizas como el ave fénix?

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«Listen to your heart. It knows all things»
—Paulo Coelho

The prevention of recurrent heart failure (HF) hospitalizations is of particular importance, as each successive event may trigger the progression of heart damage, reduce quality of life, and increase the risk of death. We have at our disposal an arsenal of drugs that, especially when correctly adjusted to the patient's clinical phenotype, can prevent HF events and death.[1] Why, then, are so many patients still hospitalized with acutely decompensated HF? The main reasons are the unpredictable course of HF and the unmet need for effective monitoring of early hemodynamic disturbances.

Implantable cardioverter-defibrillators and cardiac resynchronization therapy have been established to improve prognoses in selected patients with HF. Some of the parameters measured by these cardiac-implanted electronic devices (CIEDs) are not essential for electrotherapy and for many years were not used in general clinical practice. However, the awareness of such diagnostic potential has spurred interest in studies investigating its ability to identify patients at risk of HF events.

The first studies focused on intrathoracic impedance as a marker of pulmonary congestion alone, but most failed to provide strong evidence for identifying patients at risk of HF deterioration. Low positive predictive values and, at the same time, low specificity for detecting HF events have shaken faith in success in this research path. Research efforts have since turned toward the analysis of several variables producing a cumulative index.[2] The HeartLogic is one such algorithm. To generate the cumulative index value, it uses not only fluid content measured by intrathoracic impedance but also other CIED parameters, such as first heart sound (S1), third heart sound (S3), the derived S3/S1 ratio, respiration, night heart rate and patient activity (table 1). The threshold is dynamic, and when an alert state (index of $\geq$ 16) is reached, the threshold automatically lowers to 6, which means that the system is now more sensitive and will repeat weekly alerts until the index falls below 6.[3] The United States Food and Drug Administration approved use of CIEDs with this feature in 2017.

The MultiSENSE study, which included over 900 HF patients, was the landmark trial for the HeartLogic algorithm.[3] The clinically unexplained alert rate was 1.47 alerts/patient-y and HF events (admissions or unscheduled visits with intravenous treatment) were detected with a sensitivity of 70% and a specificity of 87.5%. Post-hoc analysis of the MultiSENSE study[4] revealed that an increased HeartLogic index is associated with a more than 10-fold higher risk of HF events; when an increased HeartLogic index is present together with increased N-terminal pro-B-type natriuretic peptide (NT-proBNP), the HF risk increases 50-fold. The positive effects of HeartLogic use were independent of age, sex, left ventricular ejection fraction, New York Heart Association (NYHA) classification, NT-proBNP and history of ischemia, atrial fibrillation, diabetes, or renal dysfunction.

The study of de Juan Bagudá et al.[5] recently published in *Revista Española de Cardiología* provided real-world evidence that comprehensive remote management based on the HeartLogic algorithm may yield clinical benefits for HF patients with CIEDs. The RE-HEART study was performed in 15 Spanish cardiac centers as a real-life, large, partly prospective clinical registry. The researchers aimed to analyze the association between HeartLogic alerts with clinical events and NT-proBNP values in 2 scenarios: with standard treatment blinded to the HeartLogic alert state (phase 1–passive phase) and under intervention while considering HeartLogic alerts (phases 2 and 3). The follow-up of clinical events focused on unplanned HF exacerbations requiring modification of treatment or resulting in death.

The HeartLogic alert was classified as "true" when the predefined HeartLogic index exceeded the threshold less than 30 days before HF decompensation. Another possible category was an "explained alert," indicating relevant clinical conditions and potential triggers of HF deterioration (eg, medication indiscretion, decreased resynchronization percentage, onset of atrial fibrillation, infection). The alerts not meeting the aforementioned criteria were classified as "unexplained".

The study included 288 patients with implantable cardioverter-defibrillators; most (77%) were men, 75% had left ventricular ejection fraction $<$ 35%, most were in NYHA class I/II, and the

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Table 1
HeartLogic components

Physiological variable	Change in worsening HF	Clinical relevance
First heart sound (S1)	↓	Worsening left ventricular contraction
Third heart sound (S3)	↑	Elevated early diastolic filling pressure
Intrathoracic impedance	↓	Pulmonary congestion/edema
Night heart rate	↑	Worsening cardiac status and/or arrhythmia and/or sympathetic-parasympathetic imbalance
Respiration rate	↑	Shortness of breath, dyspnea, pulmonary congestion or other cause of pulmonary insufficiency
Activity	↓	Worsening global functional status

Adapted from Boehmer at al.[3] HF, heart failure.

median NT-proBNP was 1234 pg/mL. They were sufficiently well treated to mention the fact that valsartan/sacubitril was used in a half of participants. In phase 1, with a median observation period of 10 months, 8 hospitalizations and 2 emergency room admissions for HF were noted (0.10 events/patient-y). All of these occurred within the alert period, which resulted in a rate of events within the alert state of 1.23/patient-y. The total number of alerts was 73 (0.72 alerts/patient-y), covering 8% of the follow-up period. The active phases (2 and 3) had a combined median follow-up of 16 months. More alerts were detected (0.89 alerts/patient-y), but only 2 HF events occurred outside the alert state. Overall, 33 HF hospitalizations, 46 minor decompensations and 6 HF deaths occurred within the period of HeartLogic alerts, which constituted 11% of the follow-up period.

Consistent with the RE-HEART study is the experience of Italian cardiologists described in the recent article by Calò et al.[6] The authors analyzed the clinical practice of 22 centers equipped with the HeartLogic feature, which involved 366 patients with CIEDs. During the median follow-up of 11 months, the rate of alerts was low (0.76 alerts/patient-y). The time in the alert state was similar to that of the RE-HEART experience (11%), with the occurrence of HF hospitalizations (n = 36) and HF deaths (n = 8) also being similar. Notably, the basic study characteristics were comparable. The risk of exacerbating HF symptoms in the alert state was 25-fold higher than when outside the alert state. Moreover, medical intervention following a remote alert resulted in an almost 3-fold reduction of HF events.

Suppose that symptomatic worsening of HF can be likened to the sound of thunder and subclinical deterioration likened to a flash of lightning. How long is the time interval in which we have to react? The mean time from alert onset to HF hospitalization in the RE-HEART registry was 20 ± 15 days, which is shorter than in the study by Calò et al. (median of 29 days)[6] and the MultiSENSE trial (median of 34 days).[3] Capucci et al.[7] reported a median early warning of HF of as much as 38 days in the case of hospitalization and 12 days in the case of minor HF deterioration events. Somehow, it seems that the time window between the onset of hemodynamic deterioration and clinical presentation is long enough for interventions to take place.

In the RE-HEART study, the alerts prompted medical actions (treatment modification or educational intervention) in 27% of cases during phase 2 and in 39% during phase 3. Calò et al.[6] reported alert-triggered actions in 43% of cases. In the prospective multicenter registry, Santini et al.[8] reported that as many as 80% of alerts provided new relevant information. Moreover, 90% of them provoked clinical actions, such as medication changes, outpatient clinic appointments, or hospitalization.[8]

One of the main objections to early reports of remote telemonitoring of intrathoracic impedance was a high percentage of false-positive alerts. The use of combined algorithms turned out to be revolutionary. The article by de Juan Bagudá et al.[5] reported only 120 alerts (0.39 alerts/patient-y) in phases 2 and 3 that were not related to clinical events. In the retrospective analysis by Capucci et al.,[7] the unexplained alert rate was 0.41 alerts/patient-y and in the study by Santini et al.,[8] it was even lower at 0.37 alerts/patient-y. More than 80% of the alerts in phases 2 and 3 of the RE-HEART study[5] were managed remotely by phone calls. The overall workload seems reasonable, as we note that the total number of telephone calls with patients was 0.65 calls/patient-y in phase 2 and 1.12 calls/patient-y in phase 3. The authors estimated that their protocol of remote management consumed only 1 hour of work per week for 30 patients. However, one may have concerns regarding the safety aspects of remote decision-making in patients with seemingly exacerbated HF. Calò et al.[6] provided reassuring data proving that phone contacts, applied in 75% of alerts, were as safe as in-office visits.

It is widely known that volemic control is crucial to prevent HF rehospitalization.[1] Indeed, in the RE-HEART study, the most frequent clinical action was intensification of diuretic therapy.[5] Calò et al. reported symptoms of congestion (mostly dyspnea, fatigue and orthopnea) in 39% of alerts, and increasing the dose of diuretics was the most frequent recommendation. Likewise, in the TRIAGE-HF Plus study,[9] low thoracic impedance (ie, high OptiVol) was, besides low physical activity, the most frequently detected abnormality (72.3%).[9] However, it should be emphasized that other HeartLogic components (heart rate variability, arrhythmia, and activity) may also have a strong pathophysiological relationship to fluid overload. The clinical relevance of CIED multisensor indices in detecting volume overload is enhanced by reports of their association with NT-proBNP levels. In the RE-HEART study, the median NT-proBNP value was higher within the HeartLogic alert state than outside the alert state (7378 vs 1210 pg/mL; $P < .001$). Likewise, in the MOMOTARO study, B-type natriuretic peptide (BNP) values were significantly higher at the time of the alert issued by the OptiVol algorithm.[10]

There are still many questions to be answered regarding a standardized protocol of HeartLogic use. The frequency of data revision, roles of the medical team (technician, nurse, and physician) and rules for medical interventions should be clearly defined. There are still fundamentally divergent approaches. For instance, Treskes et al.[11] applied an intensive protocol of scheduled revisions. Remote monitoring data were reviewed on a daily basis by a trained technician and/or a HF nurse. In case of an alert, the report was transferred to the HF caregiver, who contacted the patient within 72 hours by phone. Conversely, de Juan Bagudá et al.[5] proposed only a weekly revision of HeartLogic indications. Moreover, when the index threshold was exceeded de novo, no intervention was applied; it was only when this persisted for 7 days that a telephone consultation was made and medical action taken according to the patient's clinical status. Some of these questions may be addressed in upcoming trials (MANAGE-HF [NCT03237858] and the PREEMPT-HF [NCT03579641]).

And what can we offer for patients unlucky enough to have CIEDs? In the CHAMPION study, diuretic therapy based on

pulmonary artery pressure monitoring using the CardioMEMS implantable monitor (Abbott Vascular, United States) resulted in a 39% reduction in HF readmissions.[12] In the recent GUIDE-HF trial,[13] conducted in 1000 HF patients, CardioMEMS-guided management failed to significantly reduce the incidence of a composite endpoint (mortality and total HF events) compared with the control group (hazard ratio [HR], 0.88; $P = .16$). However, the precoronavirus disease 2019 (COVID-19) impact analysis indicated a possible benefit of this form of telemonitoring on the primary outcome (HR, 0.81; $P = .049$). There have also been attempts to improve the prognosis of HF patients by using remote noninvasive hemodynamic assessment of volemia. In the IMPEDANCE-HF trial,[14] lung impedance-guided treatment was associated with a lower acute HF hospitalization rate (HR, 0.63; $P < .001$), as well as a reduction in total deaths (HR, 0.52; $P = .002$), cardiovascular deaths (HR, 0.41; $P < .001$) and deaths due to HF (HR, 0.35; $P = .001$). Another system for assessing lung hydration, the remote dielectric sensing (ReDS) system (SMILE trial), which is derived from electromagnetic energy-based technology, was used to guide therapy in the study by Abraham et al.[15] and resulted in a 48% reduction in readmissions when compared with usual care (HR, 0.52; $P = .01$).

In summary, home monitoring based on automatic multiparametric CIED algorithms enables the identification of patients at a significantly increased risk of worsening HF. Its indisputable advantage is that it requires almost no effort from the patient, because data are automatically gathered and transferred to the monitoring center. Intuitively, we feel that such an approach is a chance to provide better outpatient care and optimize the management of health care resources. However, there is a need to determine well-organized logistics, clear division of duties among caregivers and precise rules of medical intervention. User-friendly telemedicine platforms, symptom tracking apps and more advanced methods of data analysis, especially those based on artificial intelligence, should be involved in future research on remote monitoring by CIEDs.

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