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HeartLogic™
Heart Failure Diagnostic

HeartLogic Clinical Compendium

Updated as of February 2020

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THIS DOCUMENT IS A COMPILATION OF RELEVANT CLINICAL PUBLICATION REFERENCES THAT FORM THE CLINICAL FOUNDATION OF THE HEARTLOGIC HEART FAILURE DIAGNOSTIC. PUBLICATIONS ARE LISTED BY SENSOR TREND/TOPIC AREA AND THEN BY RELEVANCE ON FEASIBILITY, PHYSIOLOGIC CORRELATION AND CLINICAL EVIDENCE. EACH PUBLICATION ENTRY INCLUDES (IF AVAILABLE) ITS FULL REFERENCE, AN ABSTRACT AND A LINK TO THE FULL ARTICLE (THIS LINK MAY REQUIRE THE READER TO PAY FOR THE FULL CONTENT).

THIS DOCUMENT WILL BE UPDATED AS FUTURE PUBLICATIONS BECOME AVAILABLE.

Boehmer JP, Hariharan R, Devecchi FG, Smith AL, Molon G, Capucci A, An Q, Averina V, Stolen CM, Thakur PH, Thompson JA, Wariar R, Zhang Y, Singh JP. **A Multisensor Algorithm Predicts Heart Failure Events in Patients With Implanted Devices: Results From the MultiSENSE Study.** ***JACC Heart Fail.*** 2017; 5 (3): 216-25. http://heartfailure.onlinejacc.org/content/jhf/5/3/216.full.pdf

OBJECTIVES: The aim of this study was to develop and validate a device-based diagnostic algorithm to predict heart failure (HF) events. BACKGROUND: HF involves costly hospitalizations with adverse impact on patient outcomes. The authors hypothesized that an algorithm combining a diverse set of implanted device-based sensors chosen to target HF pathophysiology could detect worsening HF.

METHODS: The MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) study enrolled patients with investigational chronic ambulatory data collection via implanted cardiac resynchronization therapy defibrillators. HF events (HFEs), defined as HF admissions or unscheduled visits with intravenous treatment, were independently adjudicated. The development cohort of patients was used to construct a composite index and alert algorithm (HeartLogic) combining heart sounds, respiration, thoracic impedance, heart rate, and activity; the test cohort was sequestered for independent validation. The 2 coprimary endpoints were sensitivity to detect HFE >40% and unexplained alert rate <2 alerts per patient-year.

RESULTS: Overall, 900 patients (development cohort, n = 500; test cohort, n = 400) were followed for up to 1 year. Coprimary endpoints were evaluated using 320 patient-years of follow-up data and 50 HFEs in the test cohort (72% men; mean age 66.8 +/- 10.3 years; New York Heart Association functional class at enrollment: 69% in class II, 25% in class III; mean left ventricular ejection fraction 30.0 +/- 11.4%). Both endpoints were significantly exceeded, with sensitivity of 70% (95% confidence interval [CI]: 55.4% to 82.1%) and an unexplained alert rate of 1.47 per patient-year (95% CI: 1.32 to 1.65). The median lead time before HFE was 34.0 days (interquartile range: 19.0 to 66.3 days).

CONCLUSIONS: The HeartLogic multisensor index and alert algorithm provides a sensitive and timely predictor of impending HF decompensation

Gardner RS, Singh JP, Stancak B, Nair DG, Cao M, Schulze C, Thakur PH, An Q, Wehrenberg S, Hammill EF, Zhang Y, Boehmer JP. **HeartLogic Multisensor Algorithm Identifies Patients During Periods of Significantly Increased Risk of Heart Failure Events: Results From the MultiSENSE Study.** ***Circ Heart Fail.*** 2018; 11 (7): e004669. http://doi.org/10.1161/CIRCHEARTFAILURE.117.004669

BACKGROUND: Care of heart failure (HF) patients results in a high burden on healthcare resources, and estimating prognosis is becoming increasingly important to triage resources wisely. Natriuretic peptides are recommended prognosticators in chronic HF. Our objective was to evaluate whether a multisensor HF index and alert algorithm (HeartLogic) replaces or augments current HF risk stratification.

METHODS AND RESULTS: MultiSENSE (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) enrolled 900 patients with cardiac resynchronization therapy defibrillators enabled for collection of heart sounds, respiration, thoracic impedance, heart rate, and activity data. The HeartLogic algorithm automatically calculated a daily HF index and identified periods IN or OUT of an active alert state relative to a configurable threshold. Patients experienced 192 independently adjudicated HF events (average rate, 0.20/patient-year [pt-yr]) during 1 year of follow-up. HF event rates while IN alert was 10-fold higher than OUT of alert (0.80 versus 0.08 events/pt-yr). Combined with NT-proBNP (N-terminal pro-B-type natriuretic peptide) at enrollment (relative to 1000 pg/mL threshold, event rate was 0.42 [HIGH] versus 0.07 [LOW] events/pt-yr), substratification found the lowest risk group (LOW NT- proBNP and OUT of alert) experienced 0.02 events/pt-yr, whereas the highest risk group (HIGH NT-proBNP and IN alert) was associated with a 50-fold increased risk of an HF event (1.00 events/pt-yr) relative to the lowest risk group.

CONCLUSIONS: Dynamic assessment using implantable device sensors within HeartLogic by itself or in conjunction with NT-proBNP measurements can identify time-intervals when patients are at significantly increased risk of worsening HF and potentially better triage resources to this vulnerable patient population.

Capucci A, Santini L, Favale S, Pecora D, Petracci B, Calò L, Molon G, Cipolletta L, Bianchi V, Schirripa V, Santobuono VE, La Greca C, Campari M, Valsecchi S, Ammirati F, D'Onofrio A. **Preliminary Experience with the Multisensor HeartLogic Algorithm for Heart Failure Monitoring: A Retrospective Case Series Report.** ***ESC Heart Fail.*** 2019; Jan 11. doi: 10.1002/ehf2.12394. https://onlinelibrary.wiley.com/doi/10.1002/ehf2.12394

AIMS: In the Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients study, a novel algorithm for heart failure (HF) monitoring was implemented. The HeartLogic (Boston Scientific) index combines data from multiple implantable cardioverter defibrillator (ICD)-based sensors and has proved to be a sensitive and timely predictor of impending HF decompensation. The remote monitoring of HF patients by means of HeartLogic has never been described in clinical practice. We report post-implantation data collected from sensors, the combined index, and their association with clinical events during follow-up in a group of patients who received a HeartLogic-enabled device in clinical practice.

METHODS AND RESULTS: Patients with ICD and cardiac resynchronization therapy ICD were remotely monitored. In December 2017, the HeartLogic feature was activated on the remote monitoring platform, and multiple ICD-based sensor data collected since device implantation were made available: HeartLogic index, heart rate, heart sounds, thoracic impedance, respiration, and activity. Their association with clinical events was retrospectively analysed. Data from 58 patients were analysed. During a mean follow-up of 5 ± 3 months, the HeartLogic index crossed the threshold value (set by default to 16) 24 times (over 24 person-years, 0.99 alerts/patient-year) in 16 patients. HeartLogic alerts preceded five HF hospitalizations and five unplanned in-office visits for HF. Symptoms or signs of HF were also reported at the time of five scheduled visits. The median early warning time and the time spent in alert were longer in the case of hospitalizations than in the case of minor events of clinical deterioration of HF. HeartLogic contributing sensors detected changes in heart sound amplitude (increased third sound and decreased first sound) in all cases of alerts. Patients with HeartLogic alerts during the observation period had higher New York Heart Association class (P = 0.025) and lower ejection fraction (P = 0.016) at the time of activation.

CONCLUSIONS: Our retrospective analysis indicates that the HeartLogic algorithm might be useful to detect gradual worsening of HF and to stratify risk of HF decompensation.

D'Onofrio, Capucci A, Martino A, Danisi N, Pecora D, Favale S, Molon G, De Martino S, Bianchi V, Cipolletta L, Mahfouz K, La Greca C, Memeo R, Campari M, Calo L. **Preliminary Experience of Remote Management of Heart Failure Patients with the Multisensor HeartLogic Alert.** ***EP Europace***, Volume 21, Issue Supplement_2, March 2019, Pages ii883–ii889. https://academic.oup.com/europace/article/21/Supplement2/ii883/5484921

BACKGROUND: The HeartLogic index combines data from multiple implantable cardioverter-defibrillator (ICD)-based sensors and has proved to be a sensitive and timely predictor of impending heart failure (HF) decompensation.

PURPOSE: To describe a preliminary experience of remote HF management of patients who received a HeartLogic-enabled ICD or cardiac resynchronization therapy ICD (CRT-D) in clinical practice.

METHODS: The HeartLogic feature was activated in 101 patients (74 male, 71 ± 10 years, left ventricular ejection fraction (LVEF) 30 ± 7%). At baseline visit, patients underwent clinical assessment and the congestion grade was correlated with the HeartLogic index value measured on the same day of the visit. Remote data reviews and patient phone contacts were performed monthly and at the time of HeartLogic alerts (when the index crossed the nominal threshold value of 16), to assess the patient decompensation status. In-office visits were performed when deemed necessary.

RESULTS: The proportion of patients with no signs of congestion at baseline visit was higher in the group with HeartLogic index <2 (median value) (82% vs. 58% with index >2, p = 0.025). During a mean follow-up of 6 ± 3 months, 44 HeartLogic alerts were reported (0.95 alerts/pt-year) in 30 patients. 26 (59%) HeartLogic alerts were judged clinically meaningful (i.e. associated with worsening of HF or when influenced the clinician's decision to make changes to the subject's management). No clinically meaningful alert conditions nor clinical events were detected at the 567 scheduled monthly remote data reviews. The mean delay from alert to the next monthly remote data review was 18 ± 12 days.

CONCLUSION: HeartLogic index value seemed associated with the HF congestion grade, as assessed at standard in-office visit. The HeartLogic index provided clinically meaningful information for the remote management of HF patients. An alert-based remote follow-up approach allowed to detect more efficiently and earlier relevant conditions than a scheduled monthly follow-up strategy.

Capucci A, Ammirati F, Favale S, Pecora D, Petracci B, Calo L, Molon G, Cipolletta L, Bianchi V, Schirripa V, Santobuono VE, La Greca C, Guardiani S, D'Onofrio A. **Preliminary Experience with the Multisensor HeartLogic Algorithm for Heart Failure Monitoring: A case series report.** ***EP Europace***, Volume 21, Issue Supplement_2, March 2019, Pages ii251–ii531. https://academic.oup.com/europace/article/21/Supplement_2/ii251/5484960#134521499

BACKGROUND: In the MultiSENSE study, a novel algorithm for heart failure (HF) monitoring was implemented. The HeartLogic index combines data from multiple implantable cardioverter-defibrillator (ICD)-based sensors and has proved to be a sensitive and timely predictor of impending HF decompensation. The remote monitoring of HF patients by means of HeartLogic has never been described in clinical practice.

PURPOSE: We report post-implantation data collected from sensors, the combined index, and their association with clinical events during follow-up in a group of patients who received a HeartLogic-enabled device in clinical practice.

METHODS: Patients with ICD and cardiac resynchronization therapy ICD were remotely monitored. In December 2017, the HeartLogic feature was activated on the remote monitoring platform, and multiple ICD-based sensor data collected since device implantation were made available: HeartLogic index, heart rate, heart sounds, thoracic impedance, respiration, and activity. Their association with clinical events was retrospectively analyzed.

RESULTS: Data from 58 patients were analyzed. During a mean follow-up of 5 ± 3 months, the HeartLogic index crossed the threshold value (set by default to 16) 24 times (over 24 person-years, 0.99 alerts/pt-year) in 16 patients. HeartLogic alerts preceded 5 HF hospitalizations and 5 unplanned in-office visits for HF. Symptoms or signs of HF were also reported at the time of 5 scheduled visits. The median early-warning time and the time spent in alert were longer in the case of hospitalizations than of minor events of clinical deterioration of HF. HeartLogic contributing sensors detected changes in heart sound amplitude (increased third sound and decreased first sound) in all cases of alerts. Patients with HeartLogic alerts during the observation period had higher NYHA class (p = 0.025) and lower ejection fraction (p = 0.016) at the time of activation.

CONCLUSIONS: Our analysis confirmed the ability of the HeartLogic algorithm to detect gradual worsening of HF and to stratify risk of HF decompensation.

E De Ruvo, A Capucci, F Ammirati, D Pecora, S Favale, G Molon, B Petracci, V Bianchi, L Cipolletta, L Calo, V Schirripa, C La Greca, V E Santobuono, S Valsecchi, A D'onofrio. **Preliminary experience of remote management of heart failure patients with a multisensor ICD alert.** ***European Journal of Heart Failure*** 2019, 21 (Suppl. S1), p 370. https://onlinelibrary.wiley.com/doi/10.1002/ejhf.1488

BACKGROUND: The HeartLogic index combines data from multiple implantable cardioverter-defibrillator (ICD)-based sensors and has proved to be a sensitive and timely predictor of impending heart failure (HF) decompensation.

PURPOSE: To describe a preliminary experience of remote HF management of patients who received a HeartLogic-enabled ICD or cardiac resynchronization therapy ICD (CRT-D) in clinical practice.

METHODS: The HeartLogic feature was activated in 101 patients (74 male, 71±10 years, ejection fraction 30±7%). From implantation to activation (blinded phase), the HeartLogic index trend was not available, thus no clinical actions were taken in response to it. After activation (active phase), remote data reviews and patient phone contacts were performed monthly and at the time of HeartLogic alerts (when the index crossed the nominal alert threshold value of 16), to assess the patient decompensation status. In-office visits were performed when deemed necessary.

RESULTS: During the blinded phase, the HeartLogic index crossed the threshold value 24 times (over 24 person-years, 0.99 alerts/pt-year) in 16 patients. HeartLogic alerts preceded all hospitalizations and unplanned in-office visits for HF (sensitivity: 100%, median early warning: 38 days for hospitalizations, 12 days for HF visits). No clinical events were detected during or within 30 days of recovery of 10 HeartLogic alerts (unexplained alert rate: 0.41 per patient-year). Thus, the positive predictive value was 58% (14/24). During the active phase, 44 HeartLogic alerts were reported (over 46 person-years, 0.95 alerts/pt-year) in 30 patients. 26 (59%) HeartLogic alerts were judged clinically meaningful (i.e. associated with worsening of HF and/or influenced the clinician's decision to make changes to the subject's management).

CONCLUSION: In this first description of the use of HeartLogic in clinical practice, the algorithm demonstrated its ability to detect gradual worsening of HF. The results of the blinded phase of our experience favorably compare with those reported in the validation study. In the active phase, the HeartLogic index provided clinically meaningful information for the remote management of HF patients.

Gardner RS, Nair DG, Eldadah Z, Stancak B, Thakur P, Wariar R, Zhang Y, An Q, Averina V, Sweeney R, Boehmer JP. **Heart failure diagnostic sensor measurements during clinically stable epochs in ambulatory heart failure patients [abstract].** ***Eur J Heart Fail.*** 2017,19 (Suppl S1), p 277. http://dx.doi.org/10.1002/ejhf.833

BACKGROUND: A multi-sensor algorithm based on implanted device based sensor data has been shown to detect impending worsening Heart Failure (HF) events. The objective of this analysis was to characterize the "normal" range of these sensor values when patients were estimated to be clinically stable, and compare it to pre-HF event periods.

METHODS: The MultiSENSE trial enrolled 900 patients implanted with a COGNIS CRT-D and followed them up to 1 year. Device software was modified to permit collection of chronic diagnostic sensor data including heart sounds, respiration, thoracic impedance, heart rate and activity. HF status was assessed by in-office physical assessment at routine follow-up visits scheduled either every three months if the patients had remote monitoring, or 6-8 weeks if not. Patients were deemed to be clinically stable between successive follow-up visits if their NYHA classification was unchanged, weight change was within 5 lbs (2.27kg) and no adverse events were reported between the visits. Sensor data from clinically stable epochs were compared with 7 day average sensor data prior to independently adjudicated worsening HF events defined as HF admissions or unscheduled visits with intravenous HF treatment using 2 sampled t-test.

RESULTS: Of 900 patients, 676 patients yielded 1667 clinically stable epochs of duration 60± 22 days, while 88 patients had 146 HF events. Table summarizes sensor data during clinically stable epochs and prior to worsening HF as mean (μ)± standard deviation (ó).

CONCLUSIONS: All individual HF diagnostic sensors used in the multi-sensor algorithm are different when patients are clinically stable versus when they are experiencing worsening HF events. Additional studies are needed to investigate if interventions in response to early recognition of these changes will reduce HF events.

Boehmer JP, Sriratanasathavorn C, Fisher J, Bransford P, Chan R, Sweeney RJ, Ahmed R, Zhang Y, Averina V, An Q, Thakur P. **Heart Failure Diagnostics Sensor Measurements Change Prior to Heart Failure Decompensation Events [abstract].** ***J Card Fail.*** 2017; 23 (8): S65. https://www.onlinejcf.com/article/S1071-9164(17)30401-3/abstract

BACKGROUND: The Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients study (MultiSENSE) followed 900 heart failure (HF) patients with a modified CRT defibrillator for up to 1 year. HF decompensation events (HFE) were collected and adjudicated by an independent panel of clinicians. Data from multiple HF diagnostic sensors were continuously measured and saved by the modified device including: heart sounds, respiration rate, relative tidal volume, thoracic impedance, heart rate and activity.

OBJECTIVE: We examined the HF diagnostic sensor data during the periods prior to HFEs. To the extent these sensor data change prior to a HFE, they could be used to provide a warning that an HFE may soon occur.

METHODS: For all study patients with HFEs, and for each HF diagnostic sensor, we calculated a long-term (LT, -60 to -20 day) and a short-term (ST, -3 to -1 day) pre-event average. A matched-pair analysis for ST and LT values was performed for each HF diagnostic sensor using all HFEs with both LT and ST values. To prevent altered sensor data following a first HFE from influencing the LT value of the next HFE (if one existed), sensor data for 60 days after each HFE were excluded from analyses. Night heart rate was between midnight and 6:00 AM. A rapid shallow breathing index (RSBI) was computed as respiration rate/relative tidal volume. As a control, randomly selected patient-dates from patients that did not have any HFEs were used for the same matched-pair analyses.

RESULTS: Of 900 patients, 147 HFEs were experienced in 105 patients. Table 1 shows matched ST and LT values for HFEs, the number of matched pairs (N), the mean ± SE of the ST-LT differences and Wilcoxon p versus 0. The ST-LT differences from all HF sensors were highly significantly different in periods before HFEs. As expected due to the random selection of HFE times, none of the ST-LT differences from any HF sensors were significantly different from 0 in the control analyses.

CONCLUSIONS: The HF diagnostic sensor data available to automated HFE detection algorithms changed significantly in the periods prior to actual HFEs but none of the sensor data changed in the periods before randomly selected times.

J Boehmer, G Mark, G Wen, P Thakur, GZ Duray. **Impact of ethnic groups on device based diagnostic sensor measurements in ambulatory heart failure patients.** ***Eur J Heart Fail*** 2018, 20 (Suppl. S1), p 252. https://www.onlinelibrary.wiley.com/doi/10.1002/ejhf.1197

BACKGROUND: An implantable device based multi-sensor algorithm was recently shown to detect impending worsening Heart Failure (HF) events with high sensitivity. The objective of this analysis was to characterize the relationship between sensor measurements and ethnicity of HF patients.

METHODS: In the MultiSENSE trial, 792 patients implanted with a COGNIS CRT-D were enrolled in the United States, and followed up to 1 year. Device software was modified to permit collection of chronic diagnostic sensor data including heart sounds, respiration, thoracic impedance, heart rate and activity. Sensor data were combined into a multi-sensor alert algorithm (HeartLogic). Patients (N=791) were classified into four ethnic groups: Caucasian (N=602), Black or African American (N=127), Hispanic or Latino (N=50) and Others (N=12). Average sensor data from patients in different ethnic groups were compared using a one-way ANOVA.

RESULTS: At enrollment, Black/African group had significantly lower LVEF (25.89 ± 10.63) as compared to Caucasian (30.65 ± 6.62) or Hispanic group (29.85 ± 7.36), whereas Hispanic group had a greater prevalence of NYHA Class III/IV (53%) as compared to Caucasian (26%) or Black/African group (32%). On average, patients in the Black/African group had higher Day-time Rapid Shallow Breathing Index (RSBI) (Table), whereas, Caucasian group had lower activity. No statistical differences were detected in the other five sensor trends, and the resulting HeartLogic Index. With Bonferroni correction for multiple comparisons, none of the sensor trends were statistically different across the ethnic groups.

CONCLUSION: There are differences in physiologic parameters associated with heart failure between groups based on ethnicity including differences in day-time RSBI and activity despite no difference in the overall predictive score of the HeartLogic Index.

J Boehmer, G Mark, G Wen, P Thakur, GZ Duray. **Impact of body mass index on device measured diagnostic sensor measurements in ambulatory heart failure patients.** ***Eur J Heart Fail*** 2018, 20 (Suppl. S1), p 68. https://www.onlinelibrary.wiley.com/doi/10.1002/ejhf.1197

BACKGROUND: Prior studies have reported a link between obesity and the development and progression of heart failure (HF). A device based multi-sensor algorithm was recently shown to detect impending worsening HF events with high sensitivity. The objective of this analysis was to characterize the relationship between sensor measurements and body mass index (BMI) of HF patients.

METHODS: The MultiSENSE trial followed 900 patients implanted with a COGNIS CRT-D for 1 year. Device software was modified to permit collection of sensor data: heart sounds (S1 and S3), respiration, thoracic impedance (TI), heart rate (HR) and activity. Sensor data were combined into a multi-sensor alert algorithm (HeartLogic). Patients (N=892) were classified into four categories of BMI (kg/m2): Underweight/Normal (BMI<25, N=193), Overweight (25=BMI<30, N=285), Obesity I (30=BMI<35, N=229) and Obesity II/III (BMI>35, N=185). Correlations between sensor data and patients' BMI were computed, and average sensor data across BMI categories were compared using a one-way ANOVA.

RESULTS: Poor correlations between sensor measurements and BMI were observed ($|r|<0.4$) for all the sensor trends. On average, obese patients had higher TI, higher day-time Rapid Shallow Breathing Index (RSBI), and higher night HR than the other patients. No statistical differences across the four BMI categories were detected in the other four sensor trends (S1, S3, Respiratory Rate, Activity), and the resulting HeartLogic index. With Bonferroni correction for multiple comparisons, none of the sensor trends were statistically different across the BMI categories.

CONCLUSION: There are significant differences across patients in different BMI categories in TI, day-time RSBI and night HR, although the overall predictive HeartLogic Index did not vary across these groups.

Sauer A., Lam C., Ahmed R., Zhang Y., Boehmer J. **Comparison of HeartLogic Heart Failure Diagnostic Sensor Measurements and Alerts between Patients with CRT-D and ICD Devices**. ***Journal of Cardiac Failure.*** August 2019 Volume 25, Issue 8, Supplement, Page S173. https://www.onlinejcf.com/article/S1071-9164(19)31300-4/fulltext

BACKGROUND: HeartLogic®, a device-based heart failure (HF) composite index and alert algorithm, aggregates physiologic trends associated with multiple aspects of HF status (e.g. heart sounds, heart rate, thoracic impedance, respiration rate, tidal volume, and activity). The MultiSENSE study showed that HeartLogic alerts predict HF events with high sensitivity. However, it is unknown if alerts differ by type of device (CRT-D vs ICD).

OBJECTIVE: To compare HF sensor measurements and alerts between patients with CRT-D and ICD devices with HeartLogic capability.

METHODS: The ALTITUDE database collects de-identified data recorded by the implanted devices from the LATITUDE remote monitoring system. US patients with HeartLogic compatible devices with a minimum of 90 days of daily sensor data were included. HeartLogic alerts for each patient were identified when the daily HeartLogic index value crossed the nominal alert threshold of 16. The observed alert rate was calculated as the total number of alerts divided by the total patient follow-up years. 95% confidence intervals were calculated using a generalized linear model with a log link and a negative binomial distribution. Sensor measurement comparisons were performed using Student's t-test and an alpha level of 0.0001 due to the large sample size.

RESULTS: Out of 11576 US patients in ALTITUDE, 7633 (4583 CRT-D and 3050 ICD patients) contained sensor data over 90 days with an average follow-up period of 221±94.39 days (median [25th, 75th percentile] = 207 [142,286] days). Despite differences in some individual sensors (Heart Sound S1, Thoracic Impedance, Time Active) (Table 1), HeartLogic alert rates (Fig 1) were not significantly different between CRT-D and ICD (CRT-D: 1.71 (95% CI 1.67, 1.78), ICD: 1.64 (1.58, 1.73), p = 0.11). Furthermore, the real-world HeartLogic alert rates of both CRT-D and ICD patients were similar to the MultiSENSE study alert rate of 1.65 (1.50, 1.88) (CRT-D: p = 0.44 and ICD: p = 0.92).

CONCLUSION: Real-world HeartLogic alert rates did not differ between CRT-D and ICD recipients, and were similar to the MultiSENSE study, despite some differences in individual sensor measurements. Further investigation is needed to understand whether these differences relate to severity of HF or impact the predictive utility of HeartLogic for HF events.

Boehmer JP, Nair DG, Wen G, Thakur P, An Q, **Gardner RS. HeartLogic performs as well as NT-proBNP to rule out acute heart failure at point of care. *Journal of Cardiac Failure.*** August 2019 Volume 25, Issue 8, Supplement, Pages S17–S18. https://www.onlinejcf.com/article/S1071-9164(19)30827-9/fulltext

BACKGROUND: The ESC Guidelines recommend the measurement of N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration in all patients who present to emergency rooms with acute dyspnoea and suspected acute decompensated heart failure (HF), with a decision cut-off (NT-proBNP<300pg/mL) for the exclusion of acute decompensated HF (ADHF). HeartLogic is a multisensor algorithm that has been developed and validated to proactively provide alerts for worsening heart failure.

PURPOSE: The purpose of this analysis was to compare the diagnostic accuracy of NT-proBNP and HeartLogic to rule out ADHF in acute settings.

METHODS: The MultiSENSE study followed 900 HF patients with implanted CRT-Ds for up to 1 year. All hospitalizations were adjudicated by an independent panel of clinicians, and classified as HF or non-HF based on the presenting cause. Optional NT-proBNP tests were conducted when patients were hospitalized. The composite HeartLogic index of the day before each of the hospitalization dates were extracted to differentiate HF and non-HF hospitalizations. By varying the HeartLogic index decision cutoff, a ROC curve was generated to assess the prediction accuracy of HeartLogic and compared to the counterpart performance of NT-proBNP using Hanley and McNeil's method.

RESULTS: Of the total 603 hospitalizations, 76 hospitalizations (52 HF, 24 non-HF) had both valid NT-proBNP measures within 48 hours of admission (71 within 24 hours), and valid HeartLogic for the day before the hospitalization date. Figure 1 illustrates that the HeartLogic -based ROC was similar to the ROC of NT-proBNP (AUC of 0.809 and 0.803, respectively, p=0.932). An exclusion criterion of HeartLogic index <1 achieved the same performance as an NT-proBNP<300pg/ml (sensitivity 0.962, NPV 0.778), and the agreement between the two criteria was 84.2%. Limiting the evaluation to 52 hospitalizations with acute dyspnea (42 HF, 10 non-HF), the performance of HeartLogic and NT-proBNP were similar (p=0.906). Expanding the evaluation of HeartLogic across all 467 hospitalizations with HeartLogic data (89 HF, 378 non-HF), performance was still similar (sensitivity 0.934, NPV 0.876 for the criterion of HeartLogic index <1; AUC of 0.734, p=0.166).

CONCLUSION: HeartLogic showed similar accuracy for differentiating HF and non-HF hospitalizations in the MultiSENSE dataset as NT-proBNP. HeartLogic may be used in the acute setting to exclude acute decompensated heart failure.

Calò, L., Capucci, A., Santini, L. *et al.* **ICD-measured heart sounds and their correlation with echocardiographic indexes of systolic and diastolic function** *J Interv Card Electrophysiol* (2020). https://doi.org/10.1007/s10840-019-00668-y

BACKGROUND: Novel implantable defibrillators (ICDs) allow first (S1) and third (S3) heart sounds to be measured by means of an embedded accelerometer. ICD-measured S1 and S3 have been shown to significantly correlate with hemodynamic changes in acute animal models. The HeartLogic algorithm (Boston Scientific) measures and combines multiple parameters, including S3 and S1, into a single index to predict impending heart failure decompensation. We evaluated the echocardiographic correlates of ICD-measured S1 and S3 in patients with ICD and cardiac resynchronization therapy ICD.

METHODS: The HeartLogic feature was activated in 104 patients. During in-office visits, patients underwent echocardiographic evaluation, and parameters of systolic and diastolic function were correlated with S3 and S1 amplitude measured on the same day as the visit.

RESULTS: S3 amplitude inversely correlated with deceleration time of the E-wave (r = –0.32; 95%CI -0.46 – -0.17; P < 0.001), and S1 amplitude significantly correlated with left ventricular ejection fraction (r = 0.17; 95% CI 0.03–0.30; P = 0.021). S3 > 0.9mG detected a restrictive filling pattern with 85% (95%CI 72%–93%) sensitivity and 82%(95%CI 75%–88%) specificity, while S1 < 1.5 mG detected ejection fraction < 35% with 28% (95% CI 19%–40%) sensitivity and 88% (95% CI 80%–93%) specificity.

CONCLUSIONS: ICD-measured heart sound parameters are significantly correlated with echocardiographic indexes of systolic and diastolic function. This confirms their utility for remote patient monitoring when used as single sensors and their potential relevance when considered in combination with other physiological ICD sensors that evaluate various aspects of heart failure physiology.

Cao M, Gardner RS, Hariharan R, Nair DG, Schulze C, An Q, Thakur PH, Kwan B, Zhang Y, Boehmer JP. **Ambulatory monitoring of heart sounds via an implanted device is superior to auscultation for prediction of heart failure events.** *J Card Fail.* 2019;00:1–9. https://www.onlinejcf.com/article/S1071-9164(19)30492-0/fulltext

BACKGROUND: We compared the relationship between the third heart sound (S3) measured by an implantable cardiac device (devS3) and auscultation (ausS3) and evaluated their prognostic powers for predicting heart failure events (HFEs).

METHODS AND RESULTS: In the MultiSENSE study, devS3 was measured daily with continuous values, whereas ausS3 was assessed at study visits with discrete grades. They were compared among patients with and without HFEs at baseline and against each other directly. Cox proportional hazard models were developed between follow-up visits and over the whole study. Simulations were performed on devS3 to match the limitations of auscultation. We studied 900 patients, of whom 106 patients experienced 192 HFEs. Two S3 sensing modalities correlated with each other, but at baseline, only devS3 differentiated patients with or without HFEs (P < 0.0001). The prognostic power of devS3 was superior to that of ausS3 both between follow-up visits (HR = 5.7, P < 0.0001, and 1.7, P = 0.047, respectively) and over the whole study (HR = 2.9, P < 0.0001, and 1.4, P = 0.216, respectively). Simulation results suggested this superiority may be attributed to continuous monitoring and to subaudible measuring capability.

CONCLUSIONS: S3 measured by implantable cardiac devices has stronger prognostic power to predict episodes of future HFEs than that of auscultation

Siejko KZ, Thakur PH, Maile K, Patangay A, Olivari MT. **Feasibility of heart sounds measurements from an accelerometer within an ICD pulse generator.** ***Pacing Clin Electrophysiol.*** 2013; 36 (3): 334-46. https://onlinelibrary.wiley.com/doi/10.1111/pace.12059

OBJECTIVE: The feasibility of detecting heart sounds (HS) from an accelerometer sensor enclosed within an implantable cardioverter defibrillator (ICD) pulse generator (PG) was explored in a noninvasive pilot study on heart failure (HF) patients with audible third HS (S3).

METHODS: Accelerometer circuitry enhanced for HS was incorporated into non-functional ICDs. A study was conducted on 30 HF patients and 10 normal subjects without history of cardiac disease. The devices were taped to the skin surface over both left and right pectoral regions to simulate subcutaneous implants. A light-weight reference accelerometer was taped over the cardiac apex. Waveforms were recorded simultaneously with a surface electrocardiogram for 2 minutes. Algorithms were developed to perform off-line automatic detection of HS and HS time intervals (HSTIs).

RESULTS: S1, S2, and S3 vibrations were detected in all accelerometer locations for all 40 subjects, including 16 subjects without an audible S3. A substantial proportion of S3 energy was infrasonic (<20 Hz). Extending the signal bandwidth accordingly increased HS amplitudes and the ability of S3 to separate HF patients from the normal subgroup. HSTIs also separated the subgroups and were less susceptible to patient-dependent acoustic propagation properties than amplitude measures.

CONCLUSION: HS, including S3 amplitude and HSTIs, may be measured using PG-embedded circuitry at implant sites without special purpose leads. Further study is warranted to determine if relative changes in heart sounds measurements can be effective in applications such as remote ambulatory monitoring of HF progression and the detection of the onset of HF decompensation.

Cao M, Gardner R, Hariharan R, Nair D, Schulze C, An Q, Thakur P, Boehmer J. **Heart Sound Amplitudes Measured by Accelerometer Reflect Auscultated S3 Heart Sound Volume Grades.** ***Circulation.*** 2017;136:A16050. http://circ.ahajournals.org/content/136/Suppl_1/A16050

INTRODUCTION: The third heart sound (S3) is regarded as one of the earliest signs of heart failure (HF) and is typically assessed via auscultation clinically. The embedded accelerometer sensor in implant ble devices can pick up the mechanical vibration caused by S3. We compared the device-measured S3 amplitude (devS3) to auscultated S3 volume grades (audS3).

METHOD: In the MultiSENSE study, ambulatory HF patients implanted with a CRT-D were enrolled and followed up for 1 year. DevS3 amplitude was trended daily. Clinicians were asked to auscultate for S3 intensity on a graded scale (None/Low/Moderate/Loud) at baseline and each regular follow-up. Clinicians were blinded to the devS3 data at the time of assessment. We compared devS3 on the day of assessment in patients with different level of audS3 intensity. ANOVA test was used to compare the mean S3 amplitudes among groups and unpaired t-tests for between-group comparison.

RESULTS: A total of 5211 auscultation reports were obtained from the 900 patients in the study. AudS3 intensity was None in 4709, Low in 391, Moderate in 108, and Loud in 3 reports (moderate and loud were combined for this analysis). THe figure represents the devS3 amplitude (mean ± standard error) on the day of the follow-up as a function of the audS3 grades reported The mean devS3 values for None, Low, and Moderate/Loud audS3 was 0.96 ± 0.01 mG, 1.02 ± 0.02 mG, and 1.27± 0.06 mG respectively. Both ANOVA test and unpaired tests between groups were significant and remained significant after adjusting for repeated measures.

CONCLUSION: This demonstrates that device-measured S3 amplitude reflects auscultated S3 heart sound volume grades. Since device-measured S3 is an objective measure on a continuous scale as opposed to auscultation which is subjectively categorized, it could avoid inter-observer auscultation variability and enables monitoring of this clinical variables in ambulatory HF patients.

Klodas E, Thakur P, An Q, Bank A. **Third Heart Sound Measured by Implanted Accelerometer in Heart Failure Patients is Coincident with the Deceleration Phase of Early Diastolic Filling [abstract].** ***J Card Fail.*** 2017;23(8):S68-S9. http://www.onlinejcf.com/article/S1071-9164(17)30412-8/pdf

INTRODUCTION: The third heart sound (S3), an early and specific sign of heart failure and elevated filling pressure, is caused by rapid deceleration of the blood against a stiff ventricle during early diastolic filling. Prior studies have shown phonocardiogram based S3 to be coincident with the deceleration phase of E-wave. More recently, ambulatory monitoring of heart sounds (HS) has been enabled using accelerometers (XL) embedded in implantable medical devices. Whether S3 measured using this novel modality is coincident with the deceleration phase of early diastolic filling had not been previously established.

METHODS: The PRE-SENSE study enrolled patients with COGNIS CRT-D modified to enable collection of HS data using device based XL. HS waveforms were collected within 20 minutes of an echocardiogram. Waveforms were excluded if device heart rate (HR) differed from the echo reported HR by more than 5 beats per minute (bpm). An independent core laboratory measured parameters from the echo images, including E-wave timing within the cardiac cycle. An algorithm processed the individual HS waveforms to extract S3 amplitude by automatically deducing a window for S3 measurement based on a proprietary method. Timing of the S3 measurement window employed by the automatic S3 amplitude extraction algorithm was validated by comparing with E-wave timings within the cardiac cycle on the echocardiogram.

RESULTS: Of the 70 enrolled patients, 59 patients had HS data collected within 20 minutes of the echo at HR within 5 bpm. The start of S3 measurement window within the cardiac cycle occurred 624 ± 5 msec after R-event and was comparable to Q-E interval of 625 ± 9 msec ($P = .89$ paired t-test), indicating that the start of S3 window was not different from the peak of E-wave, assuming a minimal Q-R interval due to paced beats. Additionally, the end of the measurement window occurred 749 ± 5 msec after R-event, which was significantly after peak of E-wave ($P < .0001$ paired t-test), but prior to the end of E-wave obtained as the sum of Q-E interval and E-wave deceleration time (QE + EDT interval: 890 ± 16 msec; $P < .0001$ paired t-test). Thus S3 measurement window occurred substantially during the deceleration phase of E-wave.

CONCLUSION: This analysis confirms that device-measured S3 occurs during early diastolic filling, which is consistent with its known physiologic genesis. Further studies are warranted to investigate if such serial S3 measurements in ambulatory patients may enable chronic monitoring of diastolic filling patterns in heart failure patients.

Gardner R, Bank AJ, Klodas E, An Q, Thakur P, Boehmer J. **Ambulatory S3 Measured by an Implanted Device Changes Consistently with Echocardiography in Stable and Acute Decompensated Heart Failure [abstract].** ***J Card Fail.*** 2017;23(8):S64. https://www.onlinejcf.com/article/S1071-9164(17)30399-8/fulltext

INTRODUCTION: It is well known that the third heart sound (S3) has independent prognostic value in patients with heart failure (HF). Cardiac implantable devices such as pacemakers/defibrillators can measure and trend S3 cardiac vibrations in ambulatory patients. We compared ambulatory S3 with left ventricular (LV) function determined using echocardiography in both stable and acute decompensated HF patients.

METHODS: Data from two studies, namely MultiSENSE and PRE-SENSE, were used in the analysis. Both studies enrolled patients with cardiac resynchronization therapy defibrillators (CRT-Ds). Device software was modified to enable continuous collection of heart sound (HS) data, which was processed offline to extract S3. The PRE-SENSE study collected echocardiography evaluations in stable HF patients (StHF) and the MultiSENSE study optionally collected similar data in acute decompensated HF patients (ADHF). Echo parameters were assessed by an independent core laboratory blinded to device HS data. Device S3 measurements, collected in the vicinity of the times of echo, were extracted, compared between StHF and ADHF patients and correlated to mitral flow parameters indicative of restrictive filling such as E-wave deceleration time (EDT), E deceleration rate (EDR) and E/E'. Comparisons were made using an unpaired t-test or using linear Pearson correlation.

RESULTS: The StHF group contained 65 echo datasets from 65 patients (70 enrolled), and the ADHF group contained 37 from 26 patients (900 enrolled). LVEF at enrollment was higher in the StHF patients (39%±14%) compared to the ADHF patients (30%±11%, $P < .001$). Echo parameters, including LVEDV ($P < .01$), LVESV ($P < .01$), E/A ($P < .01$), were significantly worse in ADHF compared to StHF. S3 showed a consistent pattern with echo, i.e. lower in the StHF group and higher in the ADHF group. S3 was also moderately correlated to EDT ($r = -0.52$, $P < .001$, Fig. 1), EDR ($r = 0.45$, $P < .001$), and E/E' ($r = 0.39$, $P < .001$).

CONCLUSIONS: S3 showed a consistent relationship with LV function measured using echo between stable and acute decompensated HF patients. Automatic ambulatory longitudinal measurements of S3 may enable chronic monitoring of LV dysfunction in HF patients.

Cao M, Schulze C, Gardner R, An Q, Thakur P, Thompson J, Boehmer J. **Device-measured Third Heart Sound Predicts Heart Failure Events Better than Auscultated Third Heart Sound [abstract].** ***EP Europace.*** 2017;19(Suppl 3):iii332-iii3. http://dx.doi.org/10.1093/ehjci/eux158.203

INTRODUCTION: The third heart sound (S3) has traditionally been assessed by physicians via auscultation and known to carry prognostic information in patients with Heart Failure (HF). New technology has been developed to measure S3 (devS3) using accelerometers embedded in implantable devices. However, it is still unknown how well device measured S3 predicts the risk of future HF events (HFEs).

METHODS: The MultiSENSE study collected multiple sensor data from a CRTD and HFEs information from ambulatory HF patients up to 1 year. HFE was defined as a HF admission or HF outpatient visit requiring decongestive therapies and was blindly adjudicated by an independent adjudication committee. DevS3 was a daily trend with continuous values while ausS3 had one discrete value (with or without S3) for each patient collected only at enrollment. DevS3 averaged over the first 30 days of study and ausS3 at enrollment were associated with future HFEs using a Cox proportional hazard model. Hazard ratios (HR) and p-values were reported for both modalities.

RESULTS: A total of 900 patients were enrolled. Valid devS3 and ausS3 data were collected in 898 and 900 pts, respectively, within which 129 patients experienced 223 HFEs after the first 30 days of study. Patients with no ausS3 (808 patients) were grouped together and compared against patients with ausS3. Similarly, patients with devS3 less than or equal to 1 mG (636 patients) were compared against the rest. Significant separation (HR = 2.9, p<0.0001) was observed between two devS3 groups while ausS3 showed no difference (HR 1.2, p =0.56).

CONCLUSIONS: In the MultiSENSE population, a device-measured S3 has better correlation with the risk of heart failure events over one year than auscultated S3. This superiority of device-measured S3 monitoring may be attributable to the subjective nature of auscultation, limitations of frequency range of human hearing, as well as limitations of a single snap-shot auscultation assessment as opposed to a continuous device based measure. Future studies are warranted to evaluate the clinical utility of continuous S3 monitoring in ambulatory HF patients.

J Boehmer, P Thakur, Q An, V Averina, G Mark. **Third heart sound during atrial fibrillation? Confirming the existence of cardiac vibrations during deceleration phase of early diastolic filling while in atrial fibrillation.** ***Eur J Heart Fail*** 2018, 20 (Suppl. S1), p 252. https://www.onlinelibrary.wiley.com/doi/10.1002/ejhf.1197

INTRODUCTION: The third heart sound (S3), caused by rapid deceleration of the blood against a stiff ventricle during early diastolic filling, is an early and specific sign of heart failure and elevated filling pressure. Studies have shown S3 to be coincident with deceleration phase of E-wave and associated with a steeper E-wave. Atrial fibrillation (AF) is a common comorbidity in HF, however questions have arisen regarding the ability to reliably detect S3 during AF as typically it is difficult to auscultate an S3 during AF. Here we present a case of simultaneous implanted device measured heart sound and echo data while the patient was in AF.

METHOD: MultiSENSE enrolled patients implanted with COGNIS CRT-D devices and followed for up to a year. At enrollment CRT-Ds were converted to enable collection of heart sound data using device based accelerometer. Heart sound data was periodically collected as ensemble averaged (EA) waveforms of multiple neighboring beats that closely matched in RR interval. An optional echo was conducted if the patient was hospitalized for worsening HF. An independent core laboratory measured parameters from the echo images, including E-wave timing within the cardiac cycle (Q-E interval and E-wave deceleration time or EDT). EA waveforms over multiple days around the day of echo that matched the average heart rate (HR) around the echo exam to within 10 beats per min were identified and compared against E-wave timing.

RESULTS: The patient, enrolled in November 2011 and reported to have a history of AF, was hospitalized for worsening HF on day 38 post enrollment. Device interrogation revealed ongoing AF burden of 24 hours since enrollment which transiently terminated on day 41 for several days before reverting to 24 hour AF burden. Patient underwent an echocardiogram starting at 9:22AM on day 39, which showed a Q-E interval of 562msec and EDT of 169msec. Figure shows one heart sound EA recorded at 10:49AM and clearly shows cardiac vibrations during the deceleration phase of the E-wave as deduced from Q-E interval and EDT
orizontal line). This observation is consistent across all EAs collected over 5 days around the day of the echo with matched HR.

CONCLUSION: Consistent with its known physiologic genesis, S3 measured using an implanted device occurred during the deceleration phase of early diastolic filling even when the patient was in AF. A device based objective measure may provide more consistent assessment of S3 than auscultation in the midst of an arrhythmic rumble of AF.

Klodas E, An Q, Thakur PH, Beck K, Vitoff PJ, Delaney C, Bank AJ. **S3 Amplitude Measured Using a CRT-D Is Correlated to Echocardiographic Filling Parameters in Heart Failure Patients [abstract].** ***J Card Fail.*** 2013; 19 (8): S67. http://www.onlinejcf.com/article/S1071-9164(13)00405-3/pdf

INTRODUCTION: The third heart sound (S3) is a specific sign of ventricular diastolic dysfunction caused by elevated left ventricular filling pressure and/or depressed ventricular compliance and is known to carry significant diagnostic and prognostic information. Traditionally, S3 has been measured using an apical phonocardiogram. Whether S3 measured using an accelerometer (XL) within an implanted cardiac resynchronization therapy - defibrillator (CRT-D) in heart failure (HF) patients carries similar clinical information is unknown. In this study, we evaluated the relationship between S3 and echocardiographic filling parameters to demonstrate the clinical utility of device based acute S3 measurements.

METHOD: PRE-SENSE study patients with a COGNISTM CRT-D implanted, were followed for 30 days. At enrollment the CRT-Ds were converted into IDE devices, via a software download enabling collection of heart sound (HS) data using the device based XL, and an echocardiographic exam was performed. An independent core laboratory measured parameters from the echo images. Off-line processing was employed to measure S3 from the HS data and differentiate patients into two groups: high S3 and low S3, where the threshold was chosen to separate upper quartile from the rest of patients. Key echocardiographic parameters including E-wave deceleration time (EDT), E deceleration rate (EDR), early diastolic velocity (E), and early diastolic mitral annulus velocity (E'), were compared between groups using Wilcoxon rank sum test as well as correlated with measured S3.

RESULTS: A total of 71 patients were enrolled at 11 centers resulting in 68 echo recordings, of which 62 had usable HS data during the echo exams. Table 1 compares key echo measures between the two groups.
In addition, S3 correlated with EDT (r=-0.50, p<0.001), EDR (r=0.48, p<0.001), E/A Ratio (r=0.40, p=0.002), E' (r=-0.21, p=0.107) and E/E' septal ratio (r=0.32, p=0.011).

CONCLUSION: S3 signals were reliably collected using implanted CRT-Ds. Group differentiation determined by acute measurement of S3 was confirmed by significant separations in a variety of echocardiographic parameters between the high S3 and low S3 groups. S3 also significantly correlated with EDT, EDR, E/A ratio and E/E' ratio which are often used to assess LV diastolic function. Future studies are warranted to evaluate the clinical value of device-collected S3 in chronic settings.

Thakur PH, An Q, Swanson L, Zhang Y, Gardner RS. **Haemodynamic Monitoring of Cardiac Status Using Heart Sounds from an Implanted Cardiac Device.** ***ESC Heart Fail.*** 2017;4(4):605-13. http://onlinelibrary.wiley.com/doi/10.1002/ehf2.12171/epdf

AIM: The aim of this study was to evaluate the haemodynamic correlates of heart sound (HS) parameters such as third HS (S3), first HS (S1), and HS-based systolic time intervals (HSTIs) from an implantable cardiac device.

METHODS AND RESULTS: Two unique animal models (10 swine with myocardial ischaemia and 11 canines with pulmonary oedema) were used to evaluate haemodynamic correlates of S1, S3, and HSTIs, namely, HS-based pre-ejection period (HSPEP), HS-based ejection time (HSET), and the ratio HSPEP/HSET during acute haemodynamic perturbations. The HS was measured using implanted cardiac resynchronization therapy defibrillator devices simultaneously with haemodynamic references such as left atrial (LA) pressure and left ventricular (LV) pressure. In the ischaemia model, S1 amplitude (r = 0.76 ± 0.038; P = 0.002), HSPEP (r = -0.56 ± 0.07; P = 0.002), and HSPEP/HSET (r = -0.42 ± 0.1; P = 0.002) were significantly correlated with LV dP/dt_{max} . In contrast, HSET was poorly correlated with LV dP/dt_{max} (r = 0.14 ± 0.14; P = 0.23). In the oedema model, a physiological delayed response was observed in S3 amplitude after acute haemodynamic perturbations. After adjusting for the delay, S3 amplitude significantly correlated with LA pressure in individual animals (r = 0.71 ± 0.07; max: 0.92; min: 0.17) as well as in aggregate (r = 0.62; P < 0.001). The S3 amplitude was able to detect elevated LA pressure, defined as >25 mmHg, with a sensitivity = 58% and specificity = 90%.

CONCLUSIONS: The HS parameters such as S1, S3, and HSTIs measured using implantable devices significantly correlated with haemodynamic changes in acute animal models, suggesting potential utility for remote heart failure patient monitoring.

Calo L., D'Onofrio A, Cipolletta L, Santini L, Favale S, Pecora D, Petracci B, Costa A, De Ruvo E, Tavoletta V, Mahfouz K, Guaricci AI, La Greca C, Valsecchi S, Capucci A. **ICD-measured heart sounds and their correlation with echocardiographic indexes of systolic and diastolic function.** ***EP Europace,*** Volume 21, Issue Supplement_2, March 2019, Pages ii251–ii531. https://academic.oup.com/europace/article/21/Supplement_2/ii251/5484960#134521493

BACKGROUND: Novel ICDs allow the estimation of first (S1) and third (S3) heart sounds (HS) using the embedded accelerometer. ICD-measured S1 and S3 were previously shown to significantly correlate with hemodynamic changes in acute animal models. The HeartLogic algorithm (Boston Scientific) measures and combines multiple parameters, including S3 and S3/S1, in a single index to predict impending HF decompensation.

PURPOSE: To evaluate the echocardiographic correlates of ICD-measured S3 and S3/S1 in patients with ICD and cardiac resynchronization therapy ICD.

METHODS: The HeartLogic feature was activated in 75 patients (57 male, 71 ± 10 years, left ventricular ejection fraction (LVEF) 36 ± 9%). At in-office visit, patients underwent echocardiographic evaluation and parameters of systolic and diastolic function were correlated with S3 amplitude and S1/S3 ratio measured on the same day of the visit.

RESULTS: S3 amplitude significantly correlated with the deceleration time of E wave (DT) (r=-0.38, p = 0.005). Patients with S3 >0.79mG (median value) showed significantly lower values of DT than patients with lower S3 (208 ± 77ms vs. 250 ± 75ms, p = 0.046). Interestingly, S3 was detected at auscultation only in 6 patients who did not show lower DT values at echocardiography (209 ± 83ms vs. 229 ± 77ms, p = 0.566). S3/S1 ratio significantly correlated with the LVEF (r=-0.38, p = 0.001). Patients with S3/S1 >0.35 (median value) showed significantly lower values of LVEF than patients with lower S3/S1 (32 ± 8% vs. 39 ± 8%, p = 0.002).

CONCLUSION: The ICD-measured HS parameters are significantly correlated with echocardiographic indexes of systolic and diastolic function. This confirms their utility for remote HF patient monitoring when considered as single sensors, and their potential relevance when considered in combination with other physiological ICD sensors that evaluate different aspects of HF physiology.

Marcus GM, Gerber IL, McKeown BH, Vessey JC, Jordan MV, Huddleston M, McCulloch CE, Foster E, Chatterjee K, Michaels AD. **Association between Phonocardiographic Third and Fourth Heart Sounds and Objective Measures of Left Ventricular Function.** ***JAMA.*** 2005;293(18):2238-44.
https://jamanetwork.com/journals/jama/fullarticle/200866

CONTEXT: The third (S3) and fourth (S4) heart sounds detected by phonocardiography are considered to represent the criterion standards of the gallop sounds, but their test characteristics have not been explored.

OBJECTIVE: To determine the diagnostic test characteristics of the S3 and S4 for prediction of left ventricular dysfunction using a computerized heart sound detection algorithm.

DESIGN, SETTING, AND PARTICIPANTS: Prospective study of 90 adult patients undergoing elective left-sided heart catheterization at a single US teaching hospital between August 2003 and June 2004. The mean age was 62 (SD, 13) years (range, 24-90 years) and 61 (68%) were male. Within a 4-hour period, participants underwent computerized heart sound phonocardiographic analysis, cardiac catheterization, transthoracic echocardiography, and blood sampling for assessment of an S3/S4, left ventricular end-diastolic pressure (LVEDP), left ventricular ejection fraction (LVEF), and B-type natriuretic peptide (BNP), respectively.

MAIN OUTCOME MEASURES: Diagnostic test characteristics of the computerized phonocardiographic S3 and S4 using markers of left ventricular function as criterion standards. RESULTS: Mean (SD) LVEDP was significantly elevated (18.4 [6.9] mm Hg vs 12.1 [7.3] mm Hg; P<.001), mean (SD) LVEF was reduced (49.4% [20.2%] vs 63.6% [14.8%]; P<.001), and median (interquartile range) BNP was elevated (330 [98-1155] pg/mL vs 86 [41-192] pg/mL; P<.001) in those with an S3, S4, or both compared with patients without a diastolic heart sound. The sensitivities of these heart sounds to detect an elevated LVEDP, reduced LVEF, or elevated BNP were 41%, 52%, and 32% for an S3, and 46%, 43%, and 40% for an S4, respectively. For abnormal levels of the same markers of ventricular function, the specificities of the S3 were 92%, 87%, and 92%, while the specificities of the S4 were 80%, 72%, and 78%, respectively.

CONCLUSIONS: Neither the phonocardiographic S3 nor the S4 is a sensitive marker of left ventricular dysfunction. The phonocardiographic S3 is specific for left ventricular dysfunction and appears to be superior to the moderate specificity of the phonocardiographic S4.

Drazner MH, Rame JE, Stevenson LW, Dries DL. **Prognostic Importance of Elevated Jugular Venous Pressure and a Third Heart Sound in Patients with Heart Failure.** ***N Engl J Med.*** 2001;345(8):574-81. http://www.nejm.org/doi/pdf/10.1056/NEJMoa010641

BACKGROUND: The independent prognostic value of elevated jugular venous pressure or a third heart sound in patients with heart failure is not well established.

METHODS: We performed a retrospective analysis of the Studies of Left Ventricular Dysfunction treatment trial, in which 2569 patients with symptomatic heart failure or a history of it were randomly assigned to receive enalapril or placebo. The mean (±SD) follow-up was 32±15 months. The presence of elevated jugular venous pressure or a third heart sound was ascertained by physical examination on entry into the trial. The risks of hospitalization for heart failure and progression of heart failure as defined by death from pump failure and the composite end point of death or hospitalization for heart failure were compared in patients with these findings on physical examination and patients without these findings.

RESULTS: Data on 2479 patients were complete and analyzed. In multivariate analyses that were adjusted for other markers of the severity of heart failure, elevated jugular venous pressure was associated with an increased risk of hospitalization for heart failure (relative risk, 1.32; 95 percent confidence interval, 1.08 to 1.62; P<0.01), death or hospitalization for heart failure (relative risk, 1.30; 95 percent confidence interval, 1.11 to 1.53; P<0.005), and death from pump failure (relative risk, 1.37; 95 percent confidence interval, 1.07 to 1.75; P<0.05). The presence of a third heart sound was associated with similarly increased risks of these outcomes.

CONCLUSIONS: In patients with heart failure, elevated jugular venous pressure and a third heart sound are each independently associated with adverse outcomes, including progression of heart failure. Clinical assessment for these findings is currently feasible and clinically meaningful.

Shah SJ, Michaels AD. **Hemodynamic Correlates of the Third Heart Sound and Systolic Time Intervals.** ***Congest Heart Fail.*** 2006;12 Suppl 1:8-13. http://onlinelibrary.wiley.com/doi/10.1111/j.0889-7204.2006.05767.x/epdf

Bedside diagnostic tools remain important in the care of patients with heart failure. Over the past two centuries, cardiac auscultation and phonocardiography have been essential in understanding cardiac pathophysiology and caring for patients with heart disease. Diastolic heart sounds (S3 and S4) and systolic time intervals have been particularly useful in this regard. Unfortunately, auscultation skills have declined considerably, and systolic time intervals have traditionally required carotid pulse tracings. Newer technology allows the automated detection of heart sounds and measurement of systolic time intervals in a simple, inexpensive, noninvasive system. Using the newer system, the authors present data on the hemodynamic correlates of the S3 and abnormal systolic time intervals. These data serve as the foundation for using the system to better understand the test characteristics and pathophysiology of the S3 and systolic time intervals, and help to define their use in improving the bedside diagnosis and management of patients with heart failure.

Mehta NJ, Khan IA. **Third Heart Sound: Genesis and Clinical Importance.** ***Int J Cardiol.*** 2004;97(2):183-6. https://www.sciencedirect.com/science/article/pii/S0167527303004856

Auscultation of third heart sound has been performed for more than a century, an interest that not only persists today, but also has experienced renewed emphasis. Sophisticated study of the third heart sound by current investigative techniques has underscored the value of clinical detection with the time-honored stethoscope. This review re-examines the mechanisms of genesis of third heart sound in regard to the hemodynamic and echocardiographic aspects, and its clinical importance.

Luisada AA, Singhal A, Portaluppi F, Strozzi C. **Noninvasive Index of Cardiac Contractility During Stress Testing: A Collaborative Study. *Clin Cardiol.*** 1985;8(7):375-84. http://onlinelibrary.wiley.com/doi/10.1002/clc.4960080702/epdf

The present study was conducted in parallel in three different institutions with a similar purpose but using different technical setups. Based on the experimental demonstration that the external phonocardiogram is similar to the rate of acceleration (d3P/d3t) of the left ventricular pressure, and that catecholamines in a similar way increase the early positive wave of the left ventricular pressure and the first heart sound (S1) of the external phonocardiogram; knowing that exercise causes secretion of catecholamines and sympathetic reflexes, we have studied the S1 changes as a result of exertion in 34 normal young subjects. Blood pressure, heart rate, electrocardiograph, and phonocardiograph recordings of each subject were taken. In 10 subjects, cardiac output was also recorded by impedance cardiography. The result of the study was that the first heart sound increased routinely 4-5 times the normal amplitude; in a few subjects the increase was up to 15 times greater. While the extent of increase of S1 was proportional to the severity and duration of the effort and was usually proportional to the increase of other parameters, exceptions were noted as having marked increase of S1 with moderate increase of either blood pressure or heart rate. This was explained by the different receptors activated by the catecholamines and by the complexity of hormonal and neural influences acting on various organs in a stress test. The amplitude of S1 was found to be a reasonably reliable index for following changes of cardiac contractility during exercise, and the suggestion was made that this parameter should be studied in parallel with the others in routine stress tests.

JM F. **The First Heart Sound. In: Walker HK, Hall WD, Hurst JW, editors. *Clinical Methods:* The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 22.** 1990: https://www.ncbi.nlm.nih.gov/books/NBK333/pdf/Bookshelf_NBK333.pdf

Mills PG, Chamusco RF, Moos S, Craige E. **Echophonocardiographic Studies of the Contribution of the Atrioventricular Valves to the First Heart Sound. *Circulation.*** 1976;54(6):944-51. http://circ.ahajournals.org/content/54/6/944.long

The movements of the mitral, tricuspid and aortic valves have been recorded echocardiographically and related to the first heart sound (S1) in patients with various hemodynamic and conduction abnormalities. Closure of the mitral and tricuspid valves has been studied with respect to the corresponding atrioventricular pressure crossover and it is clear that both valves finish closing about 50 msec after pressure crossover. In order to clarify the relative contribution of tricuspid valve closure and aortic root events to the second high frequency component of S1, a new simultaneous dual echophonocardiographic technique was employed. This permitted the simultaneous registration of tricuspid and aortic valve movements and demonstrated that in certain circumstances the second high frequency component of S1, could be attributed to tricuspid closure, aortic root events being excluded from the genesis of this sound. These observations suggest that the two high frequency components of S1 are related to closure of the mitral and tricuspid valves. The results do not however, exclude a contribution to S1 of aortic root events, which may be of lower frequency vibrations.

Sakamoto T, Kusukawa R, Maccanon DM, Luisada AA. **Hemodynamic Determinants of the Amplitude of the First Heart Sound. *Circ Res.*** 1965;16:45-57. http://circres.ahajournals.org/content/circresaha/16/1/45.full.pdf

S Rials, M Aktas, Q An, P Thakur, Y Zhang, J Boehmer. **Continuous Respiratory Rate is Superior to Routine Outpatient Dyspnea Assessment for Predicting Heart Failure Events.** ***J Card Fail.*** 2018; 24 (8): Supplement, Pages S45. https://doi.org/10.1016/j.cardfail.2018.07.130

INTRODUCTION: Dyspnea is a common complaint in patients hospitalized for heart failure (HF). Implantable medical devices are capable of monitoring and calculating a respiratory rate trend (RRT) using transthoracic mpedance. We compared RRT to routine outpatient dyspnea assessment in identifying patients risk of acute HF events (HFEs) between follow-up (FU) visits.

METHODS: The MultiSENSE study enrolled 900 HF patients with COGNISTM CRT-Ds followed for up to 1 year. HFE including hospitalizations or outpatient administration of IV decongestive medications were independently adjudicated. Scheduled FU occurred every 6-8 weeks unless remotely monitored which allowed 3 months between FU. Dyspnea status and the daily RRT were evaluated at each FU. RRT was compared to dyspnea assessment in identifying patients risk of HFE in the next FU period. Dyspnea assessment was discrete with two grades (with or without dyspnea), RRT was a continuous value represented in breath per minute (bpm).

RESULTS: During 4635 FU periods, 135 HFEs occurred. The hazard ratio (HR) for a HFE was 2.0 (95% confidence interval: 1.4-3.0) times higher for patients with dyspnea compared to those without. The HR for RRT was similar using a threshold of 18 bpm, 2.1 (95% CI: 1.4-3.0). RRT thresholds above 18 bpm provided successively higher HR (figure below), significantly higher than that of dyspnea.

CONCLUSION: In ambulatory HF patients, an RRT was able to stratify the risk of a HFE beyond what dyspnea status could do. RRT was able to determine patients with up to 10-fold higher risk of a HFE in the next FU period. The use of automatic, device measured, objective respiration measurements in ambulatory patients may improve the ability for clinicians to identify patients at risk for HFE.

J Lindenfeld, RS Gardner, V Averina, P Thakur, Q An, J Boehmer. Readmissions or death are more likely when device-derived rapid shallow breathing index worsens during heart failure hospitalization. ***Eur J Heart Fail*** 2018, 20 (Suppl. S1), p 474. https://www.onlinelibrary.wiley.com/doi/10.1002/ejhf.1197

BACKGROUND: A multisensor algorithm has been demonstrated to predict heart failure (HF) events in patients with implanted devices with high sensitivity and low false positive rate. However, it is not known how the individual sensors change from hospital admission to discharge and whether it can be indicative of readmissions or death within 30 days.

METHODS: The MultiSENSE study followed 900 HF patients with CRT-D for up to 1 year. Devices were modified to enable the collection of first (S1) and third (S3) heart sounds, thoracic impedance (TI), respiratory rate (RR), rapid shallow breathing index (RSBI), night heart rate (nHR), and activity. All hospitalizations were adjudicated by an independent committee. Hospitalizations with HF as a primary cause (HFH) were identified. HFH with an admission outside of the customized data collection were excluded due to lack of sensor data. Each HFH was classified as unresolved if it was followed by all-cause hospitalization or death within 30 days of discharge; otherwise, it was classified as resolved. For each type of HFH, daily sensor values on the day before admission and the day before discharge were compared with a pairwise t-test. The changes in each sensor were compared between the resolved and the unresolved group via t-test. Significant difference in comparisons was defined as that with $p<0.05$.

RESULTS: Out of 149 HFHs, 109 were determined as resolved and 40 as unresolved. Additional HFHs were excluded if sensor data at admission or discharge was not available. Admission-to-discharge differences for resolved HFHs showed improvement in S3, S1, TI, and RR, and reduction in activity (see Figure). Admission-to-discharge differences for unresolved HFHs showed improvement in TI, worsening in RSBI, and reduction in activity. Changes in RSBI were significantly different between the two groups of HFHs.

CONCLUSIONS: Worsening in RSBI during hospitalization identified a group of patients with either early HF readmissions or death.

J Boehmer; M Aktas, A Capucci, RS Gardner, M Gold, G Molon, P Thakur, R Sweeney, Y Zhang, Q An, V Averina, S Rials. **Device measured rapid shallow breathing index reflects changing respiratory patterns but minute ventilation reflects changing activity during worsening heart failure in ambulatory patients.** ***Eur J Heart Fail*** 2018, 20 (Suppl. S1), p 545-546. https://www.onlinelibrary.wiley.com/doi/10.1002/ejhf.1197

BACKGROUND: Respiratory distress is common in heart failure (HF) and a primary driver for HF hospitalizations. Minute Ventilation (MV), a product of respiratory rate and tidal volume, is known to be elevated in HF patients due to ventilation/perfusion (V/Q) mismatch. However, it is not known if changes in MV accurately reflect emergence of rapid shallow breathing patterns in ambulatory patients preceding a HF event.

METHODS: The MultiSENSE trial enrolled 900 patients implanted with a COGNIS CRT-D and followed them up to 1 year. Device software was modified to permit collection of chronic diagnostic sensor data including impedance based respiration rate (RR) and tidal volume (TV), which was used to compute MV (= RR*TV) and Rapid Shallow Breathing Index (RSBI = RR/TV), and activity (XL). Daily averages were separately computed over entire 24 hours as well as during resting epochs. HF events (HFEs) were independently adjudicated and defined as HF admissions or unscheduled visits with intravenous HF treatment. Relative changes preceding HFEs were computed between a baseline 30-60 days prior to HFEs (BL) and 3-day pre-HFE (ST) as (ST-BL)/BLx100% and reported as mean±SEM. Significance was tested using Wilcoxon signed-rank test.

RESULTS: 900 patients followed for a year experienced 192 HFEs. Using 24-hour averages, significant changes were observed in RR, TV and RSBI indicating the emergence of rapid shallow breathing pattern leading up to HFE. MV average over 24 hours showed nonsignificant decrease coincident with decreased patient activity but showed no change when daily averaging was limited to resting epochs. In contrast, RR, TV and RSBI were significantly changed even at rest in directions consistent with the emergence of rapid shallow breathing pattern.

CONCLUSION: Device measured rapid shallow breathing is significantly elevated in the three day epoch preceding HFEs, whereas minute ventilation is not, in both 24-hour as well as resting period daily averages. Automatic ambulatory longitudinal monitoring of changes in rapid shallow breathing patterns may enable better monitoring for emerging respiratory distress in HF patients.

J Boehmer, M Aktas, A Capucci, RS Gardner, M Gold, G Molon, P Thakur, R Sweeney, Y Zhang, Q An, V Averina, S Rials. **Device measured rapid shallow breathing index and not minute ventilation reflects changes in dyspnea status in ambulatory heart failure patients.** ***Eur J Heart Fail*** 2018, 20 (Suppl. S1), p 546. https://www.onlinelibrary.wiley.com/doi/10.1002/ejhf.1197

BACKGROUND: Dyspnea is common in heart failure (HF) patients and a primary driver for HF hospitalizations. Minute Ventilation (MV), a product of respiratory rate (RR) and tidal volume (TV), is known to be elevated in HF patients due to ventilation/perfusion (V/Q) mismatch. However, it is not known if changes in MV accurately reflect changes in dyspnea status in ambulatory HF patients over time.

METHODS: The MultiSENSE trial enrolled 900 patients implanted with a COGNIS CRT-D and followed them for up to 1 year. Device software was modified to permit collection of chronic diagnostic sensor data including impedance based RR and TV, which was used to compute MV (RR*TV) and Rapid Shallow Breathing Index (RSBI = RR/TV). Dyspnea status was assessed on a 3-point scale (0=No dyspnea, 1=dyspnea on exertion, 2=dyspnea at rest) at routine follow-up visits scheduled either every three months if the patients had remote monitoring, or every 6-8 weeks if not. Changes in dyspnea scores between follow-ups were calculated: Improve+ (2->0), Improve (2->1 or 1->0), No change, Worsen (0->1 or 1->2), and Worsen+ (0->2). Relative changes in the respiration parameters between the start (ST) and end (ED) of each epoch were calculated as (ED-ST)/STx100%, reported as mean±SEM for each category and compared across categories using Kruskal-Wallis test.

RESULTS: Of 4717 total follow-up intervals with dyspnea assessments, 3388 had no change, 561 had 1-point worsening, 41 had 2-point worsening, 689 had 1-point improvement, while 37 had 2-point improvement. 24-hour average MV was not significantly different between dyspnea change categories (p = 0.42) and changed inconsistent with expectation (i.e. increased MV with improved dyspnea assessment). In contrast changes in 24-hour average RSBI (p=0.03) as well as day-time minimum RSBI (p <0.0001) were significantly different between categories and consistent with expectation (i.e. increased RSBI with worsening dyspnea)Conclusion: Changes in RSBI correlated with changes in patient's dyspneic status (i.e. increased rapid shallow breathing with worsening dyspnea status) whereas MV did not. Automatic longitudinal measurements of day-time minimum RSBI may better quantify the dyspneic status in ambulatory HF patients, enabling continuous monitoring of dyspnea in HF patients.

Goetze S, Zhang Y, An Q, Averina V, Lambiase P, Schilling R, Trappe HJ, Winter S, Wold N, Manola L, Kestens D. **Ambulatory Respiratory Rate Trends Identify Patients at Higher Risk of Worsening Heart Failure in Implantable Cardioverter Defibrillator and Biventricular Device Recipients: A Novel Ambulatory Parameter to Optimize Heart Failure Management.** ***J Interv Card Electrophysiol.*** 2015;43(1):21-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4438200/pdf/10840_2015_Article_9983.pdf

PURPOSE: Respiratory distress is the primary driver for heart failure (HF) hospitalization. Implantable pacemakers and defibrillators are capable of monitoring respiratory rate (RR) in ambulatory HF patients. We investigated changes in RR prior to HF hospitalizations and its near-term risk stratification power.

METHODS: NOTICE-HF was an international multi-center study. Patients were implanted with an implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator, capable of trending daily maximum, median, and minimum RR (maxRR, medRR, minRR). RR from 120 patients with 9 months of follow-up was analyzed. One-tailed Student's t test was used to compare RR values prior to HF events to baseline defined as 4 weeks prior to the events. A Cox regression model was used to calculate the hazard ratios (HR) for the 30-day HF hospitalization risk based on RR values in the preceding month.

RESULTS: Daily maxRR, medRR, and minRR were significantly elevated prior to HF events compared to baseline (DeltamaxRR 1.8 ± 3.0; p = 0.02; DeltamedRR, 2.1 ± 2.8; p = 0.007; DeltaminRR, 1.5 ± 2.1, p = 0.008). Risk of experiencing HF events within 30-days was increased if the standard deviation of medRR over the preceding month was above 1.0 br/min (HR = 12.3, 95% confidence interval (CI) 2.57-59, p = 0.002). The risk remained high after adjusting for clinical variables that differed at enrollment.

CONCLUSION: Ambulatory daily respiratory rate trends may be a valuable addition to standard management for HF patients.

Aktas MK, Nair DG, An Q, Zhang Y, Thakur PH, Averina V, Thompson J, Gardner R. **Patients with Elevated Respiratory Rates are at Higher Risk of Heart Failure Events in 30 Days [abstract].** ***Heart Rhythm.*** 2016;13(5):S270. https://www.heartrhythmjournal.com/article/S1547-5271(16)30071-6/pdf

INTRODUCTION: Patients (pts) admitted with heart failure (HF) often present with dyspnea, and have a rapid shallow breathing pattern that can be characterized by elevated respiratory rates (RR). We hypothesized that an elevated RR is associated with increased risk of experiencing HF events.

METHODS: The MultiSENSE study enrolled pts with COGNIS® CRT-Ds that can monitor and record daily maximum (max), median (med) and minimum (min) respiratory rate trends (RRTs) for up to 1 year. RRT data were averaged every month and divided into high and low groups. This dichotomization was chosen so that 80% of data was classified into the low RRT group. A cox proportional hazard model was used to estimate hazard ratios (HR) of experiencing HF events within the next month for the different groups.

RESULTS: Of 532 enrolled pts, 498 pts had RRT data for a duration of 309 ± 106 days. A total of 61 pts experienced 118 HF events at least 30 days after enrollment. Patients with high med (>19.6 breaths/minute, br/min) or min (>14.4 br/min) RRT showed an elevated risk of worsening HF in the next 30 days with HR of 3.1 and 2.1 (both $p<0.001$) when compared to pts with low med or min RRT, respectively. The risk for HF events remained high after adjusting for age, gender, New York Heart Association class and left ventricular ejection fraction (HR = 2.8 and 1.6, $p<0.001$ and $p=0.029$, respectively). No difference in HF events was observed in the high versus low max (28.5 br/min) RRT group ($p=0.77$)

CONCLUSIONS: This study shows that respiratory rate data obtained from a COGNIS® CRT-D can help identify patients who are at higher risk of HF events in 30 days. These results may be helpful in HF risk assessment.

Boehmer JP, An Q, Zhang Y, Shih, A.,**Variation in Daily Median Respiratory Rate Identifies Patients at Higher Risk of Worsening HF in 30 Days [abstract].** ***Heart Rhythm.*** 2013;10(5):S66. https://www.heartrhythmjournal.com/article/S1547-5271(13)00286-5/fulltext

INTRODUCTION: Heart failure (HF) patients (pts) often present with rapid shallow breathing patterns, which can be characterized by an elevated respiratory rate (RR). It is, however, unclear how variation in daily RR trends may be related to HF deterioration. This study evaluated the ability of variation in RR to predict HF events in ambulatory HF pts.

METHODS: MultiSENSE study enrolled pts implanted with COGNIS® CRT-D devices, which were converted to a research device with daily maximum (max), median (med) and minimum (min) respiratory rate trends (RRTs) capability and followed for 12 months. We calculated the 10th and 90th percentile range of the three RRTs every month. Pts were classified into 2 groups depending on the range: high RRT variation (10%-90% range > 4 breaths/minute) and low RRT variation (range ≤ 4). Cox proportional hazards model was used to determine the risk of a HF event in the next 30-day window in each group.

RESULTS: We analyzed data from 160 patients who were followed for 321 ± 85 days (24 pts with 46 HF events at least 30 days after enrollment). Daily max and daily min RRTs showed a higher variation than daily med RRT. Pts with a higher 30-day variation in daily med RRT had 4.9-fold increased risk of HF hospitalization within the next month (HR (95% CI): 4.9 (2.2 - 11), $p<0.001$, see figure). The risk remained high (HR (95% CI): 5.9 (2.5 - 14), $p<0.001$) after adjusting for clinical variables (age, gender, NYHA, LVEF).

CONCLUSION: Initial data from the MultiSENSE study indicates that 30-day variation in daily median RRT identifies pts at a higher risk of experiencing worsening HF in the next month. Further evaluation is warranted to confirm these results with the full study data set at the conclusion of the trial.

Vollmann D, Nagele H, Schauerte P, Wiegand U, Butter C, Zanotto G, Quesada A, Guthmann A, Hill MR, Lamp B. **Clinical Utility of Intrathoracic Impedance Monitoring to Alert Patients with an Implanted Device of Deteriorating Chronic Heart Failure.** ***Eur Heart J.*** 2007;28(15):1835-40. https://doi.org/10.1093/eurheartj/ehl506

AIMS: To evaluate the utility of intrathoracic impedance monitoring for detecting heart failure (HF) deterioration in patients with an implanted cardiac resynchronization/defibrillation device.

METHODS AND RESULTS: Patients enrolled in the European InSync Sentry Observational Study were audibly alerted by a device algorithm if a decrease in intrathoracic impedance suggested fluid accumulation. Clinical HF status and device data were assessed at enrollment, during regular follow-up, and if patients presented with an alert or HF deterioration. Data from 373 subjects were analysed. Fifty-three alert events and a total of 53 clinical events (HF deterioration defined by worsening of HF signs and symptoms) were reported during a median of 4.2 months. Adjusted for multiple events per patient, the alert detected clinical HF deterioration with 60% sensitivity (95% CI 46-73) and with a positive predictive value of 60% (95% CI 46-73). Higher NYHA class at baseline was predictive for adequate alert events during follow-up ($P < 0.05$). In 11 of 20 HF deteriorations without preceding alert, an upstroke of the fluid index occurred without reaching the programmed alert threshold.

CONCLUSION: A device-based algorithm that alerts patients in case of decreasing intrathoracic impedance facilitates the detection of HF deterioration. Future randomized, controlled trials are needed to test whether the tailored use of intrathoracic impedance monitoring can improve the ambulatory management of patients with chronic HF and an implanted device.

Yu C-M, Wang L, Chau E, Chan RH-W, Kong S-L, Tang M-O, Christensen J, Stadler RW, Lau C-P. **Intrathoracic Impedance Monitoring in Patients with Heart Failure. Correlation with Fluid Status and Feasibility of Early Warning Preceding Hospitalization.** 2005;112 (6):841-8. http://circ.ahajournals.org/content/circulationaha/112/6/841.full.pdf

BACKGROUND: Patients with heart failure are frequently hospitalized for fluid overload. A reliable method for chronic monitoring of fluid status is therefore desirable. We evaluated an implantable system capable of measuring intrathoracic impedance to identify potential fluid overload before heart failure hospitalization and to determine the correlation between intrathoracic impedance and standard measures of fluid status during hospitalization.

METHODS AND RESULTS: Thirty-three patients with NYHA class III and IV heart failure were implanted with a special pacemaker in the left pectoral region and a defibrillation lead in the right ventricle. Intrathoracic impedance was regularly measured and recorded between the lead and the pacemaker case. During hospitalizations, pulmonary capillary wedge pressure and fluid status were monitored. Ten patients were hospitalized for fluid overload 25 times over 20.7±8.4 months. Intrathoracic impedance decreased before each admission by an average of 12.3±5.3% (P<0.001) over an average of 18.3±10.1 days. Impedance reduction began 15.3±10.6 days (P<0.001) before the onset of worsening symptoms. There was an inverse correlation between intrathoracic impedance and pulmonary capillary wedge pressure (r=–0.61, P<0.001) and between intrathoracic impedance and net fluid loss (r=–0.70, P<0.001) during hospitalization. Automated detection of impedance decreases was 76.9% sensitive in detecting hospitalization for fluid overload, with 1.5 false-positive (threshold crossing without hospitalization) detections per patient-year of follow-up.

CONCLUSIONS: Intrathoracic impedance is inversely correlated with pulmonary capillary wedge pressure and fluid balance and decreased before the onset of patient symptoms and before hospital admission for fluid overload. Regular monitoring of impedance may provide early warning of impending decompensation and diagnostic information for titration of medication.

Wang L. **Fundamentals of Intrathoracic Impedance Monitoring in Heart Failure.** ***Am J Cardiol.*** 2007; 99(10A):3G-10G. https://www.ncbi.nlm.nih.gov/pubmed/17512421

The primary objective of the first-generation implantable cardiac pacemakers was to provide critical heart rate support, but these devices did not have any diagnostic capabilities. In the intervening decades, the number, type, and complexity of implantable devices has greatly expanded. Today, implantable devices not only provide heart rate support but they also provide protection from sudden cardiac death with implantable cardioverter defibrillators (ICDs) and reduce symptoms and increase survival with cardiac resynchronization therapy (CRT). Furthermore, information on physiologic variables has been collected in patients with implanted devices for the purpose of providing sophisticated closed-loop optimization of their pacing and defibrillation algorithms. Thoracic fluid status monitoring via intrathoracic impedance is the newest device-based diagnostic capability. For those patients with heart failure who are already targeted to receive an ICD or CRT with defibrillator implant, the ability to monitor fluid status can provide additional insight into the difficult problem of evaluating and managing these patients. This article reviews the basics of measuring intrathoracic impedance via OptiVol fluid status monitoring (Medtronic, Inc., Minneapolis, MN), as well as clinical results regarding the utility of evaluating OptiVol intrathoracic impedance data trends.

Wang L, Lahtinen S, Lentz L, Rakow N, Kaszas C, Ruetz L, Stylos L, Olson WH. **Feasibility of Using an Implantable System to Measure Thoracic Congestion in an Ambulatory Chronic Heart Failure Canine Model.** ***Pacing Clin Electrophysiol.*** 2005;28(5):404-11. http://onlinelibrary.wiley.com/doi/10.1111/j.1540-8159.2005.40009.x/epdf

BACKGROUND: Noninvasive measures of impedance reflect alterations in thoracic fluid and pulmonary edema in acute animal and human studies.

MATERIALS AND METHODS: We evaluated the feasibility of using an implantable impedance measuring device and cardiac lead system to monitor intrathoracic congestion in a pacing-induced heart failure canine model. Three devices were implanted in each of five dogs: a modified pacemaker to measure impedance from a defibrillation lead implanted in the right ventricle; an implantable hemodynamic monitoring device to measure left ventricular end diastolic pressure (LVEDP) and a second pacemaker to deliver rapid (240 pulses per minute) ventricular pacing to induce heart failure.

RESULTS: All five dogs developed severe heart failure after 3-4 weeks of rapid pacing and recovered following pacing termination. The LVEDP increased and impedance decreased during pacing-induced heart failure and recovered after pacing cessation. At the end of pacing, there was a mean impedance reduction of 10.6 ± 8.3% and a mean LVEDP increase of 18.1 ± 4.5 mmHg compared to baseline. The impedance and LVEDP were inversely correlated ($r = -0.41$ to -0.85, all $P < 0.05$).

CONCLUSIONS: In the canine model, measurement of chronic intrathoracic impedance with an implantable system effectively revealed changes in thoracic congestion due to heart failure reflected by LVEDP. These data suggest that implantable device-based impedance measurement merits further investigation as a tool to monitor the fluid status of heart failure patients.

Hariharan R, Molon G, An Q, Zhang Y, Averina V, Thakur PH, Thompson J, Boehmer JP. **Patients with Reduced Level of Physical Activity are at Higher Risk of Worsening Heart Failure Events in 30 Days [abstract].** ***Heart Rhythm.*** 2016;13(5):S149-S150. https://www.heartrhythmjournal.com/article/S1547-5271(16)30069-8/pdf

INTRODUCTION: Physical activity is known to have long-term prognostic value in HF patients (pts). Reduced level of activity is associated with high mortality and risk of HF events (HFEs). However, association between reduced activity levels and HF risk within a shorter time window is unknown.

METHODS: MultiSENSE study enrolled pts with COGNIS® CRT-D with modified firmware that are capable of monitoring daily activity level, represented as hours of activity above 28 milligravity (mG) within a day as measured by the implanted accelerometer (Tact), up to 1 year. Tact were averaged every month and divided into high and low groups. The threshold was chosen so that 70% of data were classified into a low group. A cox proportional hazard model is used to estimate the hazard ratio (HR) of experiencing HFEs in the next 30 days between two groups.

RESULTS: Of the 974 patients enrolled in the trial, 532 were delegated to the algorithm development set. Of these, 500 pts had Tact data with a length of 317±102 days. There were 118 HFEs in 61 pts at least 30 days after enrollment. The group with low daily Tact (<3.0 hours) showed an elevated risk of HFEs in the next 30 days with a HR of 4.0 (95% confidence interval (CI): 2.1 - 7.7, p < 0.001, see figure), and the risk remained high after adjusting for age, gender, New York Heart Association class and left ventricular ejection fraction (HR = 2.7, 95% CI: 1.6- 4.3, p<0.001).

CONCLUSIONS: The MultiSENSE study demonstrates that patients with reduced 30-day activity levels are at higher risk of experiencing HFEs in the next 30 days. The results may be helpful in near-term HF risk assessment.

Kadhiresan VA, Pastore J, Auricchio A, Sack S, Doelger A, Girouard S, Spinelli JC. **A Novel Method—the Activity Log Index—for Monitoring Physical Activity of Patients with Heart Failure.** ***Am J Cardiol.*** 2002; 89(12):1435-7. https://www.ncbi.nlm.nih.gov/pubmed/12062745

Vegh EM, Kandala J, Orencole M, Upadhyay GA, Sharma A, Miller A, Merkely B, Parks KA, Singh JP. **Device-Measured Physical Activity Versus Six-Minute Walk Test as a Predictor of Reverse Remodeling and Outcome after Cardiac Resynchronization Therapy for Heart Failure.** ***Am J Cardiol.*** 2014;113(9):1523-8. https://www.ncbi.nlm.nih.gov/pubmed/24641966

Implanted devices can provide objective assessment of physical activity over prolonged periods. The purpose of this study was to investigate the prognostic value of device-measured physical activity data compared with a six-minute walk test (6MWT) in predicting clinical response to cardiac resynchronization therapy (CRT). This was a single-center study in which patients who underwent CRT for standard indications were evaluated. Daily physical activity and 6MWT were evaluated postimplant at 1, 3, and 6 months. The primary end point was a composite of heart failure hospitalization, transplant, left ventricular (LV) assist device, and all-cause death at 3 years. Echocardiographic response, defined as a >/=10% improvement in LV ejection fraction (LVEF), at 6 months was the secondary end point. About 164 patients were included: average age was 67.3 +/- 12.9 years, 77% were men, baseline LVEF was 25% +/- 7%. Kaplan-Meier curves showed superior freedom from the composite end point in the highest tertile of both 6MWT and physical activity compared with the lowest tertile (41 vs 23 cases, respectively, p <0.001) for 6MWT and for activity (22 vs 7 cases, respectively, p = 0.001). In an adjusted multivariate model, independent predictors of improved clinical outcome included 1-month physical activity (hazard ratio 0.546, 95% confidence interval [CI] 0.361 to 0.824, p = 0.004) and 6MWT (hazard ratio 0.581, 95% CI 0.425 to 0.795, p = 0.001). An additional hour of higher activity at 1 month translated to a 1.38 times (95% CI 1.075 to 1.753, p = 0.011) higher likelihood of improved echocardiographic response. In conclusion, device-based measures of physical activity may be useful in predicting echocardiographic reverse remodeling and long-term clinical outcome in patients receiving CRT.

Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M. **Resting Heart Rate in Cardiovascular Disease. *J Am Coll Cardiol.*** 2007;50(9):823-30. https://www.ncbi.nlm.nih.gov/pubmed/17719466

The importance of resting heart rate (HR) as a prognostic factor and potential therapeutic target is not yet generally accepted. Recent large epidemiologic studies have confirmed earlier studies that showed resting HR to be an independent predictor of cardiovascular and all-cause mortality in men and women with and without diagnosed cardiovascular disease. Clinical trial data suggest that HR reduction itself is an important mechanism of benefit of beta-blockers and other heart-rate lowering drugs used after acute myocardial infarction, in chronic heart failure, and in stable angina pectoris. Pathophysiological studies indicate that a relatively high HR has direct detrimental effects on the progression of coronary atherosclerosis, on the occurrence of myocardial ischemia and ventricular arrhythmias, and on left ventricular function. Studies have found a continuous increase in risk with HR above 60 beats/min. Although it may be difficult to define an optimal HR for a given individual, it seems desirable to maintain resting HR substantially below the traditionally defined tachycardia threshold of 90 or 100 beats/min. These findings suggest that the potential role of HR and its modulation should be considered in future cardiovascular guidance documents.

Adamson PB, Smith AL, Abraham WT, Kleckner KJ, Stadler RW, Shih A, Rhodes MM. **Continuous Autonomic Assessment in Patients with Symptomatic Heart Failure: Prognostic Value of Heart Rate Variability Measured by an Implanted Cardiac Resynchronization Device. *Circulation.*** 2004;110(16):2389-94. http://circ.ahajournals.org/content/circulationaha/110/16/2389.full.pdf

BACKGROUND: Heart rate variability (HRV) as an indirect autonomic assessment provides prognostic information when measured over short time periods in patients with heart failure. Long-term continuous HRV can be measured from an implantable device, but the clinical value of these measurements is unknown.

METHODS AND RESULTS: A total of 397 patients with New York Heart Association class III or IV heart failure were studied. Of these, 370 patients had information from their implanted cardiac resynchronization device for mortality risk stratification, and 288 patients had information for measured parameters (ie, HRV, night heart rate, and patient activity) and clinical event analyses. Continuous HRV was measured as the standard deviation of 5-minute median atrial-atrial intervals (SDAAM) sensed by the device. SDAAM <50 ms when averaged over 4 weeks was associated with increased mortality risk (hazard ratio 3.20, P=0.02) and SDAAM were persistently lower over the entire follow-up period in patients who required hospitalization or died. SDAAM decreased a median of 16 days before hospitalization and returned to baseline after treatment. Automated detection of decreases in SDAAM was 70% sensitive in detecting cardiovascular hospitalization, with 2.4 false-positives per patient-year of follow-up.

CONCLUSIONS: This study demonstrates that SDAAM continuously measured from an implanted cardiac resynchronization device is lower in patients at high mortality and hospitalization risk. SDAAM declines as patient status decompensates. Continuous long-term SDAAM may be a useful tool in the clinical management of patients with chronic heart failure.

Rials SJ, Hatlestad JD, Smith A, Pubbi D, Slotwiner D, Boehmer JP. **Night-time Elevation Angle in Heart Failure Patients Indicates Orthopnea and Paroxysmal Nocturnal Dyspnea [abstract].** ***Eur J Heart Fail.*** 2017;19:109. https://www.bostonscientific.com/content/dam/bostonscientific/Rhythm%20Management/Clinical%20Science/2017%20ESC-HF_Night-time%20elevation%20angle%20in%20HF%20patients%20indicates%20O-PND.pdf.

BACKGROUND: Orthopnea and paroxysmal nocturnal dyspnea (O-PND) are cardinal signs of worsening heart failure (HF). Guidelines for HF patient management recommend routine assessment of O-PND. These postural symptoms are typically assessed by asking about patients' sleep angle in terms of number of pillows. We evaluated the use of automated posture sensing in assessing O-PND in HF patients.

METHODS: 46 HF patients (35 male, 45-83 years of age, NYHA class I-III) in the MultiSENSE study wore an external posture monitoring device for a few days (0.9-14) at a time. At each patient visit, O-PND symptoms were assessed. We compared the device-determined night-time elevation angle (NTEA) for patient visits with & without reported O-PND symptoms.

RESULTS: Patient visits associated with O-PND (n=24) had an average NTEA of 23.2±2.8 (mean±standard error), compared to an average NTEA of 10.7±1.7 for those patient visits not associated with O-PND (n=41, p=0.0001 using non-paired t-test). A receiver operating characteristic (ROC) curve analysis (see figure) yielded an area under the curve of 0.79 for NTEA detecting O-PND. Selecting an NTEA threshold of 14.8 yielded a sensitivity of 83% and specificity of 76%.

CONCLUSION: Orthopnea & PND are key symptoms of HF. Night-time elevation angle is indicative of these symptoms, presumably reflecting the tendency of patients to sleep partially elevated to avoid dyspnea. Monitoring posture in future devices may provide valuable insight for the remote management of HF patients.

Beck da Silva L, Mielniczuk L, Laberge M, Anselm A, Fraser M, Williams K, Haddad H. **Persistent Orthopnea and the Prognosis of Patients in the Heart Failure Clinic. C*ongest Heart Fail.*** 2004;10 (4):177-80. http://onlinelibrary.wiley.com/doi/10.1111/j.1527-5299.2004.03317.x/epdf

Heart failure (HF) is a public health problem with ever-growing costs. Signs such as jugular venous pressure and third heart sound have been associated with disease prognosis. Symptoms of heart failure are frequently subjective, and their real value is often overlooked. The authors aimed to assess the relationship between orthopnea and left ventricular ejection fraction (LVEF) and hospitalization rate in patients referred to the HF clinic. One hundred fifty-three new consecutive patients referred to the HF clinic from September 2001 to July 2002 were reviewed. Information about orthopnea was available at baseline and at a 6-month to 1-year follow-up. One hundred thirty-one patients had a baseline multigated radionuclide ventriculogram scan, and 68 patients had a follow-up multigated radionuclide ventriculogram scan available. The patients were divided into groups by presence of orthopnea and compared with respect to LVEF and hospitalization rate. Patients with or without orthopnea had similar LVEFs at baseline (32%±17% vs. 33%±15%, respectively; p=NS). However, patients who were orthopnea-free at the follow-up visit had a significant LVEF improvement whereas patients with ongoing orthopnea at follow-up had no LVEF improvement (11%±13% vs. -1%±6%; p<0.001). Patients who presented with persistent orthopnea had a significantly higher rate of hospitalization (64% vs.15.3%; p=0.0001). Persistent orthopnea in HF patients is associated with a significantly higher rate of hospitalization and with worsening or no improvement in LVEF. Patients with persistent orthopnea may require a more aggressive approach to improve their outcome. This result may help centers with limited access to LVEF measurements to better stratify HF patients' risk.

Lucas C, Johnson W, Hamilton MA, Fonarow GC, Woo MA, Flavell CM, Creaser JA, Stevenson LW. **Freedom from Congestion Predicts Good Survival Despite Previous Class IV Symptoms of Heart Failure.** ***Am Heart J.*** 2000;140(6)840-7. https://www.sciencedirect.com/science/article/pii/S0002870300957880

BACKGROUND: This study determined whether evidence of congestion after 4 to 6 weeks of heart failure management predicted outcome for patients hospitalized with chronic New York Heart Association class IV symptoms. Class IV symptoms predict high mortality rates, but outcome is not known for patients who improve to establish freedom from congestion. Revised estimates at 1 month could facilitate decisions regarding transplantation and other high-risk interventions.

METHODS: At 4 to 6 weeks after hospital discharge, 146 patients were evaluated for congestion by 5 criteria (orthopnea, jugular venous distention, edema, weight gain, and new increase in baseline diuretics). Heart failure management included inpatient therapy tailored to relieve congestion, followed by adjustments to maintain fluid balance during the next 4 weeks.

RESULTS: Freedom from congestion was demonstrated at 4 to 6 weeks in 80 (54%) patients, who had 87% subsequent 2-year survival compared with 67% in 40 patients with 1 or 2 criteria of congestion and 41% in 26 patients with 3 to 5 criteria. The Cox proportional hazards model identified left ventricular dimension, pulmonary wedge pressure on therapy, and freedom from congestion as independent predictors of survival. Persistence of orthopnea itself predicted 38% 2-year survival (without urgent transplantation) versus 77% in 113 without orthopnea. Serum sodium was lower and blood urea nitrogen and heart rate higher when orthopnea persisted.

CONCLUSIONS: The ability to maintain freedom from congestion identifies a population with good survival despite previous class IV symptoms. At 4 to 6 weeks, patients with persistent congestion may be considered for high-risk intervention.

F R Gilliam III GAE, and R J Sweeney. **Feasibility of Automated Heart Failure Decompensation Detection Using Remote Patient Monitoring: Results from the Decompensation Detection Study.** ***J Innov Cardiac Rhythm Manage.*** 2012;3(2012):735-45. http://www.innovationsincrm.com/images/pdf/crm-03-04-735.pdf

ABSTRACT: The decompensation detection (DECODE) study collected data from cardiac resynchronization therapy device (CRT-D) patients via a remote monitoring system to develop and evaluate automated algorithms for detecting heart failure (HF) decompensation events. Patients were enrolled for up to 2 years. Device-based and patient-based data were collected via normal use of the remote monitoring system. Quarterly phone screening identified patients with potential HF events, and when events were confirmed that patient entered a more detailed following status where all medical records were examined from the time of enrollment through the completion of the study. For each such patient with a HF event, another patient without a HF event was randomly selected from the same center for data collection in the more detailed following status. These patients with more detailed following status were randomly assigned to either the development set, used to create a probability model for predicting HF events, or the sequestered evaluation set, used to evaluate the model created from the development set. We were able to produce 48% sensitivity (with two false detections per patient-year) in the development set but only 35% in the evaluation set, and we demonstrated that combining multiple measures improved performance for detection of documented HF hospital admissions or HF intravenous (IV) therapies. Automated early detection of HF decompensation using combined remote-monitored data is possible but, for the data available in this study, the performance was modest, suggesting that additional sensors that are more closely related to HF pathophysiology will be required.

Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. **Patterns of Weight Change Preceding Hospitalization for Heart Failure.** ***Circulation.*** 2007;116(14):1549-54. http://circ.ahajournals.org/content/circulationaha/116/14/1549.full.pdf

BACKGROUND: Weight gain is used by disease-management programs as a marker of heart failure decompensation, but little information is available to quantify the relationship between weight change in patients with heart failure and the risk for imminent hospitalization.

METHODS AND RESULTS: We conducted a nested case-control study among patients with heart failure referred to a home monitoring system by managed care organizations. We matched 134 case patients with heart failure hospitalization to 134 control patients without heart failure hospitalization on the basis of age, sex, duration of home monitoring, heart failure severity, and baseline body weight. Compared with control patients, case patients experienced gradual weight gain beginning approximately 30 days before hospitalization; changes in daily weight between case and control patients were statistically significant (P<0.001). Within the week before hospitalization, when weight patterns in case and control patients began to diverge more substantially, mean increases of more than 2 and up to 5 pounds, more than 5 and up to 10 pounds, and more than 10 pounds (relative to time of enrollment in the monitoring system) were associated with matched adjusted odds ratios for heart failure hospitalization of 2.77 (95% confidence interval 1.13 to 6.80), 4.46 (95% confidence interval 1.45 to 13.75), and 7.65 (95% confidence interval 2.22 to 26.39), respectively, compared with mean increases of 2 pounds or less.

CONCLUSIONS: Increases in body weight are associated with hospitalization for heart failure and begin at least 1 week before admission. Daily information about patients' body weight identifies a high-risk period during which interventions to avert decompensated heart failure that necessitates hospitalization may be beneficial.

N Varma, M Cao, EJ Schloss, R Ahmed, C Stolen, JP Boehmer. **Progressive worsening in device-base failure sensors measurements are associated with sub-optimal BiV pacing percentages in CRT-D patients.** ***European Journal of Heart Failure 2019,*** 21 (Suppl. S1), p 370. https://onlinelibrary.wiley.com/doi/10.1002/ejhf.1488

BACKGROUND: Lower percentages of BiV pacing (<98%) have been associated with significantly worse survival in a cohort of >35000 remotely monitored CRT patients. HeartLogic (HL), a heart failure (HF) composite index and alert algorithm available in both CRT-D and ICD devices, aggregates physiologic trends associated with multiple aspects of HF status (e.g. heart sounds, heart rate, thoracic impedance, respiration rate, tidal volume, and activity). HL alerts were recently shown to detect HF events with 70% sensitivity, and identify patients with 10-fold increased risk of worsening HF.

OBJECTIVE: We plan to investigate association between daily % BiV pacing and device measured individual heart failure sensors and HeartLogic.

METHODS: The LATITUDE database collects de-identified data recorded by the implanted devices from the LATITUDE remote monitoring system. Patients with HeartLogic enabled CRT-D devices and a minimum of 30 days of daily sensor data were included. All days with AF burden were excluded. Each patient day was grouped into 6 groups based on the daily % BiV pacing values (<90%, 90-91%, 92-93%, 94-95%, 96-97%, and ≥98%). For each pacing group, themean of different device sensors, the HeartLogic index, and the proportion of days in HeartLogic alert were evaluated.

RESULTS: Out of 2736 CRT-D patients, 594 met the selection criteria and had 248 alerts over 155.1 years. Sub-optimal BiV pacing percentages were associated with progressively worse device sensor values (see figure). HeartLogic index reflected significant worsening even for a small reduction in % BiV pacing. The proportion of days in HeartLogic alert was about 2x higher with <90% BiV pacing (19.08%; 95% CI 18.0-20.19) vs. ≥98% (11.29%; 95% CI 10.99-11.60; p<0.0001). Further, each individual sensor worsens with sub-optimal compared with optimal BiV pacing.

CONCLUSION: Lower %BiV pacing is associated with multiple worsening heart failure sensors. This analysis provides strong evidence that the poor survival associated lower %BiV pacing is likely caused by worsening heart failure.

N Varma, KM Stein, PH Thakur, PW Jones, R Ahmed, J Boehmer. **Multiparametric Analysis of Device Based Physiological Sensors May Identify ICD Patients Reacting Adversely to Right Ventricular Pacing [abstract]**. ***Heart Rhythm. 2019;*** 16(5):S58-S59. https://www.heartrhythmjournal.com/article/S1547-5271(19)30313-3/pdf

BACKGROUND: Uncertainty exists about the threshold of %RV pacing that might trigger heart failure in ICD recipients. Ranges between 20-40% are cited. HeartLogic is a novel devicebased multi-sensor diagnostic that collects continuous heart failure trends, and gives advance warning of heart failure decompensation.

OBJECTIVE: We sought to compare daily %RV pacing with device measured individual heart failure sensors and HeartLogic.

METHODS: The ALTITUDE database collects de-identified data recorded by connected implanted devices (LATITUDE remote monitoring). Patients with HeartLogic enabled dual chamber ICDs and a minimum of 90 days of daily sensor data were included. Each patient day was grouped as having 0 %RV pacing, and the remaining daily measurements from all patients were equally divided into 5 groups by daily %RV pacing values (1%, 2-4%, 5-10%, 11-60%, and 61-100%). For each pacing group, the mean of the HeartLogic index and each of the HeartLogic sensors were evaluated, as well as the proportion of days in HeartLogic alert.

RESULTS: Among 1654 eligible patients, 545 met inclusion criteria. Increased %RV Pacing progressively worsened some individual sensor values (figure). HeartLogic index was significantly worse for RV Pacing >10%. The proportion of days in HeartLogic alert was higher with >10% (16.01%; 95% CI 15.1- 16.9) vs <10% RV pacing (8.56%; 8.3-8.9; p<0.0001).

CONCLUSION: Individual heart failure parameters may progressively worsen with increased RV pacing, but their composite indicates risk with >10% RV pacing. Heartlogic may identify patients vulnerable to RV pacing and permit targeted interventions to improve outcomes.

Hayes DL, Boehmer JP, Day JD, Gilliam FR, 3rd, Heidenreich PA, Seth M, Jones PW, Saxon LA. **Cardiac Resynchronization Therapy and the Relationship of Percent Biventricular Pacing to Symptoms and Survival. *Heart Rhythm*.** 2011;8(9):1469-75. https://www.sciencedirect.com/science/article/pii/S1547527111004760

BACKGROUND: With the advent of cardiac resynchronization therapy, it was unclear what percentage of biventricular pacing would be required to obtain maximal symptomatic and mortality benefit from the therapy. The optimal percentage of biventricular pacing and the association between the amount of continuous pacing and survival is unknown.

OBJECTIVE: The purpose of this study was to assess the optimal percentage of biventricular pacing and any association with survival in a large cohort of networked patients.

METHODS: A large cohort of 36,935 patients followed up in a remote-monitoring network, the LATITUDE Patient Management system (Boston Scientific Corp., Natick, Massachusetts), was assessed to determine the association between the percentage of biventricular pacing and mortality.

RESULTS: The greatest magnitude of reduction in mortality was observed with a biventricular pacing achieved in excess of 98% of all ventricular beats. Atrial fibrillation and native atrial ventricular condition can limit a high degree of biventricular pacing. Incremental increases in mortality benefit are observed with an increasing percentage of biventricular pacing.

CONCLUSION: Every effort should be made to reduce native atrioventricular conduction with cardiac resynchronization therapy systems in an attempt to achieve biventricular pacing as close to 100% as possible.

M Cao, EJ. Schloss, JH Lobban, R Ahmed, CM Stolen, JP Boehmer. **Reduced LV Pacing Percentages are Associated with Progressively Worse Measures of Heart Failure Physiology in CRT Patients.** ***J Card Fail.*** 2018; 24 (8): Supplement, Pages S65–S66. https://doi.org/10.1016/j.cardfail.2018.07.282

INTRODUCTION: HeartLogic, an implanted device based heart failure (HF) index and alert algorithm, aggregates physiologic trends associated with multiple aspects of heart failure status (e.g. heart sounds, heart rate, thoracic impedance, respiration rate, tidal volume, and activity). HeartLogic alerts were recently shown to detect HF events with 70% sensitivity and 34 days of advanced warning, and identify patients with 10-fold increased risk of worsening HF. Separately, lower LV pacing percentages have been associated with significantly worse survival in a cohort of >35000 remotely monitored CRT patients. This current analysis investigated whether a deteriorating HF status would be suggested by continuous measures of heart failure pathophysiology at lower pacing percentages.

METHODS: Sensor data was obtained from 900 ambulatory HF patients with implanted CRT devices for up to a year in the MultiSENSE study. The percent of heart beats with LV pacing was assessed for periods (median = 7.3 days; IQR: 6.4 - 43.4) between data downloads (median = 55 periods/patient; IQR: 10 - 68) and compared to the sensor data. the subjective nature of auscultation, limitations of frequency range of human hearing, as well as limitations of a single snap-shot auscultation assessment as opposed to a continuous device based measure. Future studies are warranted to evaluate the clinical utility of continuous S3 monitoring in ambulatory HF patients.

RESULTS: Worsening sensor trends were found with progressively lower pacing percentages. While IN the HeartLogic alert state (above an Index of 16) the odds of optimal LV pacing (>98%) were less than when OUT of the HeartLogic alert state for a given subject (OR: 0.655; 95% CI: 0.626 - 0.686; p<0.0001).

CONCLUSION: Lower LV pacing percent is associated with multiple markers of worsening HF, and patients in HeartLogic alert are more likely to have sub-optimal LV pacing. The impact of HeartLogic alert driven interventions on the percent biventricular pacing and outcomes is being assessed in the MANAGE-HF clinical trial.

Boehmer J, Healey J, Gold M, Ahmed R, Zhang Y, Thakur P, Jones P, Capucci A. **Temporal Association of Atrial Fibrillation with Device Based Heart Failure Status in Patients with CRT. *Journal of Cardiac Failure.*** August 2019 Volume 25, Issue 8, Supplement, Page S82. https://www.onlinejcf.com/article/S1071-9164(19)31006-1/fulltext

BACKGROUND: Atrial Fibrillation (AF) is common in Heart Failure (HF). Whether AF triggers or is triggered by worsening HF is debated, although both are likely. Recently, a device based multisensory algorithm (HeartLogic) was developed that detected worsening HF events with high sensitivity. Daily sensor measurements provide detailed information about HF condition around the time of AF progression. We sought to investigate whether HF status impacted the risk of AF and if AF onset changed the risk of HF.

METHODS: The MultiSENSE study followed 900 CRT-D patients for 1 year and collected HF diagnostic sensor data including heart sounds, respiration, thoracic impedance, heart rate and activity. Patients were grouped by the longest daily atrial high rate event (AHRE) burden (24 hours, 6min to < 24 hrs, and <= 6min). HF risk was separately evaluated during the period from enrollment to AHRE and after AHRE via time to event analysis. Sensor data was aligned to the first 24-hr AF day analyzed from -60 to +60 days. For patients with no AHRE, a randomly selected day was chosen as the first AHRE day. AF risk was evaluated separately with and without sensor data via cox proportional hazard ratios.

RESULTS: Out of 900 patients, 98 had AHRE >24 hrs, 141 had AHRE <24 hrs, and 630 had AHRE < 6 min (no AHRE). HF risk was not significantly different in the three groups from enrollment to first AHRE but was significantly different post AHRE ($p<0.001$), suggesting AHRE leading to higher risk of HF. HeartLogic Index was significantly elevated in the 60 days after first 24 AHRE episode compared to 60 days pre-AHRE (19.2 post 24-hr AHRE vs 9.5 pre; $p <0.001$), whereas patients without AHRE had lower and unchanged HeartLogic Index (5.9 post random day vs 5.8 pre; $p =0.26$). Besides history of AF, baseline NT-proBNP and device based S3 prior to AHRE onset were independent predictors for the risk of AHRE (NT-proBNP: HR 1.25, 95% CI 1.07 - 1.46, $p = 0.004$); (S3: HR 3.31, 1.45 - 7.59, $p=0.005$), suggesting worsened HF status led to high risk of AHRE.

CONCLUSION: Device based sensors reflect the worsening of HF status preceding and following AF onset. AF onset significantly increases the risk of HF events while HF status (NT-proBNP and S3) is also an important factor in predicting the risk of AF, suggesting the bidirectional interactions between AF and HF.

JA Wong, MR Gold, A Capucci, R Ahmed, PH Thakur, J Boehmer, JS Healey. **The Impact of Subclinical Atrial Fibrillation on Device Based Heart Failure Status [abstract].** ***Heart Rhythm. 2019***; 16(5):S55. https://www.heartrhythmjournal.com/article/S1547-5271(19)30313-3/pdf

BACKGROUND: An analysis of the ASSERT study showed that progression of device detected subclinical AF (SCAF) was strongly associated with heart failure (HF) hospitalization. Recently, a device based multisensor algorithm (HeartLogic) was developed and shown to detect worsening HF events with high sensitivity.

OBJECTIVE: To investigate the relationship between HF and SCAF progression as assessed by HeartLogic and its individual sensors.

METHODS: The MultiSENSE study followed 900 HF patients for up to 1 year to collect HF diagnostic sensor data. At enrollment, prior year's AF data was downloaded. Patients with no history of AF and maximum duration of device detected atrial tachyarrhythmia (AADur) >6 min and <24 hrs pre-enrollment, were divided into two groups: those who progressed to 24+ hrs (at least one day of 24hr AADur) and those who did not. Sensor data was compared between the two groups using the Wilcoxon rank sum test.

RESULTS: Out of 129 patients with no history of AF at enrollment and <24 hrs of SCAF pre-enrollment, 6 experienced at least one SCAF >24 hrs. Consistent with the ASSERT analysis, SCAF progression was associated with a higher risk of HF events (age and gender adjusted relative risk: 5.93, 95% CI 1.2, 30.0, $p = 0.0366$). Multiple individual sensors and the HeartLogic index showed significant changes post SCAF progression, even though they were similar between the two groups at baseline (Table).

CONCLUSION: Multiple individual sensors and the HeartLogic index significantly change post SCAF progression and may help predict worsening of HF associated with SCAF progression.

Capucci A, Merkely B, Sweeney RJ, Zhang Y, Thakur PH, An Q, Averina V, Boehmer JP. **Atrial Arrhythmia Burden Increases Prior to Worsening Heart Failure Events [abstract].** ***Heart Rhythm.*** 2017;14(5):S216. https://www.heartrhythmjournal.com/article/S1547-5271(17)30424-1/pdf

BACKGROUND: The MultiSENSE study followed 900 heart failure (HF) patients with a CRT device for up to 1 year. Episodes of HF decompensations were collected and adjudicated as worsening HF events (WHE) by a panel of clinicians. Devices collected daily duration in atrial tachyarrhythmia (AADur) as time above atrial tachyarrhythmia trigger rate.

OBJECTIVE: We examined the relationship of AADur to WHE.

METHODS: For each patient, we found an average Atrial Arrhythmia Burden (AADur/day). Patients were grouped as Group 0 (no decompensations) or Group 1 (≥ 1 decompensations). We compared AADur/day between groups. We also compared AAdur/day in the periods prior to WHE versus other times in the same patients.

RESULTS: Of 900 enrolled patients, 870 patients had AADur measurements. Patients who decompensated had significantly ($p<0.004$) higher AADur/day than those who did not (Group 1: 97 patients, AADur/day = 124 ± 325 minutes, Group 0: 773 patients, AADur/day =73 ± 277 minutes). Ninety-six of the 97 patients who decompensated had AADur/day measures in periods prior to WHE. The table shows AADur/day during pre-event periods (up to 56-days) versus other times in the same patients.

CONCLUSION: Patient who decompensated had an increased AF burden compared to patients who did not decompensate. This burden became more pronounced in the weeks before WHE.

Pubbi D, Hudson M, Molon G, Capucci A, Slotwiner D, Cao M, Thakur PH, Averina V, Zhang Y, Wariar R, Thompson J. **AF in HF: The Chicken or the Egg? Role of CRT Device Based Sensor Data in Identifying a Causal Relationship Between AF and Worsening HF [abstract].** ***J Card Fail.*** 2016;22:S65. https://www.onlinejcf.com/article/S1071-9164(16)30331-1/abstract

PURPOSE: Atrial Fibrillation (AF) is a common co-morbidity in Heart Failure (HF). Whether AF triggers or is triggered by worsening HF is debated, although both are likely. We present a patient diagnosed with worsening HF secondary to AF with device-based sensor data that show temporal relationship between AF and HF status.

METHOD: MultiSENSE is an international multi-center feasibility study which collected up to 1 year of device-based sensor data including third heart sound (S3), intrathoracic impedence (Z), respiration rate (RR) and night-time heart rate (nHR). The sensor data were compared with clinical data such as adverse events and medication changes. Treating physicians were blinded to device sensor data.

RESULTS: The patient, enrolled on 7-Dec-11 with no history of AF, was seen by primary care physician on 1-Oct-12 and started on 20 mg/day furosemide for lower extremity edema. AF was subsequently diagnosed by cardiologist on 4-Oct and physical exam confirmed worsening HF secondary to new onset AF. Furosemide was uptitrated to 200 mg/day and patient was cardioverted on 20-Nov. Consistent with clinical presentation, acute progression of worsening HF immediately following the AF onset on 22-Sep is indicated by increased S3, RR and nHR and decreased Z. Signals improve briefly following the diuretic intervention but then worsen prior to cardioversion. AF cardioversion leads to substantial signal changes indicating an improved HF status.

CONCLUSION: In this case, device-based sensor data reflect hemodynamic impact of AF on HF status and may help identify the trigger: AF or worsening HF. Additional studies are warranted to understand if such causal relationship as established by device-based monitoring can be used to guide targeted intervention.

Hariharan R, Cao M, Sweeney RJ, Zhang Y, Averina V, An Q, Thakur PH, Boehmer JP. **Heart Failure Diagnostic Sensor Measurements Change During Atrial Arrhythmias.** ***Heart Rhythm 2017;***14(5S):S404. https://www.heartrhythmjournal.com/article/S1547-5271(17)30428-9/pdf

BACKGROUND: The Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients study (MultiSENSE) followed 900 heart failure patients with a CRT defibrillator for up to 1 year. Device software was modified to permit heart failure diagnostic sensor data to be measured and saved including - heart sounds, respiration rate and tidal volume, thoracic impedance, heart rate and activity. Devices also saved daily duration in atrial tachyarrhythmia (AADur) as time above atrial tachyarrhythmia trigger rate.

OBJECTIVE: We examined how heart failure diagnostic sensor data changed while atrial arrhythmia was present.

METHODS: On days when AADur was > 4 hours, that day was marked as AA+ while AADur < 4 hours was marked AA-. Patients were excluded from analysis if they had < 10 days with AADur or if every day was AA+ or every day was AA-. In the remaining patients (both AA+ and AA- days), we compared sensor data between AA+ and AA- days in the same patient. Wilcoxon test was used to compare AA+ versus AA- sensor data.

RESULTS: Of 900 patients, 170 were included in this analysis (43 with < 10 AADur, 17 with AA+ and 670 with AA- on all days were excluded). The table shows matched HF sensor data for AA+ versus AA- days, the % difference and Wilcoxon p for AA+ versus AA-. All heart sounds, respiration and heart rate sensors were highly significantly different while thoracic impedance and activity were not. While these AA+ measurements are in a worsening direction, it remains to be determined if this reflects worsening HF status in the presence of AF.

CONCLUSION: Heart failure diagnostic sensors including heart sounds, respiration and heart rate are significantly affected (by up to 15%) in the presence of Atrial Arrhythmia.

R Hariharan, KM Stein, RJ Sweeney, P Jones, PH Thakur, J Boehmer. **Atrial Arrhythmias Alter Device Detected Heart Failure Metrics [abstract].** ***Heart Rhythm.*** 2019; 16(5):S221-S222. https://www.heartrhythmjournal.com/article/S1547-5271(19)30315-7/pdf

BACKGROUND: The association of heart-failure (HF) trends with atrial arrhythmias (AA) has not been well quantified. Remote monitoring of devices with multiple HF sensors provides a unique opportunity to evaluate effect of AA. Objective: To determine the relationship of AA to HF as measured by heart-failure device sensors.

OBJECTIVE: To determine the relationship of AA to HF as measured by heart-failure device sensors.

METHODS: The analysis used de-identified data from US patients implanted with ICD (53) and CRT-D (159) devices capable of storing data from multiple HF sensors (Resonate™ family, Boston Scientific). Each patient day was labeled AA+ or AA-. The total duration of Atrial Tachy Response episodes for each day determined if it was AA+ (> 4 hours) or AA-. Patients with fewer than 200 days were excluded. If HF sensor data was present for both AA+ and AA- days in the same patient, it was compared using a Wilcoxon test.

RESULTS: Among 4391 eligible patients, 212 had both AA+ and AA- days. S3 heart sound was not different between AA+ and AA- days while RRT (respiratory-rate trend, 3.5%), thoracic impedance (-1%), RSBI (rapid-shallow-breathing-index, 3.3%) and respiration rate (2.5%) were slightly different. Night-time HR (12.6%) was higher for AA+ while S1 (-15.3%) and patient activity defined as accelerometer time above 28 mG (-11.5%) were lower for AA+. Finding were similar for ICD and CRT-D.

CONCLUSION: HeartLogic diagnostics are significantly affected by the presence of atrial arrhythmias and have HF diagnostic sensor changes in a direction consistent with worsening HF including patients are less active, breathe faster, have reduced S1 and higher nocturnal HR.

Cesario DA, Powell B, Cao M, Saxon L, Day J, Wold N. **Atrial Fibrillation and Outcomes in a Large Cohort of CRT Recipients: Results from the ALTITUDE Study [abstract].** ***J Am Coll Cardiol.*** 2011;57(14):E153. http://www.onlinejacc.org/content/57/14_Supplement/E153

BACKGROUND: Atrial fibrillation (AF) is a common co-morbidity in patients (pts) receiving Cardiac Resynchronization Therapy defibrillators (CRT-D). The effect of AF on pt outcomes in CRT-D remains incompletely understood. We sought to evaluate outcomes in CRT-D pts according to AF burden, using the Boston Scientific LATITUDE® remote monitoring system ALTITUDE database.

METHODS: The AF burden was determined in the first year of implant using atrial tachycardia response (ATR) episode length and pacing mode. Pts were grouped as having Persistent AF (ATR > 7 days or programmed VVI/R, DDI/R mode), Paroxysmal AF 1-7 days (1 day < ATR < 7 days), Paroxysmal AF < 1day (1 minute < ATR < 1 day), or no AF (all others). Survival after the first year was evaluated between groups using Cox Proportional Hazard models adjusting for age, gender, percent CRT pacing and shock therapy in year 1.

RESULTS: The 23,743 pts studied consisted of pts with no AF (N=13,331, 56%), Persistent AF (N=4,711, 20%), Paroxysmal AF 1-7 days (N=896, 4%), and Paroxysmal AF < 1 day (N=4,805, 20%). Pts with AF were more likely to be male (78% vs 68%), older (72 ± 11 vs 69 ± 11), have lower CRT pacing (median 97% vs 99%) and more likely to have a shock episode within 1 year post implant (13% vs 6.4%), all p<.001. When compared to no AF, all 3 AF groups exhibited decreased survival.

CONCLUSION: In a large cohort of CRT recipients, AF was identified as an independent marker for decreased survival. This observation was significant even for a very low burden of AF.

Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. **Relationship between Atrial Tachyarrhythmias and Symptoms.** ***Heart Rhythm.*** 2005;2(2):125-31. https://www.sciencedirect.com/science/article/pii/S1547527104007829

OBJECTIVES: The purpose of this study was to correlate patient-reported symptoms of atrial fibrillation with the underlying rhythm.

BACKGROUND: The reliability of patient-reported symptoms as a marker of atrial fibrillation recurrence has not been well studied.

METHODS: This prospective multicenter trial correlated the recurrence of atrial tachyarrhythmias with symptoms in patients with a history of atrial fibrillation and a standard indication for permanent pacing. Pacemaker-detected atrial tachyarrhythmia events were correlated with symptoms. Patients logged symptomatic events into the device's memory via an external manual activator. Patients were followed for 12 months and were contacted weekly to ensure compliance with activator usage. Episodes were classified as symptomatic atrial tachyarrhythmia, asymptomatic atrial tachyarrhythmia, or symptomatic nonatrial tachyarrhythmia depending on concordance between patient symptoms and the rhythm.

RESULTS: Forty-eight patients underwent implantation of a DDDRP pacemaker and were followed for 12 ± 2 months. A median of 25.0 (4.0-55.8) symptomatic events attributed to atrial fibrillation. A median of 1.0 (0.0-10.0) symptomatic atrial tachyarrhythmia episodes were documented during follow-up. Symptoms related to atrial fibrillation were reported in 6% of atrial tachyarrhythmia episodes identified by the pacemaker. The probability that symptoms were associated with an atrial tachyarrhythmia (positive predictive value) was 17%. The ventricular rate between symptomatic and asymptomatic atrial tachyarrhythmia events was not significantly different.

CONCLUSIONS: Among patients with symptomatic bradycardia and a history of atrial fibrillation, symptoms of atrial fibrillation often were not associated with documented atrial tachyarrhythmias, and more than 90% of atrial tachyarrhythmias were clinically silent.

Stevenson WG, Stevenson LW. **Atrial Fibrillation and Heart Failure—Five More Years.** ***N Engl J Med.*** 2004;351(23):2437-40. http://www.nejm.org/doi/pdf/10.1056/NEJMe048248

Drazner MH, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Califf RM, Nohria A. **Value of Clinician Assessment of Hemodynamics in Advanced Heart Failure: The ESCAPE trial.** ***Circ Heart Fail.*** 2008;1(3):170-7. http://circheartfailure.ahajournals.org/content/circhf/1/3/170.full.pdf

BACKGROUND: We determined whether estimated hemodynamics from history and physical examination (H&P) reflect invasive measurements and predict outcomes in advanced heart failure (HF). The role of the H&P in medical decision making has declined in favor of diagnostic tests, perhaps due to lack of evidence for utility.

METHODS AND RESULTS: We compared H&P estimates of filling pressures and cardiac index with invasive measurements in 194 patients in the ESCAPE trial. H&P estimates were compared with 6-month outcomes in 388 patients enrolled in ESCAPE. Measured right atrial pressure (RAP) was <8 mm Hg in 82% of patients with RAP estimated from jugular veins as <8 mm Hg, and was >12 mm Hg in 70% of patients when estimated as >12 mm Hg. From the H&P, only estimated RAP ≥12 mm Hg (odds ratio [OR] 4.6; P<0.001) and orthopnea ≥ 2 pillows (OR 3.6; P<0.05) were associated with pulmonary capillary wedge pressure (PCWP) ≥ 30 mm Hg. Estimated cardiac index did not reliably reflect measured cardiac index (P=0.09), but "cold" versus "warm" profile was associated with lower median measured cardiac index (1.75 vs. 2.0 L/min/m(2); P=0.004). In Cox regression analysis, discharge "cold" or "wet" profile conveyed a 50% increased risk of death or rehospitalization.

CONCLUSIONS: In advanced HF, the presence of orthopnea and elevated jugular venous pressure are useful to detect elevated PCWP, and a global assessment of inadequate perfusion ("cold" profile) is useful to detect reduced cardiac index. Hemodynamic profiles estimated from the discharge H&P identify patients at increased risk of early events.

Senni M, Tribouilloy CM, Rodeheffer RJ, Jacobsen SJ, Evans JM, Bailey KR, Redfield MM. **Congestive Heart Failure in the Community: A Study of all Incident Cases in Olmsted County, Minnesota, in 1991.** ***Circulation.*** 1998;98(21):2282-9. http://circ.ahajournals.org/content/circulationaha/98/21/2282.full.pdf

BACKGROUND: Data are limited regarding the classification and prognosis of patients with congestive heart failure (CHF) in the community.

METHODS AND RESULTS: Using the resources of the Rochester Epidemiology Project, we evaluated all patients receiving a first diagnosis of CHF in Olmsted County, Minnesota, in 1991 (n=216). Among these patients, 88% were ≥ 65 years and 49% were ≥ 80 years of age. The prognosis of patients with a new diagnosis of CHF was poor; survival was 86±2% at 3 months, 76±3% at 1 year, and 35±3% at 5 years. Of the 216 patients, 137 (63%) had an assessment of ejection fraction. In these patients, systolic function was preserved (ejection fraction ≥ 50%) in 59 (43%) and reduced (ejection fraction ≥ 50%) in 78 (57%). Survival adjusted for age, sex, NYHA class, and coronary artery disease was not significantly different between patients with preserved and those with reduced systolic function (relative risk, 0.80; P=0.369). ACE inhibitors were used in only 44% of the total population with CHF.

CONCLUSIONS: The present study reports the clinical characteristics and natural history of CHF as it presents in the community in the vasodilator era. CHF is a disease of the "very elderly," frequently occurs in the setting of normal ejection fraction, and has a poor prognosis, regardless of the level of systolic function. Diagnostic and therapeutic methods are underused in the community.

Stevenson LW, Perloff JK. **The Limited Reliability of Physical Signs for Estimating Hemodynamics in Chronic Heart Failure.** ***JAMA.*** 1989;261(6):884-8. https://jamanetwork.com/journals/jama/article-abstract/376284?redirect=true

The cardiovascular physical examination is used commonly as a basis for diagnosis and therapy in chronic heart failure, although the relationship between physical signs, increased ventricular filling pressure, and decreased cardiac output has not been established for this population. We prospectively compared physical signs with hemodynamic measurements in 50 patients with known chronic heart failure (ejection fraction, .18 ± .06). Rales, edema, and elevated mean jugular venous pressure were absent in 18 of 43 patients with pulmonary capillary wedge pressures greater than or equal to 22 mm Hg, for which the combination of these signs had 58% sensitivity and 100% specificity. Proportional pulse pressure correlated well with cardiac index (r = .82), and when less than 25% pulse pressure had 91% sensitivity and 83% specificity for a cardiac index less than 2.2 L/min/m^2. In chronic heart failure, reliance on physical signs for elevated ventricular filling pressure might result in inadequate therapy. Conversely, the adequacy of cardiac output is assessed reliably by pulse pressure. Our results facilitate decisions regarding treatment in chronic heart failure.

Fonarow GC. **The Acute Decompensated Heart Failure National Registry (ADHERE): Opportunities to Improve Care of Patients Hospitalized with Acute Decompensated Heart Failure.** ***Rev Cardiovasc Med.*** 2003;4 Suppl 7:S21-30. http://medreviews.com/sites/default/files/2016-11/RICM_4Supp7_S21_0.pdf

Heart failure is a leading cause of hospitalization for adults in the United States. Patients hospitalized with acute decompensated heart failure (ADHF) face a substantial risk of in-hospital mortality and rehospitalization. Despite the large number of patients hospitalized and this substantial risk, data on these patients have been limited and there has been little effort to improve the quality of care for patients hospitalized with ADHF. The Acute Decompensated HEart Failure National REgistry (ADHERE™) was designed to bridge this gap in knowledge and care by prospectively studying characteristics, management, and outcomes in a broad sample of patients hospitalized with ADHF. Participating community and university hospitals identified patients with a primary or secondary discharge diagnosis of heart failure and collected medical history, management, treatments, and health outcomes via secure web browser technology. As of July 2003, 65,180 patients have been enrolled from 263 hospitals. Initial data have provided important insights into the clinical characteristics, patterns of care, and outcomes of these patients. ADHERE documents significant delays in diagnosis and initiation of ADHF therapies as well as substantial under-use of evidence-based, guideline-recommended chronic heart failure therapies at hospital discharge. As such, there are substantial opportunities to improve the quality of care for ADHF patients in the nation's hospitals. The ADHERE Hospital Toolkit has been designed to provide hospital teams with effective proactive instruments to improve the quality of care for patients with ADHF. If successfully implemented, the improvements in short- and long-term clinical outcomes for ADHF patients are expected to be substantial.

CRT-D Systems –RESONATE™HF, RESONATE™, RESONATE™X4, VIGILANT™, VIGILANT™X4, MOMENTUM™, MOMENTUM™ X4

INDICATIONS AND USAGE
These Boston Scientific Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive stable optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications: Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms; or left bundle branch block (LBBB) with QRS duration ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure

CONTRAINDICATIONS
There are no contraindications for this device.

WARNINGS
Read this manual thoroughly before implantation to avoid damage to the pulse generator and/or lead. For single patient use only. Do not reuse, reprocess, or resterilize. Always have external defibrillation equipment available during implant and electrophysiologic testing. Ensure that an external defibrillator and medical personnel skilled in CPR are present during post-implant device testing should the patient require external rescue. Do not use defibrillation patch leads with the pulse generator system. Do not use this pulse generator with another pulse generator. Program the pulse generator Tachy Mode(s) to Off during implant, explant, or postmortem procedures. Do not kink, twist, or braid the lead with other leads. For leads that require the use of a Connector Tool, use caution handling the lead terminal when the Connector Tool is not present on the lead. Do not directly contact the lead terminal with any surgical instruments or electrical connections such as PSA (alligator) clips, ECG connections, forceps, hemostats, and clamps. Do not contact any other portion of the DF4–LLHH or DF4–LLHO lead terminal, other than the terminal pin, even when the lead cap is in place. Do not contact any other portion of the IS4–LLLL lead terminal, other than the terminal pin, even when the lead cap is in place. When implant a system that uses both a DF4–LLHH or DF4–LLHO and IS4–LLLL lead, ensure that the leads are inserted and secured in the appropriate ports. Do not use atrial tracking modes in patients with chronic refractory atrial tachyarrhythmias. Do not use atrial-only modes in patients with heart failure. Left ventricular lead dislodgement to a position near the atria can result in atrial oversensing and left ventricular pacing inhibition. Physicians should use medical discretion when implanting this device in patients who present with slow VT. Advise patients to seek medical guidance before entering environments that could adversely affect the operation of the active implantable medical device, including areas protected by a warning notice that prevents entry by patients who have a pulse generator. RESONATE HF, RESONATE, and MOMENTUM devices except for those with an RA: IS-1; RV: IS-1/DF-1; LV: LV-1 lead connection are considered MR Conditional. VIGILANT devices are considered MR Conditional. For these devices, unless all of the MRI Conditions of Use are met, MRI scanning of the patient does not meet MR Conditional requirements for the implanted system, and significant harm to or death of the patient and/or damage to the implanted system may result. For potential adverse events applicable when the Conditions of Use are met or not met, refer to the MRI Technical Guide. Do not subject a patient with an implanted pulse generator and/or lead to diathermy. If desired, ensure that Patient Triggered Monitor (PTM) is enabled prior to sending the patient home by confirming the magnet response is programmed to Store EGM. Once the PTM feature has been triggered and the magnet response set to Inhibit therapy the patient should not reapply the magnet.

PRECAUTIONS
For specific information on precautions, refer to the following sections of the product labeling: clinical considerations, sterilization and storage, implantation, device programming, environmental and medical therapy hazards, hospital and medical environments, follow up testing, explant and disposal, supplemental precautionary information. Advise patients to avoid sources of EMI because EMI may cause the pulse generator to deliver inappropriate therapy or inhibit appropriate therapy.

POTENTIAL ADVERSE EVENTS
Based on the literature and on pulse generator and/or lead implant experience, the following alphabetical list includes the possible adverse evets associated with the included devices: Air embolism; Allergic reaction; Bleeding; Bradycardia; Cardiac tamponade; Chronic nerve damage; Component failure; Conductor coil fracture; Death; Electrolyte imbalance/dehydration; Elevated thresholds; Erosion; Excessive fibrotic tissue growth; Extracardiac stimulation (muscle/nerve stimulation); Failure to convert an induced arrhythmia; Fluid accumulation; Foreign body rejection phenomena; Formation of hematomas or seromas; Heart block; Inability to defibrillate or pace; Inappropriate therapy (e.g., shocks and antitachycardia pacing (ATP) where applicable, pacing); Incisional pain; Incomplete lead connection with pulse generator; Infection including endocarditis; Insulating myocardium during defibrillation with internal or external paddles; Lead dislodgement; Lead fracture; Lead insulation breakage or abrasion; Lead perforation; Lead tip deformation and/or breakage; Local tissue reaction; Loss of capture; Myocardial infarction (MI); Myocardial necrosis; Myocardial trauma (e.g., tissue damage, valve damage); Myopotential sensing; Oversensing/undersensing; Pacemaker-mediated tachycardia (PMT); Pericardial rub, effusion; Pneumothorax; Pulse generator migration; Shunting current during defibrillation with internal or external paddles; Syncope; Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation; Thrombosis/thromboemboli; Valve damage; Vasovagal response; Venous occlusion; Venous trauma (e.g., perforation, dissection, erosion); Worsening heart failure.

For a list of potential adverse events associated with MRI scanning, refer to the MRI Technical Guide

Patients may develop psychological intolerance to a pulse generator system and may experience the following: Dependency; Depression; Fear of premature battery depletion; Fear of a device malfunction.
Additionally, potential adverse events associated with the implantation of a coronary venous lead system include: Allergic reaction to contrast media; Breakage/failure of implant instruments; Prolonged exposure to fluoroscopic radiation; Renal failure from contrast media used to visualize coronary veins. 92436222 (Rev. A)

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.

RESONATE™ HF, RESONATE™ EL, PERCIVA™ HF, PERCIVA™, VIGILANT™ EL, MOMENTUM™ EL ICD

INDICATIONS AND USAGE
Boston Scientific implantable cardioverter defibrillators (ICDs) are intended to provide ventricular antitachycardia pacing (ATP) and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias.

CONTRAINDICATIONS
Use of these Boston Scientific pulse generators are contraindicated for the following: patients whose ventricular tachyarrhythmias may have reversible cause, such as: digitalis intoxication, electrolyte imbalance, hypoxia, sepsis; or patients whose ventricular tachyarrhythmias have a transient cause, such as: acute myocardial infarction (MI), electrocution, drowning; or patients who have a unipolar pacemaker.

WARNINGS
Read this manual thoroughly before implantation to avoid damage to the pulse generator and/or lead. For single patient use only. Do not reuse, reprocess, or resterilize. Always have external defibrillation equipment available during implant and electrophysiologic testing. Ensure that an external defibrillator and medical personnel skilled in CPR are present during post-implant device testing should the patient require external rescue. Do not use this pulse generator with another pulse generator. Program the pulse generator Tachy Mode(s) to Off during implant, explant, or postmortem procedures to avoid inadvertent high voltage shocks. Do not kink, twist, or braid the lead with other leads as doing so could cause lead insulation abrasion damage or conductor damage. For leads that require the use of a Connector Tool, use caution handling the lead terminal when the Connector Tool is not present on the lead. Do not directly contact the lead terminal with any surgical instruments or electrical connections such as PSA (alligator) clips, ECG connections, forceps, hemostats, and clamps. Do not contact any other portion of the DF4–LLHH or DF4–LLHO lead terminal, other than the terminal pin, even when the lead cap is in place. Do not use atrial tracking modes in patients with chronic refractory atrial tachyarrhythmias. Tracking of atrial arrhythmias could result in ventricular tachyarrhythmias. Advise patients to seek medical guidance before entering environments that could adversely affect the operation of the active implantable medical device, including areas protected by a warning notice that prevents entry by patients who have a pulse generator. RESONATE HF, RESONATE, PERCIVA HF, PERCIVA, VIGILANT and MOMENTUM devices are considered MR Conditional. For these devices, unless all of the MRI Conditions of Use are met, MRI scanning of the patient does not meet MR Conditional requirements for the implanted system, and significant harm to or death of the patient and/or damage to the implanted system may result. Do not expose patients with non-MR conditional devices to MRI scanning. For potential adverse events applicable when the Conditions of Use are met or not met, refer to the MRI Technical Guide. Do not subject a patient with an implanted pulse generator and/or lead to diathermy. If desired, ensure that Patient Triggered Monitor is enabled prior to sending the patient home. Once the Patient Triggered Monitor feature has been triggered by the magnet and an EGM has been stored, or after 60 days have elapsed from the day that Store EGM was enabled, the patient should not apply the magnet.

PRECAUTIONS
For specific information on precautions, refer to the following sections of the product labeling: clinical considerations, sterilization and storage, implantation, device programming, environmental and medical therapy hazards, hospital and medical environments, home and occupational environments, follow up testing, explant and disposal, supplemental precautionary information.

POTENTIAL ADVERSE EVENTS
Based on the literature and on pulse generator and/or lead implant experience, the following alphabetical list includes the possible adverse evets associated with the included devices: Air embolism; Allergic reaction; Bleeding; Bradycardia; Cardiac tamponade; Chronic nerve damage; Component failure; Conductor coil fracture; Death; Elevated thresholds; Erosion; Excessive fibrotic tissue growth; Extracardiac stimulation (muscle/nerve stimulation); Failure to convert an induced arrhythmia; Fluid accumulation; Foreign body rejection phenomena; Formation of hematomas or seromas; Heart block; Heart failure following chronic RV apical pacing; Inability to defibrillate or pace; Inappropriate therapy (e.g., shocks and antitachycardia pacing (ATP) where applicable, pacing; Incisional pain; Incomplete lead connection with pulse generator; Infection including endocarditis; Insulating myocardium during defibrillation with internal or external paddles; Lead dislodgement; Lead fracture; Lead insulation breakage or abrasion; Lead perforation; Lead tip deformation and/or breakage; Local tissue reaction; Loss of capture; Myocardial infarction (MI); Myocardial necrosis; Myocardial trauma (e.g., tissue damage, valve damage); Myopotential sensing; Oversensing/undersensing; Pacemaker-mediated tachycardia (PMT); Pericardial rub, effusion; Pneumothorax; Pulse generator migration; Shunting current during defibrillation with internal or external paddles; Syncope; Tachyarrhythmias, which include acceleration of arrhythmias and early, recurrent atrial fibrillation; Thrombosis/thromboemboli; Valve damage; Vasovagal response; Venous occlusion; Venous trauma (e.g., perforation, dissection, erosion); Worsening heart failure.

For a list of potential adverse events associated with MRI scanning, refer to the MRI Technical Guide

Patients may develop psychological intolerance to a pulse generator system and may experience the following: Dependency; Depression; Fear of premature battery depletion; Fear of a device malfunction. 92436178 (Rev. B)

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.

LATITUDE™ NXT Patient Management System

INTENDED USE
The LATITUDE™ NXT Patient Management System is intended for use to remotely communicate with a compatible pulse generator from Boston Scientific CRM and transfer data to a central database. The LATITUDE NXT System provides patient data that can be used as part of the clinical evaluation of the patient.

CONTRAINDICATIONS
The LATITUDE NXT Patient Management System is contraindicated for use with any implanted device other than a compatible Boston Scientific implanted device. Not all Boston Scientific implanted devices are compatible with the LATITUDE NXT System. For contraindications for use related to the implanted device, refer to the System Guide for the Boston Scientific implanted device being interrogated.

PRECAUTIONS
Alerts may appear on the LATITUDE NXT website on a daily basis. Primary notification of alert conditions is through the View Patient List page on the LATITUDE NXT website. The clinician needs to log onto the LATITUDE NXT website in order to receive alerts. Although secondary notification through email and SMS text messages is available, these reminders are dependent on external systems and may be delayed or not occur. The secondary notification feature does not eliminate or reduce the need to check the website. Implanted device data and alerts are typically available for review on the LATITUDE NXT website within 15 minutes of a successful interrogation. However, data uploads may take significantly longer (up to 14 days). If the Communicator is unable to interrogate the implanted device or if the Communicator is unable to contact the LATITUDE NXT server to upload data, up to 14 days may elapse before the LATITUDE NXT server detects these conditions and informs the clinic user that monitoring is not occurring. If both of these conditions occur at the same time, this notification could take up to 28 days. Implanted device data and alert notification may be delayed or not occur at all under various conditions, which include but are not limited to the following: System limitations; the Communicator is unplugged; the Communicator is not able to connect to the LATITUDE NXT server through the configured phone system; the implanted device and the Communicator cannot establish and complete a telemetry session; the Communicator is damaged or malfunctions; the patient is not compliant with prescribed use or is not using the LATITUDE NXT System as described in the patient manual; if subscribed to the LATITUDE Cellular Data Plan, missing two or more payments discontinues the subscription; the clinic user can identify any patients that are not being monitored as described above by using the Not Monitored filter on the View Patient List.

ADVERSE EFFECTS:
None known.

SYSTEM LIMITATIONS:
The LATITUDE NXT System does not provide continuous real-time monitoring. As a remote monitoring system, the LATITUDE NXT System provides periodic patient monitoring based on clinician configured settings. There are many internal and external factors that can hinder, delay, or prevent acquisition and delivery of implanted device, sensor, and patient information as intended by the clinician. These factors include: implanted device clock; patient environment; cellular data service; telephone system; communicator memory capacity; clinic environment; schedule/configuration changes; or data processing. 92436260 (Rev. A)

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician. Rx only. Prior to use, please see the complete "Directions for Use" for more information on Indications, Contraindications, Warnings, Precautions, Adverse Events, and Operator's Instructions.

Boston Scientific
Advancing science for life™

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Patients and Families:
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CRM-544804-AC

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