Welcome to issue 28 of Heart Failure Research Review.

Research selected for this issue includes a paper on takotsubo (stress) cardiomyopathy, reporting increased prevalences of neurological and psychiatric disorders. Research in elderly patients hospitalised with pneumonia found that the risk of new-onset HF is increased in the intermediate- and long-term postdischarge periods. Danish researchers found that important prognostic information for CRT candidates was provided by contraction pattern assessment to identify true LBBB activation. This issue concludes with research reporting a prognostic role for CHA\_2DS\_2-VASc risk stratification for predicting future thromboembolic events in patients with HF in sinus rhythm.

I hope you find the research selected for this issue interesting. I enjoy your feedback, so please keep it coming.

Kind Regards,
Dr. John Atherton
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Adaptive servo-ventilation for central sleep apnea in systolic heart failure

Authors: Cowie MR et al.

Summary: Patients with CSA (central sleep apnoea), LVEF ≤45%, AHI (apnoea-hypopnea index) of ≥15 events per hour and a predominance of central events (n=1325) were randomised to receive guideline-based medical treatment with or without adaptive servoventilation. The mean AHI at 12 months was 6.6 events per hour in the adaptive servoventilation arm. No significant difference was seen between the adaptive servoventilation and control arms for the primary endpoint of death from any cause, lifesaving CV intervention or unplanned hospitalisation for worsening HF (54.1% vs. 50.8% [p=0.10]), but adaptive servoventilation was associated with higher risks of all-cause and CV mortality (respective HRs 1.28 [95% CI 1.06–1.55] and 1.34 [1.09–1.65]).

Comment: CSA is an adverse prognostic marker in HF. The CANPAP study previously demonstrated no benefit of continuous positive airways pressure in HFREF patients with predominant CSA; however, a subsequent post hoc analysis suggested that mortality was lower in patients whose CSA was largely abolished by continuous positive airways pressure. However, the SERVE-HF study demonstrated that whilst adaptive servoventilation was successful in treating CSA, it did not improve outcomes in HFREF patients with predominant CSA. Indeed, the group randomised to receive servoventilation had higher CV mortality. This study suggests that CSA may be an adaptive (rather than maladaptive) response, and that the primary therapeutic approach should be to treat the underlying HF.


Abstract

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Abbreviations used in this issue:

2D-SE = two-dimensional strain echocardiography; AF = atrial fibrillation; CRT = cardiac resynchronisation therapy; CSA = central sleep apnoea; CV = cardiovascular; ECG = electrocardiography; EF = ejection fraction; HF = heart failure; HFREF = HF (with preserved/reduced) EF; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LV = left ventricular; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

In this issue:

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- Impaired systolic function in HFPEF and the impact of spironolactone
- Changes in LVEF and outcomes in primary prevention ICD and CRT recipients
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- Thromboembolic risk stratification of patients hospitalised with HF in sinus rhythm

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Clinical features and outcomes of takotsubo (stress) cardiomyopathy

Authors: Templin C et al.

Summary: These authors reported clinical features, prognostic predictors and outcomes of 1750 patients (89.8% women) registered in the International Takotsubo Registry. Physical triggers were more common than emotional ones (36.0% vs. 27.7%), and no trigger was evident for 28.5% of the patients. Compared with patients with acute coronary syndromes, patients with takotsubo cardiomyopathy had higher rates of neurological or psychiatric disorders (55.8% vs. 25.7% [p<0.001]) and their mean LVEF was lower (40.7% vs. 51.5% [p<0.001]), but severe in-hospital complications, including shock and death, did not differ significantly (p=0.95). Independent predictors of in-hospital complications were physical triggers, acute neurological or psychiatric diseases, high troponin levels and low EF on admission. The respective major adverse cardiac/cerebrovascular event and mortality rates were 9.9% and 5.6% per patient-year over long-term follow-up.

Comment: The 91 female predominance for takotsubo cardiomyopathy is well established, with 79% of patients in this study women aged over 50 years. Whilst emotional triggers were identified in approximately one-quarter of cases, over one-third were preceded by a physical trigger. Although often considered relatively benign, the in-hospital rate of major adverse events was similar to that seen in patients with acute coronary syndromes, and the subsequent mortality rate was 5.6% per annum. The rate of recurrence was 1.8% per annum, spanning between 25 days and 9 years. The high prevalence of neurological and psychiatric disorders is interesting, and suggests that these factors should be considered in the secondary prevention of further episodes.


Abstract

Soluble CD146, a new endothelial biomarker of acutely decompensated heart failure

Authors: Gayat E et al.

Summary: These researchers measured NT-proBNP and soluble CD146 levels in 391 patients presenting to an emergency department with acute dyspnoea. Areas under the receiver operating characteristic curves for acute decompensated HF diagnosis were 0.86 and 0.90 for soluble CD146 and NT-proBNP, respectively. Adding soluble CD146 to NT-proBNP levels improved the diagnostic performance for patients lying in the NT-proBNP grey zone (p=0.02) and had potential for ruling-out acute decompensated HF. An experimental rat model of acute decompensated HF suggested that CD146 expression occurs in the intima of large arteries and is associated with both LV function and organ congestion.

Comment: This multicentre study involving four European countries demonstrated that soluble CD146 (which has up to now been considered a marker of endothelial dysfunction) had similar diagnostic accuracy to NT-proBNP in distinguishing cardiac and noncardiac dyspnoea in the emergency department setting. Furthermore, it appeared to be particularly useful in reclassifying patients with a 'grey-zone' NT-proBNP. These findings will need to be independently validated, and future studies will need to evaluate its incremental utility compared with other putative HF biomarkers.


Abstract

Intermediate and long-term risk of new-onset heart failure after hospitalization for pneumonia in elderly adults

Authors: Corrales-Medina VF et al.

Summary: The relationship between pneumonia and HF was explored in 5513 elderly US Cardiovascular Health Study enrollees without baseline HF during 1989–1994 who were followed until 2010. There were 652 participants hospitalised for pneumonia still alive and free of HF by day 30 posthospitalisation, and new-onset HF occurred in 22 participants during days 31–90 (HR 6.9 [95% CI 4.46–10.63]), 14 between 91 days and 6 months (3.2 [1.88–5.50]), 20 between 6 months and 1 year (2.6 [1.64–4.04]), 76 during 1–5 years (1.7 [1.30–2.12]) and 71 after 5 years (2.0 [1.56–2.58]).

Comment: Although pneumonia has previously been identified as a trigger for HF, this analysis suggests a longer term risk of incident HF, similar to that seen with established HF risk factors. Whilst it is difficult to completely exclude the possibility of pre-existing subclinical HF or shared risk factors, the authors undertook a number of analyses that suggest there may be a mechanistic link. Either way, these findings suggest that a diagnosis of pneumonia may provide an opportunity to screen for HF or structural heart disease. Furthermore, they emphasise the importance of considering broader approaches to disease management in chronic disease.


Abstract

Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation

Authors: Russo AM et al.

Summary: This research in 38,912 patients aged >65 years from the US NCDR (National Cardiovascular Data Registry) who received single- or dual-chamber ICDs for primary prevention compared postdischarge procedure-related complications and outcomes between genders. Compared with men, women had greater comorbidity and more advanced HF at ICD implantation, and had higher rates of device-related complications (7.2% vs. 4.8%; adjusted odds ratio 1.39 [95% CI 1.26–1.53]), 6-month mortality (6.5% vs. 5.6%; 1.08 [0.98–1.20]), 6-month all-cause readmissions (37.2% vs. 31.7%; 1.22 [1.16–1.28]) and 6-month HF readmissions (14.0% vs. 10.0%; 1.32 [1.23–1.42]).

Comment: Women have been under-represented in the randomised controlled trials evaluating the efficacy of ICD therapy; however, a recent meta-analysis reported no significant difference in the mortality relative odds ratios between men and women. The current study compared older men and women who received a primary prevention ICD in real-world practice, with a focus on postdischarge outcomes. Whilst the higher complication rate in women may be anticipated based upon differences in body size and underlying disease severity, these differences persisted in adjusted analyses and were accompanied by higher HF and all-cause hospitalisation rates and a trend to higher mortality. Whilst the possibility of unmeasured residual confounders such as frailty and comorbidity severity remains, future studies will need to determine whether these findings apply in other healthcare systems.


Abstract

Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone

Authors: Shah AM et al.

Summary: Using two-dimensional speckle-tracking echocardiography, these researchers ascertained that 52% of 447 participants with HFPEF from the TOPCAT trial had impaired LV longitudinal strain. During median follow-up of 2.6 years, 115 participants experienced a primary composite outcome event (CV death, HF hospitalisation or aborted cardiac arrest), and the risk was increased in the participants with impaired LV longitudinal strain (adjusted HR 2.14 [95% CI 1.26–3.66]), as were the individual risks of CV death (3.20 [1.44–7.12]) and HF hospitalisation (2.23 [1.16–4.28]). Furthermore, among echocardiographic predictors of the composite outcome, LV longitudinal strain was the strongest. An exploratory analysis of 131 participants with LV longitudinal strain assessed after 12–18 months showed that spironolactone was associated with a trend toward LV longitudinal strain improvement, but only in participants enrolled in the Americas, not in Russia or Georgia.

Comment: Previous studies using myocardial deformation indices have identified abnormal systolic function in some patients with HFPEF. This subgroup analysis from the TOPCAT study identified that 52% of their HFPEF patients had reduced absolute mean longitudinal strain (<15.8%), although >90% of these patients had associated LV hypertrophy and/or increased E/E'. Abnormal longitudinal strain was an adverse prognostic marker, even when the analysis was restricted to patients with an LVEF >55%. Our current definition of HFPEF captures a broad range of cardiac and noncardiac conditions with differing mechanisms contributing to their clinical phenotype. Ideally, future HFPEF studies should include measures of myocardial deformation to determine whether this could be used to guide treatment selection and monitor response to therapy.


Abstract
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**Prognostic role of serum chloride levels in acute decompensated heart failure**

**Authors:** Grodin JL et al.

**Summary:** This research investigated the prognostic significance of serum chloride levels in relation to serum sodium levels in 1318 consecutive patients with chronic HF admitted for acute decompensated HF. An independent inverse association was seen between each unit change in serum chloride level on admission and long-term mortality (adjusted HR 0.93 [95% CI 0.90–0.97]), whereas sodium levels on admission were not significantly related after multivariate risk adjustment (p=0.05); a similar relationship was seen between each unit change in serum chloride level on admission and 1-year mortality in an independent validation cohort of 876 patients with acute decompensated HF (HR 0.95 [0.92–0.99]).

**Comment:** In this cohort of consecutive patients admitted with acute decompensated HF, serum chloride levels were inversely associated with markers of neurohormonal activation and mortality, with serum chloride levels <96 mEq/L being associated with higher mortality. Furthermore, serum chloride level appeared to be a stronger prognostic marker than serum sodium level, which was no longer predictive in a multivariable model that incorporated serum chloride level. These results were subsequently confirmed in a validation cohort. Future studies are required to confirm these findings and determine whether they apply in patients with either HFPEF or HFrEF.

**Reference:** J Am Coll Cardiol 2015;66(6):659–66

**Abstract**

**Thromboembolic risk stratification of patients hospitalized with heart failure in sinus rhythm**

**Authors:** Wolok E et al.

**Summary:** These researchers investigated the use of CHA2DS2-VASc score for identifying, and its prognostic value for, thromboembolic complications in a cohort of 136,545 oral anticoagulant nonrecipients admitted with HF in sinus rhythm. Patients with all CHA2DS2-VASc risk factors were at greater risk of thromboembolism than those with HF alone (HR 9.2 [95% CI 6.8–12.5]), with clinically significant rates averaging 6.0 events per 100 patient-years during the first year postdiagnosis. Independent risk factors for thromboembolism included diabetes, age, vascular disease and prior thromboembolism.

**Comment:** This study identified that the CHA2DS2-VASc score was predictive of thromboembolic events in HF patients with no documented AF or atrial flutter. Although the event rates were higher in the early postdischarge period, the subsequent rates were lower than that seen in AF. Whilst it is possible that some patients had either undocumented or undiagnosed AF, this study suggests that thromboembolic scoring systems could be used to risk stratify HF patients in sinus rhythm. However, previous randomised controlled trials of warfarin therapy have not identified a favourable risk-benefit profile. Studies are required to address the safety and efficacy of NOACs (nonvitamin K oral anticoagulants) in this setting.

**Reference:** Eur J Heart Fail 2015;17(8):828–36

**Abstract**

**Identification of typical left bundle branch block contraction by strain echocardiography is additive to electrocardiography in prediction of long-term outcome after cardiac resynchronization therapy**

**Authors:** Rísum N et al.

**Summary:** The association between absence of a typical LBBB mechanical activation pattern by 2D-SE (two-dimensional strain echocardiography) and unfavourable long-term outcomes was explored in 208 candidates for CRT (New York Heart Association classes II–IV, EF ≤35%, QRS duration ≥120 msec) with LBBB on ECG; a typical LBBB contraction pattern was identified in 63% of the patients. A primary endpoint event (death, LV assist device or heart transplant over 4 years) was recorded for 23% of the patients. The risk of an adverse outcome was increased for using echocardiographic-dyssynchrony measures (using time-to-peak indices) to select patients for CRT. In this study, 2D-SE was performed in patients with LBBB on their 12-lead ECG who were undergoing CRT. Patients without a typical LBBB contraction pattern had worse outcomes. Whilst, it is tempting to speculate that these patients were ‘CRT nonresponders’, the absence of a control group does not allow this. It would be interesting to test whether 2D-SE could be used to select CRT in patients with an intermediate QRS duration (120–140 msec), especially given that only one-third of these patients had a typical LBBB contraction pattern. However, even if 2D-SE did identify CRT responders, broader application would require vendor-independent measures and be facilitated by an automated approach.

**Comment:** The PROSPECT and ECHO-CRT studies have decreased enthusiasm for using echocardiographic-dyssynchrony measures (using time-to-peak indices) to select patients for CRT. In this study, 2D-SE was performed in patients with LBBB on their 12-lead ECG who were undergoing CRT. Patients without a typical LBBB contraction pattern had worse outcomes. Whilst, it is tempting to speculate that these patients were ‘CRT nonresponders’, the absence of a control group does not allow this. It would be interesting to test whether 2D-SE could be used to select CRT in patients with an intermediate QRS duration (120–140 msec), especially given that only one-third of these patients had a typical LBBB contraction pattern. However, even if 2D-SE did identify CRT responders, broader application would require vendor-independent measures and be facilitated by an automated approach.

**Reference:** J Am Coll Cardiol 2015;66(8):631–41

**Abstract**

**Changes in follow-up left ventricular ejection fraction associated with outcomes in primary prevention implantable cardioverter-defibrillator and cardiac resynchronization therapy device recipients**

**Authors:** Zhang Y et al.

**Summary:** Changes in LVEF over mean 4.9 years of follow-up after ICD implantation for primary prevention were evaluated in a prospective cohort of 538 patients. Decreases in LVEF were seen in 13.0% of the patients, increased in 40.0% and there was no change in 47.0%. Compared with no change in LVEF, an improved LVEF was associated with significant reductions in the risks of death (HR 0.33 [95% CI 0.18–0.59]) and appropriate (i.e. for ventricular tachyarrhythmia) shock (0.29 [0.11–0.78]). An LVEF improvement to >35%, which was seen in one-quarter of the patients, decreased but did not eliminate their risk of appropriate shock.

**Comment:** These findings are consistent with other observational studies and a recent report from MADIT-CRT. As expected, improved LVEF was associated with better survival and a reduced rate of appropriate shocks, although appropriate shocks still occurred in four out of 134 patients whose LVEF had increased to >35%. Unfortunately, the event rate in patients with an LVEF >55% were not reported separately, although the final numbers would have been small. This study suggests that whilst the decision to replace an ICD generator (or downgrade to CRT alone) may be informed by the subsequent change in LVEF, other factors also contribute to the residual risk of sudden death events.

**Reference:** J Am Coll Cardiol 2015;66(5):524–31

**Abstract**

**Heart Failure Research Review**

**Independent commentary by Dr. John Atherton**

Director of Cardiology at the Royal Brisbane and Women’s Hospital, Associate Professor, University of Queensland and Adjunct Professor, Queensland University of Technology. He previously chaired the Asia-Pacific Acute Decompensated Heart Failure Registry SAC and the CSANZ Heart Failure Council. He has been an appointed member of the Australian Government Medical Services Advisory Committee and sat on the National Heart Foundation Heart Failure Guidelines executive writing group. Research interests include investigating novel methods to detect presymptomatic cardiac disease and cardiac genetics. Contributions to statewide service enhancement include coordinated heart failure disease management and co-establishing a cardiac genetics service.