Exercise intolerance due to chronotropic incompetence uncovered by cardiopulmonary exercise test: an often overlooked manifestation of ischaemic heart disease

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Abstract
A 60-year-old delivery man was referred for evaluation of unexplained exertional dyspnoea despite initial non-diagnostic investigations, including pulmonary function tests and dobutamine stress echocardiography. A symptom-limited cardiopulmonary exercise test (CPET) revealed chronotropic incompetence (CI), reduced oxygen uptake (VO2)/work slope at moderate–high workload, and ST-segment depression on recovery electrocardiogram. Coronary angiogram confirmed severe stenosis in right coronary artery and left anterior descending artery, for which he underwent percutaneous coronary stenting and cardiac rehabilitation. An interval CPET showed improvement in heart rate (HR) response and aerobic capacity. CI is characterized by an attenuated HR response to incremental exercise or an increased HR reserve despite maximal effort. Clinically, it is an independent predictor of adverse cardiovascular events and mortality. CI is frequently overlooked, highlighting the importance of CPET in the diagnostic workup of unexplained dyspnoea.

Introduction
Exertional dyspnoea is commonly encountered in clinical practice. Differential diagnoses range from cardiorespiratory diseases and muscular dysfunction to metabolic disorders and even psychogenic factors. We present a case of unexplained dyspnoea with exercise-induced chronotropic incompetence (CI) discovered on a cardiopulmonary exercise test (CPET), detailing the cause of CI, its implication on CPET interpretation, and response to treatment.

Case Report
A 60-year-old salt delivery man, ex-smoker of 40 pack-year smoking history, presented with a one-year history of worsening exertional dyspnoea associated with mild intermittent central chest discomfort. His effort tolerance reduced to 600 m distance and he was unable to complete his weekly recreational football game. He denied other respiratory symptoms or orthopnoea. His only medical history was hyperlipidaemia on diet control. On examination, he was afebrile with a heart rate (HR) of 67 beats per minute (bpm), blood pressure of 137/77 mmHg, respiratory rate of 20 breaths per minute, and oxygen saturation of 98% on room air. Cardiovascular and respiratory systems were unremarkable. Blood investigations including complete blood count, renal profile, thyroid function test, and troponin I were normal. Chest radiograph and electrocardiogram (ECG) were normal. He was referred to respiratory medicine for evaluation following a negative dobutamine-atropine stress echocardiogram (DSE), which demonstrated preserved left ventricular ejection fraction (55%), no structural abnormalities, and absence of inducible ischemia at a maximal HR of 148 bpm (92% maximal age-predicted HR (MAPHR)). Pulmonary function tests showed normal ventilatory capacity, lung volumes, and gas transfer: forced expiratory volume in 1 sec (FEV1) 2.50 L (106% predicted); forced vital capacity (FVC) 2.94 L (104% predicted); FEV1/FVC 85%; total lung capacity 4.58 L (101% predicted); and carbon monoxide diffusing capacity (DLCO) of 6.21 mM/min/kPa (79% predicted).
A symptom-limited CPET was performed, which showed a low normal peak oxygen uptake (VO₂) (84% predicted), mildly reduced anaerobic threshold (AT) (45% predicted peak VO₂), and a blunted VO₂/work slope (7.8 mL/min/W) (Table 1). Peak oxygen pulse appeared elevated. Notably, after AT, the HR plateaued despite increasing workload (>90 W), and peak HR was significantly reduced at 73% maximum age-predicted HR, consistent with the diagnosis of CI. There was attenuated HR versus VO₂ response (Fig. 1A); the rhythm was sinus and without evidence of heart block during exercise or recovery. Ventilatory response was otherwise normal with adequate breathing reserve, normal tidal volume recruitment and end-tidal gas responses, and no oxygen desaturation.

ECG during exercise recovery was positive for ischaemic changes (ST-segment depression) in the inferior and anteroseptal leads. Coronary angiogram confirmed severely stenosed right coronary artery and left anterior descending artery, which were successfully stented.

An interval CPET showed improvement in HR response and longer time to AT, despite on bisoprolol 1.25 mg, consistent with his reported improvement in submaximal exercise tolerance (Fig. 1, Table 1).

### Discussion

Unexplained exertional dyspnoea poses significant diagnostic challenge in clinical practice. CPET is often utilized to study exercise response systematically [1]. CI is uncommonly encountered and, in our case, the primary physiological abnormality observed on CPET. Normally, HR increases linearly with exercise intensity. This is initially mediated by vagal withdrawal, followed by subsequent increase in sympathetic activity [1]. CI is diagnosed when there is failure to achieve >85% MAPHR or HR reserve ((maximum exercise HR – resting HR)/(MAPHR – resting HR)) of <80% [2]. It is observed in patients with coronary artery disease (CAD), heart failure, sick sinus syndrome, and atrioventricular block [2]. Although the exact pathophysiology of CI remains unclear, proposed mechanisms include: altered carotid baroreceptor sensitivity;

### Table 1. Summary exercise data before and after intervention.

| Measurement                     | Predicted | Before   | After   |
|---------------------------------|-----------|----------|---------|
| Maximum work (W)                | 116       | 123      | 125     |
| Peak VO₂ (mL/kg/min)            | 29.6      | 25.0     | 26.2    |
| Peak VO₂ (% predicted)          | —         | 84       | 89      |
| VO₂/work (mL/min/W)             | >8.5      | 7.8      | 8.6     |
| HR (bpm (rest, max))            | —, 160    | 71, 117  | 56, 131 |
| Maximum HR (% predicted)        | —         | 73       | 82      |
| Peak O₂ pulse (mL/beat)         | 10        | 12       | 11      |
| BP (mmHg (rest, max))           | —         | 138/70, 198/74 | 131/66, 207/83 |
| AT (mL/kg/min)                  | >14.7     | 13.4     | 14.5    |
| AT (% predicted peak VO₂)       | 50        | 45       | 49      |
| Time to AT (min)                | —         | 5:45     | 7:03    |
| Maximum VE (L/min)              | 98        | 49       | 54      |
| VE/VCO₂ at or lowest            | 32        | 31       | 32      |
| RER at peak VO₂                 | —         | 1.12     | 1.18    |
| RPE at peak exercise and symptoms limiting exercise | — | Chest discomfort (Borg 6), leg fatigue (Borg 5) | Breathlessness (Borg 6), leg fatigue (Borg 3) |
| Positive ischaemia on ECG       | —         | Yes, on recovery | No      |

The patient was exercised on a cycle ergometer at 15 W/min incremental work rate until symptom limitation or exhaustion. Initial study (‘Before’) showed a borderline reduced peak oxygen uptake (at 84% predicted) and AT (at 45% predicted peak VO₂), significantly reduced maximal HR (73% maximum age-predicted HR), and blunted VO₂/work slope (7.8 mL/min/W) consistent with circulatory impairment. Exercise was repeated following percutaneous coronary stenting and cardiac rehabilitation (‘After’). While maximum oxygen uptake was similar when compared to pre-intervention level, HR response significantly improved and AT was delayed. These changes support the patient’s reported improvement in submaximal exercise tolerance.

AT, anaerobic threshold, identified using the V-slope technique; BP, blood pressure; bpm, beats per minute; ECG, electrocardiogram; HR, heart rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion using the Borg scale; VE, minute ventilation; VE/VCO₂, ventilatory equivalent for carbon dioxide; VO₂, oxygen uptake.
downregulation of sinus node beta-adrenergic receptors caused by a chronically heightened sympathetic activation, leading to post-synaptic desensitization; increased vagal activity from stimulation of ventricular mechanoreceptor due to abnormal contraction of the ischaemic ventricle; and latent ischaemia of the sinus node [3]. In our patient, the latter two mechanisms likely played a significant role given the severe CAD, which after intervention, demonstrated improvement in HR response.

Prior to diagnosing CI, confounders such as HR-lowering medication and submaximal effort need to be excluded. As the usual criteria of using peak exercise HR is not applicable, alternative assessment of maximal effort should be employed, such as clinical observation of effort, rate of perceived exertion, and respiratory exchange ratio >1.1 [2]. Of note, whilst the HR is clearly attenuated in our patient, his peak VO₂ (a marker of aerobic capacity) is only borderline reduced at 84% predicted. This should be interpreted with caution in individuals who are very fit or who regularly perform demanding physical activities (the latter in our case). Reference for peak VO₂ may be derived from a relatively sedentary ‘normal’ cohort and a pathological reduction in aerobic capacity may be well within the expected predicted range, which highlights the need to examine the physiological response to exercise and not just the end points. Also, in CI, the typical features of cardiovascular limitations, that is low oxygen pulse (VO₂/HR) and elevated HR versus VO₂ response, are not seen. In fact, our patient demonstrated an

Figure 1. Circulatory response to incremental exercise before (A) and after (B) percutaneous coronary intervention and cardiac rehabilitation. Plot 1 shows VO₂ and VCO₂ response and work rate increment over time. Plot 2 shows HR and oxygen pulse (VO₂/HR) response over time. Plot 3 shows HR and VCO₂ response to VO₂. Before intervention, HR response was normal at lower work rate but plateaued at moderate exercise intensity after AT was reached (plot 2, A). This was accompanied by a continuing increase in oxygen pulse. Similarly, a decrease in HR versus VO₂ response was notable from mid-exercise onward (plot 3, A), deviating from the expected trajectory (solid red arrow) towards the intersect of predicted peak HR and peak VO₂ (red cross). After intervention, HR response and HR versus VO₂ slope improved (plots 2 and 3, B). AT, anaerobic threshold; HR, heart rate; RC, respiratory compensation point; VCO₂, carbon dioxide output; VO₂, oxygen uptake.
increased VO₂/HR, which is a non-invasive surrogate for stroke volume (Fick’s equation rearrange: VO₂/HR = SV × arteriovenous oxygen content difference): This is possibly due to increased ventricular filling time leading to larger stroke volume via the Starling mechanism [4].

Interestingly, the initial pharmacological stress echocardiography in our patient was falsely negative. While DSE achieved a higher peak HR pharmacologically, our patient reported significantly worse dyspnoea during CPET when compared to DSE, especially during the last 3–4 min of intensive exercise. We postulate that the apparent difference in diagnostic yield in our case is likely due to higher and sustained myocardial stress during incremental exercise. Previous study suggested that DSE is associated with a lower peak wall motion score index and rate–pressure product, which may lead to a lower sensitivity when compared to exercise stress study [5]. Another possibility is the interval worsening of CAD between the tests, but this is unlikely as DSE and CPET were conducted just one month apart.

In summary, CPET is an important and sensitive diagnostic tool for unexplained dyspnoea. When interpreting CPET, interrogation of HR response should be routinely performed. CI is an under-appreciated cause of exercise limitation in clinical practice, and if present, warrants further investigation for the underlying aetiology.

Disclosure Statement
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement
Conception or design of the work, the acquisition, analysis, or interpretation of data for the work: Sharlene Ho, Danqing Qi, and Geak Poh Tan. Drafting the work or revising it critically for important intellectual content: Sharlene Ho and Geak Poh Tan. Final approval of the version to be published: Sharlene Ho and Geak Poh Tan.

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