Title

Making sense of the unfavourable systematic review of exercise-based cardiac rehabilitation in the modern era: how should we proceed?

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Abstract

A systematic review of exercise-based cardiac rehabilitation has recently been published, the results of which indicate lack of efficacy for mortality and hospital admissions. This review was undertaken to address the lack of evidence that reflects contemporary medical management of cardiovascular disease. The review is important because it challenges current thinking on cardiac rehabilitation and provokes cardiac health professionals to consider the intent of cardiac rehabilitation. Issues with the review include failure to assess exercise 'dose' and adherence, and failure to consider other key outcomes such as exercise capacity and symptom control, which ultimately reduce health burden, and are valuable to patients. Contemporary models of care, the evolving patient population and the importance of cardiac rehabilitation in low and middle-income countries are also overlooked. The substantial heterogeneity of complex interventions like cardiac rehabilitation demands that reviews address not only efficacy, but also effectiveness for varying content, delivery methods and contexts.

Introduction

International guidelines recommend exercise-based cardiac rehabilitation (EBCR) to promote secondary prevention and support recovery following cardiovascular disease (CVD) events (1). Although the effectiveness of EBCR has been questioned due to poor delivery and participation (2), the efficacy of EBCR for reducing mortality and morbidity has not been challenged given the Class 1A evidence available (3). However, in January 2018, BMJ Open published a well-performed and well-reported systematic review that questions the efficacy of EBCR for reducing mortality in the contemporary era (4). Powell et al's work is important because shortcomings of previous reviews may have led to overestimates of the benefits of EBCR for current practice given improvements in intervention delivery and the evolving management of CVD and its associated risk factors. The results reported in Powell et al's systematic review challenge cardiac health professionals to consider the value of EBCR for CVD patients, however, we encourage readers to consider several important caveats when reflecting on the results and conclusions of the review.

Contemporary models of care, cardiac patients and treatment

International guidelines detail the core components necessary for effective contemporary EBCR delivery and benefit (5). These move EBCR beyond the early models of "exercise-only care" to include the management of risk factors and co-morbidities, provision of psychosocial care, and facilitation of behaviour change and adherence. Despite reporting that multiple components were used to deliver "best practice EBCR" in the majority of trial interventions, Powell et al made little attempt to ensure that included studies contained these particular core components important for contemporary effectiveness. Furthermore, an examination of the variation in outcomes based on these components was also lacking.

The failure of the review to demonstrate mortality benefits may also reflect the evolving nature of usual care treatments and clinical CR populations. Advances in CVD diagnosis and treatment have resulted in declining mortality rates in recent decades, but led to an aging clinical population with co-morbidities, increased risk factor burden and high risk of recurrent events (6-8). Consequently, the use of cardio-active medications and promotion of evidence-based CVD risk reduction in cardiology and general practice has increased (7, 8). It could be expected therefore that in contemporary trials, usual care will often contain one or more "active" components of EBCR. In these cases, a much smaller incremental effect of EBCR would be expected on all clinical outcomes, due to "over-dosing" of the control arm intervention. While it could be easy to dismiss the incremental benefit offered by EBCR over usual care in the contemporary era, this would overlook the vital role this intervention plays in providing a structured learning environment to promote adherence to a range of other CVD therapies (9).

Importance of intervention content, exercise dose and adherence

Powell et al's review includes trials that vary substantially in exercise content and delivery, yet this core component of exercise participation is poorly addressed by the authors. Exercise participation at sufficient intensity, frequency and duration is proposed to be the key mechanism for improvements in cardiorespiratory fitness, and thus reduction in mortality and morbidity. Research has repeatedly demonstrated a dose-response gradient between volume of exercise and clinical outcomes in EBCR patients (10-12), as well as significant heterogeneity in the magnitude of exercise capacity increases observed across individual trials (13). Additionally, there seems to be an incremental positive impact of exercise adherence independent of the dose received (10, 14). Despite this, Powell et al acknowledge that exercise participation was not examined in their review. The relative contributions of exercise dose and adherence to outcomes could therefore not be determined. This potential under-dosing of the exercise intervention could explain some of

the lack of effectiveness observed. Indeed, some of the included trials could be considered semi-structured exercise programs (15, 16) and thus may represent an under-dosing of the required intervention, rather than genuine ineffectiveness of EBCR as a whole. We agree with Powell et al, that analysis of this type is complicated by poor reporting of exercise interventions in existing trials. However, it is possible to obtain a large amount of information about missing intervention parameters by contacting authors directly (17).

Inherent difficulties of evaluating complex interventions

Complex interventions, such as EBCR are "built up from a number of components, which may act both independently and inter-dependently" (18). This presents a significant challenge for evaluation, as a wide range of factors could mediate either the intervention itself or subsequent outcomes. One method of dealing with this complexity is to take a realist approach to evaluation (19). This approach aims to not only establish success or failure, but also to explore the mechanism of effect by context i.e. "What works for whom, when and why" (19). Organisational, environmental, professional and patient factors can be considered in relation to intervention effects using a theoretical framework. Thus, the impact of EBCR upon mortality in the contemporary era is not dismissed without knowledge about the characteristics that influence effectiveness, the influence of context, or the mechanisms of intervention effect. Realist review methods help to determine if an intervention is wholly ineffective or whether it is only effective in certain contexts. Despite reporting heterogeneous intervention content, participants, geographical locations, pharmaceutical therapy and exercise training protocols in their review, Powell et al. do little to account for this complexity in their analysis or discussion. Their findings do, however, highlight a potential need to adopt a realist approach to future evaluation given the heterogeneity and complexity of interventions that are now "branded" as EBCR, and the unexplained variation in effectiveness observed across the large body of literature.

Complex health interventions produce multidimensional outcomes, spanning domains of mortality, morbidity, patient satisfaction, health service use, societal impact and cost (14). Additionally, the causal chain linking interventions with outcomes is longer and more complex in these situations. This means that while we agree that recent research has challenged the purported benefits of EBCR in the contemporary era, we also argue that evaluation should include a broader range of outcomes than mortality alone. Consideration of additional outcomes that patient's value would also provide a better understanding of overall efficacy. Consequently, it is suggested that a variety of measures capable of capturing these different dimensions of health and non-health outcomes should be used in future evaluation (18, 20). Selected outcomes would ideally relate to the World Health Organisation's proposed goals for EBCR and include mortality, morbidity, physical and psychological functioning, symptom control, return to work, health related quality of life, cost-effectiveness and independence. Indeed, the review authors concede that there is evidence that EBCR may lead to improvements in some of these domains.

Value of cardiac rehabilitation in low and middle-income countries (LMICs)

Broad declarations of declining benefits of contemporary EBCR are not likely to apply to LMICs, given their rapid rise in CVD and a smaller decrease in age-standardised death rates compared to high-income countries in recent times (21). The advances in CVD treatment and management that are claimed to attenuate the effect of CR on mortality in Western countries are less recognised in these settings with limited resources, high pharmacological costs and variable access to care (22, 23). Indeed, while delivery of and adherence to secondary prevention therapies may be suboptimal world-wide (24), evidence-practice gaps are more marked in LMICs where patients are less likely to receive evidence based risk-factor management, medication, or surgical interventions for CVD (25, 26). Until the overall

standard of cardiology care in LMICs can be improved, an organised, effective, low cost option for co-ordinating the treatment of CVD is still important in this setting.

Conclusion

The Powell et al systematic review of the efficacy of contemporary EBCR on mortality and readmission outcomes is an important publication because it challenges current concepts of EBCR. However, sweeping statements included that suggest the case is closed oversimplify the multifocal intent of EBCR. We agree with the authors that further research in the area is needed, and recommend that new approaches for conducting systematic reviews of complex interventions like EBCR are essential.

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