Institution: Buckinghamshire New University

Unit of Assessment: 3 - Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Clinical applications of non-invasive cardiac output measurements

Period when the underpinning research was undertaken: 2006 - 2010

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
David Brodie	Professor of Cardiovascular Health (Emeritus Professor of Cardiovascular Health)	1.1 2001 to 31.7.2010 (1.8.2010 – current)

Period when the claimed impact occurred: 2014 to 2020

Is this case study continued from a case study submitted in 2014? Y

1. Summary of the impact (indicative maximum 100 words)

The research team from Buckinghamshire New University (BNU) originally validated novel non-invasive technologies for cardiac output and cardiac power output measurements and then applied it to a group of patients with end-stage heart failure. The continuing benefits since 2014 have shown how the original information was adopted for clinical applications both in the UK and abroad. Cardiac power output continues to be an important measure for people using left ventricular assist devices. The benefits of cardiac function testing are now being recognised in primary care.

2. Underpinning research (indicative maximum 500 words)

The research into cardiac power output (CPO) was co-ordinated by Professor Brodie of BNU during the period 2004 to 2012. The team included Professor Sir Magdi Yacoub, (Heart Science Centre, Harefield Hospital), Professor Emma Birks, (currently Director, Heart Failure, Transplant and Mechanical Support Programme, University of Kentucky), Dr Richard Grocott-Mason (Consultant Cardiologist, Hillingdon Hospital), Dr Djordje Jakovljevic (currently Professor and Research Lead, Cardiovascular and Exercise Sciences, Coventry University) and a small group of PhD students.

The initial focus of the research was to explore the reliability and validity of CPO as an integral measure of both flow- and pressure-generating capacities of the heart. This involved a comparison of different rebreathing methods and resulted in the conclusion that inert gas rebreathing measured cardiac output more precisely than the alternative carbon dioxide rebreathing methods (1). As the target patient group was those with chronic heart failure, it was essential to explore the reproducibility of CPO in such groups and this was established with a low coefficient of variation (2). The outcome was a clear demonstration that CPO was an excellent prognostic marker and was subsequently strongly advised in the assessment of patients with chronic heart failure undergoing cardiopulmonary exercise testing. The process of cardiac rehabilitation can include both aerobic and resistance training and it was important to determine which was the most effective in improving cardiac function using CPO as the main determinant. Our work (3) demonstrated that aerobic exercise training increased the maximal flow-generating capacity of the heart and delayed anaerobic metabolism in patients with stable chronic heart failure.

Much of our work was in association with the Magdi Yacoub Institute involving patients on the ‘Bridge to Recovery’ programme at Harefield Hospital. These patients were initially in end-stage

heart failure, awaiting heart transplantation, but as a result of the programme, involving the use of a left ventricular assist device (LVAD) many recovered sufficiently to avoid transplantation. Our findings demonstrated that CPO differentiates well during cardiac restoration using LVADs and can be used as marker of cardiac recovery (4). Another important contribution to the programme was our investigation into the impact of acute reduction of continuous-flow LVAD support on cardiac and exercise performance. We showed for the first time that the LVAD can confer both resting and peak cardiac functional benefits to patients with end-stage heart failure (5). We also showed that exercise-derived prognostic indicators demonstrated a limited capacity in reflecting cardiac pumping capability in patients treated with LVADs (6). Thus the interpretation of cardiac organ function would benefit substantially by the inclusion of CPO.

3. References to the research (indicative maximum of six references)

1. Jakovljevic DG, Nunan D, Donovan g, Hodges LD, Sandercock GR, Brodie DA, Comparison of cardiac output determined by different rebreathing methods at rest and at peak exercise. Eur. J. Appl. Physiol. 2008, Mar 102(5) 593-9
2. Jakovljevic DG, Seferovic PM, Nunan D, Donovan G, Trenell MI, Grocott-Mason R, Brodie DA, Reproducibility of cardiac power output and other cardiopulmonary exercise indices in patients with chronic heart failure. Clin. Sci. (London) 2012 Feb 122 (4) 175-181
3. Jakovljevic DG, Nunan D, Donovan G, McDonagh S, Trenell MI, Grocott-Mason R, Brodie DA, The effect of aerobic versus resistance exercise training on peak cardiac power output and physical functional capacity in patients with chronic heart failure. Int J. Cardiol. 2010, Dec 3 145(3) 526-8
4. Jakovljevic DG, George, RS, Donovan G, Nunan D, Henderson K, Bougard RS, Yacoub MH, Birks EJ, Brodie DA, Comparison of cardiac power output and exercise performance in patients with left ventricular assist devices, explanted (recovered) patients, and those with moderate to severe heart failure. Am J. Cardiol. 2010, June 15, 105 (12), 1780-5
5. Jakovljevic DG, George RS, Nunan D, Donovan G, Bougard RS, Yacoub MH, Birks EJ, Brodie DA, The impact of acute reduction of continuous-flow left ventricular assist device support on cardiac and exercise performance. Heart 2010 Sept 96 (17) 1390-5
6. Jakovljevic DG, Birks EJ, George, RS, Trenell MI, Seferovic PM, Yacoub MH, Brodie DA, Relationship between peak cardiac pumping capability and selected exercise- derived prognostic indicators in patients treated with left ventricular assist devices. Eur J. Heart Fail. 2011 Sept 13 (9) 992-9

4. Details of the impact (indicative maximum 750 words)

The ideal non-invasive measure of the heart's pumping performance is cardiac power output (CPO). This continued case study demonstrates how other institutions, have adopted the validation of the use of CPO, nationally and internationally. Since 2014, there has been a recognition that it is necessary to measure both flow and pressure-generating capacities of the heart to determine overall cardiac function meaningfully. One measure of the impact of a new procedure is the extent that it has been adopted outwith the original location of the research. Cardiac power output has been adopted and its use sustained in a number of places since 2014. A good example of this is the adoption of CPO at the Translational and Clinical Research Institute at Newcastle University. A specialist laboratory has been established within this Institute and this laboratory now includes the measurement of CPO routinely. Professor Guy MacGowan's work concentrates on heart failure and now uses CPO as part of his non-invasive testing. His testimony states:

"*Cardiac power output (CPO), as a novel integrative measure of overall function and pumping capability of the heart, has been used at Freeman Hospital to assess eligibility of patients with advanced heart failure for heart transplantation and/or treatment with mechanical circulatory support. We also use CPO to follow-up patients after the surgery, determine their prognosis and recovery*." (Professor MacGowan, Consultant Cardiologist, Newcastle Freeman Hospital, UK) [5.1]

Non-invasive cardiac output and CPO assessment is used to help clinicians identify the causes of exercise intolerance. The beneficiaries of the use of CPO include a number of clinical groups including those with cardiovascular (n=421), metabolic (type 2 diabetes, liver disease, n=382) and neurological disorders (n=161). Following our work, CPO is also now used by Dr Sandeep Hothi who states:

"*I recommend the use and wide adoption of cardiac power output measurement in clinical practice to evaluate patients with heart failure, improve risk stratification, assess the degree of cardiac dysfunction and guide decision making for pharmacological and non-pharmacological interventions*." (Dr Hothi, Consultant Cardiologist, New Cross Hospital, Wolverhampton) [5.2]. The numbers of patients involved in this work at New Cross Hospital is approximately 120 per annum.

The impact of our original work on CPO has seen the adoption of the procedure abroad. Its application follows the work we established at Harefield Hospital. It is part of the portfolio of procedures now available to patients following surgery at both the Aswan Heart Centre in Egypt and the Sidra Medical and Research Centre in Doha, Qatar. The Head of the Department of Cardiology in Aswan has stated:
"*In the Aswan Heart Centre we use non-invasive measures of cardiac output and cardiac power output in children and adults to help us define severity of cardiac dysfunction and inform decisions about the best treatment options for our heart failure patients*." (Dr ElGuindy, Head of Cardiology, Aswan Heart Centre, Egypt) [5.3]. The numbers of patients involved in Aswan is approximately 160 per annum.

In the 2014 case study, we showed the importance of cardio-respiratory fitness in people with chronic heart failure. A common precursor of heart failure is metabolic syndrome, yet little is known about the nature of its association with cardio-respiratory fitness (CRF) across the age strata in the UK. The continuing impact of this work is predominantly in preventative health. Public health messages are now advocating the need for an improvement in CRF alongside weight management for enhancing cardiometabolic health. This policy change is currently being driven by the private health sector such as Nuffield Health The NHS is progressively adopting a policy of including CRF assessments in UK health screening. It is now policy for all cardiac rehabilitation units, a decision made when Prof Brodie was Scientific Advisor to the British Association for Cardiovascular Prevention and Rehabilitation.

Cardiac power output was one of the markers we used monitor the progress of patients with end-stage heart failure. Alongside CPO, we used heart rate variability (HRV) to observe the patterns of cardiac autonomic nervous system (ANS) activity. The desired clinical endpoint for patients with a left ventricular assist device (LVAD) is to have it successfully explanted. Our 2014 study showed that implanted LVAD patients showed a partial normalisation of the HRV profile, with little difference between these patients and controls. The continuing impact of this work is that we now know that end-stage heart failure patients, who are characterised by severe autonomic derangement, can show a high level of cardiac ANS normality following implantation of the LVAD. A more important impact is that this cardiac ANS normalisation appears to be maintained following explantation. The overall impact is that for the first time, we can be confident that such patients can return, with suitable pharmacological support, to live without their previous chronic end-stage heart failure.

Since 2014, we are now able to show that in patients with advanced heart failure, awaiting transplantation, there was a significantly better cardiac performance and functional capacity among those in whom LVADs were explanted. A substantial proportion of these patients attained peak cardiac power output and peak oxygen consumption in the range of healthy individuals. A further impact is that we now know that prospective clinical trials are needed to define optimal pharmacological and physiological strategies to enhance myocardial recovery and allow for the use of LVADs as a bridge to recovery of cardiac function. One of our co-workers at Harefield was Professor Emma Birks, who now works at the Gill Heart and Vascular Institute in Lexington, USA commented

"*In our extensive heart transplant and mechanical circulatory support programme we use measurements of cardiac output and cardiac power output in evaluation and risk stratification of patients with advanced heart failure undergoing heart transplantation and ventricular assist device therapy*." (Professor Birks, Consultant Cardiologist and Director, Department of Cardiology, Gill Heart and Vascular Institute, University of Kentucky, Lexington, Kentucky, USA) [5.4].

The numbers of individuals worldwide, who have undertaken the LVAD procedure, is comparatively small. Yet individual case studies have shown that they exhibit improved cardiac function, the disease progression is slowed, further hospitalisation is decreased and the quality of their lives enriched. Our work on CPO has been a determining factor in measuring LVAD readiness and outcome. At the time of our original work in 2008, only one other centre (Leeds Medical School) used CPO. Since that time, and as a result of our publication profile, its adoption in the UK and worldwide has escalated.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Professor MacGowan, Consultant Cardiologist, Newcastle Freeman Hospital, UK

5.2 Dr Hothi, Consultant Cardiologist, New Cross Hospital, Wolverhampton

5.3 Dr ElGuindy, Head of Cardiology, Aswan Heart Centre, Egypt. https://myf-egypt.org/

5.4 Professor Birks, Consultant Cardiologist and Director, Department of Cardiology, Gill Heart and Vascular Institute, University of Kentucky, Lexington, Kentucky, USA