

Chronotropic incompetency during stress echocardiography: a new paradigm for mortality and cardiac event prediction?

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This editorial refers to ‘Chronotropic incompetence during exercise or pharmacological stress is associated with reduced survival in patients with chronic coronary syndromes’, by L. Cortigiani et al. <https://doi.org/10.1093/eurjpc/zwaf492>.

Introduction

Stress echocardiography (SE) has gained recognition as a non-invasive diagnostic imaging modality to assess patients with suspected chronic coronary syndrome (CCS). Since exercise SE was introduced in the 1970s, the widened spectrum of stressors such as inodilators (dobutamine) or vasodilators (adenosine, dipyridamole, and recently regadenoson) continues to be rolled out to patients who are otherwise unsuitable for treadmill or supine bicycle ergometer exercise. The last three decades of advancement of ultrasound technology including transducer and software technology, iterative image reconstruction, and the development of ultrasound enhanced agents led to significant improvement of ultrasound image quality and accurate detection of inducible regional wall motion abnormalities (RWMA).¹ This contributed to the level I-A recommendation of SE in the diagnosis of CCS patients.²

Heart rate response during stress echocardiography and all-cause mortality

In this current report by Cortigiani et al.,³ the ‘Stress Echo 2030’ consortium analysed data collected prospectively between August 2001 and February 2024 across 19 echocardiography centres in 10 countries. Analysis consisted of 13 445 patients investigated with various

SE modalities. Dipyridamole SE was most commonly used (63%). Chronotropic incompetence (CI) was defined based on the heart rate (HR) response to stress. For exercise and dobutamine SE, this was 85% of maximum age predicted HR (MPHR) and for vasodilator SE a HR reserve (peak/rest HR) of ≤ 1.22 and ≤ 1.17 for those in atrial fibrillation (AF). The prognostic value of CI over a median follow-up of 3.4 years was assessed. Mortality at 10 years was nearly two-fold higher in patients with CI (39% vs. 21%; $P < 0.0001$). In multivariate analysis, significant independent predictors of mortality were age, male sex, diabetes mellitus (DM), left ventricular ejection fraction (LVEF), resting HR, and CI. Predictors of CI were age, DM, hypertension, prior myocardial infarction (MI) and coronary artery bypass grafting (CABG), LVEF, resting HR, and ongoing beta-blocker therapy. In a sensitivity analysis, multivariable analysis found that CI predicted all-cause mortality regardless of SE modality. Further, CI showed prognostic value in patients with and without inducible RWMA. Lastly, CI predicted mortality in both normal sinus rhythm (SR) and in those with AF.

Definition of chronotropic incompetence

In this study, the definition of CI was different between SE modalities, which carries a theoretical as well as methodological contradiction. In a pivotal paper in 1993, Katritsis and Camm⁴ proposed a definition of CI as ‘the inability of the heart to increase its rate in proportion to metabolic demand derived from exercise induced HR changes’.

This and subsequent studies proposed different cut points of defining CI, with 85% of MPHR being consistently used during exercise and dobutamine stress tests.⁵ There was an attempt to adopt CI into vasodilator stress with albeit less established evidence, proposed as HR reserve,⁶ used in the current study. Importantly, there is a strong association between CI and several chronic medical conditions relevant in patients undergoing SE that can influence HR response to stress (e.g.

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DM, hypertension, coronary disease, and other conditions such as hypertrophic cardiomyopathy, heart failure with preserved left ventricular systolic function, etc.).

The mechanism of heart rate response to different stress echocardiography modalities

Exercise stress echocardiography

The mechanism of HR response to exercise is primarily due to parasympathetic withdrawal and sympathetic augmentation.⁷ Noradrenaline as the mediator of increased sympathetic tone during exercise is released by cardiac afferent nerve endings. These afferents relay signals from baroreceptors and the intrinsic cardiac nervous system to the brainstem via the nucleus tractus solitarius, activating cardiac efferent nerves that stimulate the sinus node via β_1 receptors and parasympathetic withdrawal via muscarinic receptors.

Dobutamine stress echocardiography

Heart rate response to dobutamine stress is a result of a combined direct stimulatory effect of dobutamine on α , β_1 , and β_2 receptors on the sinus node the myocardium and the vasculature and it acts as a venodilator.⁸ Dobutamine SE protocol encompasses the use of atropine as a reversible non-specific muscarinic receptor antagonist, with affinity for the M1-5, receptor subtypes causing parasympathetic blockade on the sinus node and AV node.⁹ The authors did not provide detail on the use of atropine, which could influence the achieved maximum HR and thus CI, particularly in blunted HR responses. Authors stated that a maximum 1 mg IV atropine was used at the operator's discretion which is lower than routine practice and recommendations by societal guidelines (1.2–2 mg IV in total).¹⁰ Importantly, some SEs may be stopped prematurely if extensive RWMA develop (peak WMSI: 1.45 or more) or widespread ST changes or limiting anginal symptoms were triggered potentially affecting achieved maximum HR.

Vasodilator stress echocardiography

With vasodilator stress, exogenous adenosine or endogenous adenosine (after dipyridamole infusion) activates cardiac afferent neurons via A2 adenosine receptors.¹¹ The effect via the A2 receptors causes maximal vasodilatation in the vasculature including the coronary arteries that results in three- to five-fold increase of the basal blood flow. During vasodilator SE, the blood can be stolen from the already maximally vasodilated coronaries due to flow limiting stenosis that can lead to RWMA. The effect of adenosine on the HR regulation is less established. A recent review article summarizes the A2 agonistic effect of vasodilators predominantly causing bradycardia and potentially inducing hypotension that subsequently can cause reflex HR elevation.¹²

Chronotropic incompetence as autonomic function, a claim step too far?

Chronotropic incompetence as a marker of autonomic dysfunction needs further verification. Non-invasive assessment of autonomic function based on short-term (5–10 min) HR variability (HRV) to characterize sympathovagal balance by spectral analysis or simultaneous recording of R-R intervals and beat-by-beat systolic blood pressure variability and the derived short-term baroreflex sensitivity (BRS) could

still be a future sub-study of the authors' claim of the association between CI and autonomic dysfunction.

Chronotropic incompetence during exercise and dobutamine stress echocardiography in patients with normal sinus rhythm: complimentary results from the Stress Echo 2030 and EVAREST studies

Considering the ambiguity regarding the regulations of HR in AF and the various CI definitions, it was encouraging to see a sub-analysis of the data in both exercise and dobutamine SE in those with SR only (4881/13446, 36%). Adjusted prognostic value of CI on all-cause mortality remained similar to the entire cohort. Further, this sub-analysis demonstrated the independent prognostic value of various demographic and physiological variables on all-cause mortality (Supplementary Table 3).³

Comparatively, the EVAREST study in the UK has provided a secondary analysis of 5752 patients undergoing dobutamine (73%) and exercise SE (27%) with mean follow-up of 2.7 years. Normal SR was present in 3601 participants with details of HR response during SE (THR defined as 85% of MPHR), with a prevalence of CI of 18% (664/3601). A composite endpoint of cardiovascular mortality and non-fatal MI was established. There were 102 cardiovascular deaths and non-fatal MIs (2.8%). Survival analysis showed a significant difference of the composite outcome between the CI negative (74) and positive (28) cases (Figure 1). Intriguingly, multivariate analysis showed that age, male sex, SE positivity, CI, DM, and baseline HR were independent predictors of the composite outcome. Beta-blocker therapy, however, was not (Figure 1). The effect in the EVAREST cohort was much smaller due probably to the lower risk group recruited or limitations in outcome data linkage to national databases. The patients in the EVAREST cohort with CI were younger, 62 vs. 65 years, with less hypertension (49% vs. 54%), a higher proportion of prior MI (19% vs. 16%), prior PCI (31% vs. 26%), more positive tests, (20% vs. 15%), lower baseline HR (73 b.p.m. vs. 78 b.p.m.), lower peak HR (127 b.p.m. vs. 143 b.p.m.), and lower peak systolic BP (152 mmHg vs. 158 mmHg) compared with patients with no CI (all $P < 0.05$).

Conclusion

These results from Cortigiani *et al.* are unique and important to understanding the prognostic value of HR response in SE, beyond inducible RWMA. New data from the EVAREST study complement this work by illustrating the prognostic value of CI in predicting cardiac-specific outcomes. These results are intriguing, but the clinical value is debatable. As trained specialists in SE, we should still focus on the assessment of RWMA as the hallmark of inducible ischaemia during any form of SE and the addition of distal left anterior descending artery coronary flow velocity reserve especially in non-occlusive coronary artery disease. The CI as a marker of autonomic dysfunction during pharmacological SE is contentious. Future sub-studies using HRV or BRS, could shed some light on this assertion. Perhaps, a meta-analysis of the existing data and/or an AI-based algorithm can help to interpret and use extended SE data including the SE 'alphabet' and CI for diagnosing and more importantly risk stratifying patients for early intervention if intensified risk management and guideline-directed medical therapy fails. Still,

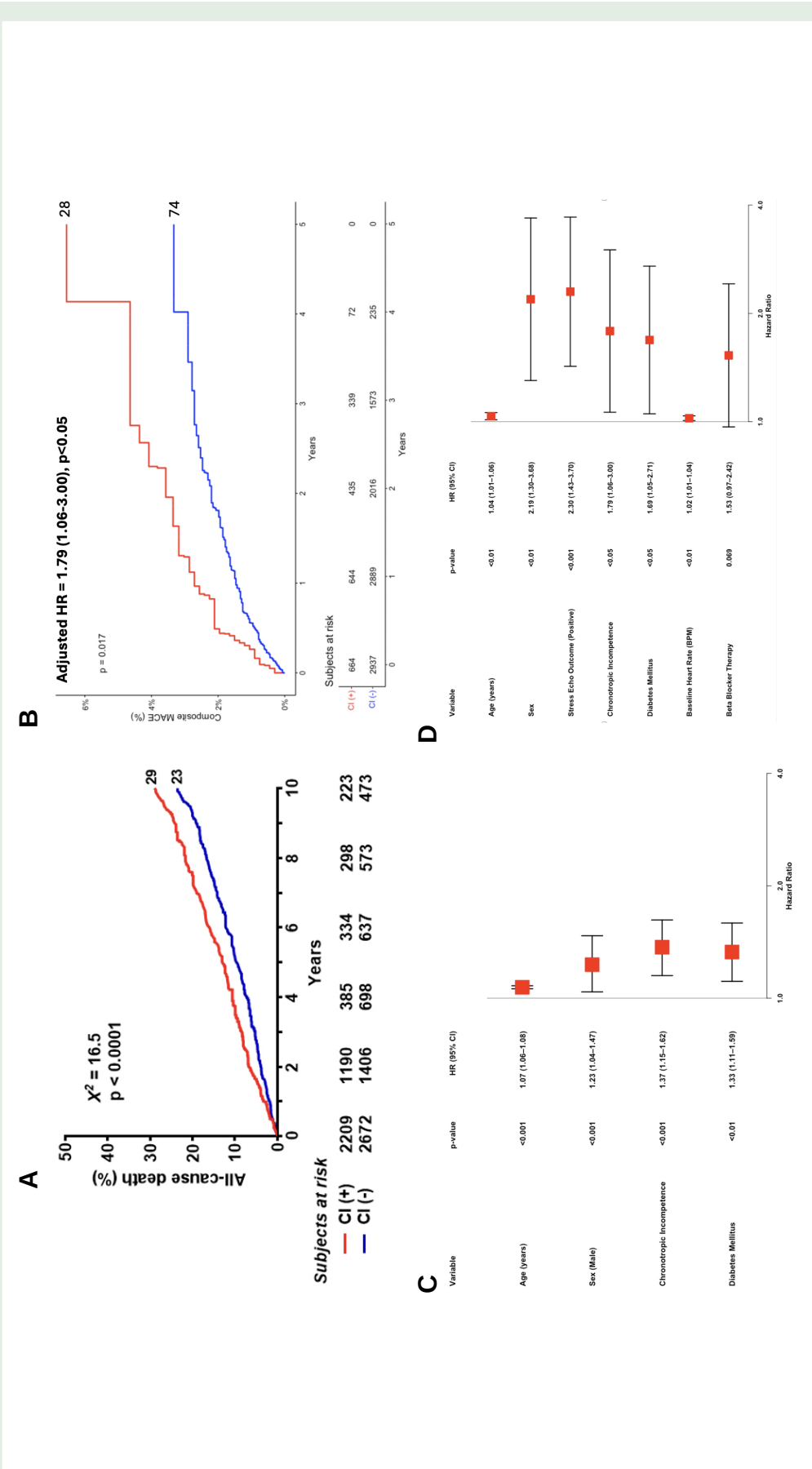


Figure 1 Kaplan–Meier survival curves of patients in normal sinus rhythm with and without chronotropic incompetence undergoing dobutamine or exercise stress echocardiography in the Stress Echo 2030 and EVAREST studies. (A) The Stress Echo 2030 database shows all-cause mortality over 10 years of follow-up. (B) The EVAREST study shows the 5-year composite endpoint of cardiac death and non-fatal myocardial infarction. The lower panel shows the forest plot of the Cox proportional hazard for multivariable analysis for (C) the Stress Echo 2030 database and (D) the EVAREST study. Note the independent predictive value of long-term outcome of chronotropic incompetence in both cohorts. (A and C) Unpublished results by Cortigiani *et al.*, (B and D) Unpublished results by the authors of the editorial.

we must continue to utilize echocardiography as an accessible, accurate, and cost-effective test for helping diagnose and guide management of our patients.

Author contribution

A.K. was asked to write an accompanying editorial. A.K. has conceived the context, EVAREST data collection, and idea for sub-analysis of the database for helping data comparison for editorial. A.K. has requested the corresponding authors from the original manuscript (Cortigiani L) to provide time to event analysis on the subgroup, compiled the figure, and drafted the editorial with critical final appraisal. C.J. has analysed the EVAREST sub-study and interpretation of data, contributed to the figure design, and gave critical appraisal to the final draft of the editorial. P.L. is the chief investigator for EVAREST, approved the figure, and critically appraised the final draft of the editorial.

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Data availability

Data Availability-On request data are available at the discretion of the authors.

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