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From a cardio-vascular reserve hypothesis to a proposed measurable index: A pilot empirical validation

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ABSTRACT

Background: Cardiovascular reserve index (CVRI) was previously proposed as an estimate of the assumed (momentary) cardiovascular reserve as a function of stroke volume (SV), systemic vascular resistance (SVR), respiratory rate (RR) and body surface area (BSA). Conversion through conventional hemodynamic equations reveals an equivalent, simpler, vital signs based function. We evaluated the association between CVRI and diverse conditions along the hemodynamic spectrum.
Methods: CVRI was retrospectively computed for each subject of 3 existing patient databases. 1) Acute severe hospital admissions [N = 333] classified by disease course to: "shock on arrival", "developing shock" and "non-shock". 2) Heart failure (HF) patients [N = 71] classified by HF severity to: mild, moderate and severe HF. 3) Cardio-pulmonary exercise testing (CPX) [n = 387] classified by exercise capacity (EC) to: normal, mildly decrease, moderately decrease and severely decreased EC. CVRI association with these hemodynamic conditions was evaluated through ANOVA.
Results: 'Normal EC' has the highest CVRI of 0.97 (0.88, 1.06), and in decreasing CVRI order 'mildly decrease EC', 'moderately decrease EC', 'mild HF' which was similar to 'severely decrease EC', 'moderate HF' which was similar to acute severe admission of 'non-shock', 'severe heart failure' which was similar to 'developing shock' and the lowest CVRI was observed in 'shock on arrival' with mean CVRI of 0.20 (0.19, 0.22), ANOVA $p < 0.001$.
Conclusions: Mean CVRI exhibited consistent inverse association with the severity of the hemodynamic condition. However, CVRI clinical utility of an individual patient requires further studies.

1. Background

The cardiovascular reserve hypothesis was proposed by Gabbay and Bobrovsky [1] as the common denominator for aerobic exhaustion, the diverse types of heart failure and the diverse shock types.

Exercise capacity (EC) can be defined as the highest work intensity that an individual can achieve. Even in fit, healthy individuals EC is not unlimited hence when exercise intensity reaches the highest work intensity possible the individual must either stop work or reduce the intensity. Reduced EC may be still considered within the scope of normal health, for example in sedentary, deconditioned individuals. Various disease states reduce EC, inducing physical activity intolerance which limits daily living (i.e. heart failure) [2]. Heart failure (HF) is a diverse syndrome with several underlying causes, that commonly manifests as fatigue and dyspnea either at rest or while performing insignificant physical activity considerably below that expected in the healthy. The mechanism of the limitation is either low or high cardiac output [3].

Shock refers to generalized inadequate perfusion which triggers a chain of devastating consequences (cellular hypoxia, anaerobic metabolism, cell death, organ failure) inevitably leading to death in the absence of effective intervention. The underlying mechanism is either low cardiac output, or low systemic vascular resistance, or both [4,5].

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The hypothesized (momentary) cardiovascular reserve may be described as the momentary hemodynamic capability to adapt to increasing metabolic demand. Accordingly, a healthy, fit subject at rest has maximal reserve. A healthy but unfit subject has reduced exercise capacity that only limits high intensity activity. Heart failure patients are expected to have even lower cardiovascular reserve, inversely related to the severity of the HF, which limits them even in daily activities. The cardiovascular reserve is expected to decrease during exercise (in accordance with the activity intensity) until it reaches an assumed (common) exhaustion threshold, at which point dyspnea and exhaustion prevent gaining or even restoring this activity. The healthy, well trained individual may reach the exhaustion threshold with extremely intensive exercise (due his high cardiovascular reserve at rest). HF patients are expected to reach the exhaustion threshold with low-intensity activity (due to low cardiovascular reserve at rest). An acute illness which is associated with hemodynamic deterioration (e.g. myocardial infarction, hypovolemia or sepsis) may decrease the assumed cardiovascular reserve, according to the hypothesis, below the exhaustion threshold even with no activity. In these severely ill patients the assumed cardiovascular reserve may further deteriorate toward an assumed sustainability limit in which shock is manifested [1].

In order to quantify the assumed cardiovascular reserve, a cardiovascular reserve index (CVRI) was proposed, based on a theoretical analysis of the cardiovascular open loop gain (OLG) [6]. OLG is a control engineering term which indicates the robustness of a control system to response for increasing demand [7]. OLG is proportional to the product of the gains of each individual element in a control loop. As already known the cardiovascular feedback mechanism is mainly composed of three elements: the heart, for which the main gain is stroke volume (SV); the vasculature and blood volume, for which the main gain is systemic vascular resistance (SVR); and baro-receptor sensitivity. Several studies indicate that the baro-receptor sensitivity is reciprocally associated with respiratory rate (RR) [8]. CVRI was thus proposed as the product of SV, SVR and 1/RR, divided by Body Surface Area (BSA) (to normalize for size), and by 4 (in order to normalize CVRI of a healthy individual to approximately 1.0) [9]:

$$CVRI = SV^{*}SVR/(RR^{*}BSA^{*}4) \quad (1)$$

As neither SV nor SVR can be reliably measured non-invasively, and given that SV = CO / HR (where CO is cardiac output and HR is heart rate) and SVR = 80 ∗ (MABP − CVP) / CO (where MABP is mean arterial blood pressure, CVP is central vein pressure and CO is cardiac output), conversion of SV and SVR accordingly provides an equivalent CVRI formula which is considerably simpler to measure [9]:

$$CVRI = 20^{*}(MABP-CVP)/(RR^{*}HR^{*}BSA). \quad (2)$$

The aim of this study was to perform a proof-of-principle pilot empirical validation whether or not CVRI correlates with the assumed cardiovascular reserve over a wide range of conditions across the hemodynamic spectrum.

2. Methods

The study was designed as correlative study between CVRI (retrospectively computed out of the documented physiological measures of existing patients' data) and diverse hemodynamic conditions. In order to cover the entire hemodynamic spectrum, we utilized three unrelated databases in which each patient record included a predetermined hemodynamic condition (as already determined in the data base) and the essential physiological measurements through which CVRI may be retrospectively computed i.e. blood pressure, CVP, HR and RR. Missing measurements of CVP and BSA were tolerated as described below. The three databases included in the study were:

1) A compilation of case reports of acute severe hospital admissions (either illness or injury) published in peer reviewed journals during 2000–2012. The search terms used to search case reports in Pub-Med were: 'acute admission', 'case report', 'severe' and 'respiratory'. The inclusion criteria were case reports of acute severe hospital admissions, in which the condition at admission and the acute morbidity course were reported by the authors (enabling classification to one of the three study sub-groups according to the course of the acute illness: "shock on arrival"; "developing shock" in those where shock was not yet onset on admission, but developed later on in the course of the acute illness; and "Non-shock" — admissions of acute severe illness in which shock was not developed at all. Inclusion criteria included reporting of the physiological measurements at admission, from which CVRI was computed independently of the above mentioned classifications.
2) A compilation of case reports of case reports of HF patients published in peer reviewed journals during 2000–2012. The search terms used to search case reports in Pub-Med were: 'heart failure', 'case report', 'severity' and 'respiratory'. The inclusion criteria were HF case reports which reported HF Classification as mild, moderate, and severe HF. Inclusion criteria included the reporting of the physiological measurements from which CVRI was computed independently of the HF classifications.
3) The database of patients who underwent cardio-pulmonary exercise testing (CPX) due to diverse clinical indications at the Lung institute; Sheba Medical Center, Ramat-Gan, Israel, which were already categorized by the CPX to four sub-groups of exercise capacity (EC): normal EC, mildly decreased EC, moderately decreased EC and severely decreased EC. The inclusion criteria included the physiological measurements at rest (before exercising) from which CVRI was computed independently of the EC classifications. The protocol was approved by the Sheba Medical Center ethics committee. The requirement for informed consent was waived as the study involved a retrospective analysis of de-identified data.

2.1. Data structure

Individual patients' data were entered into a single record which included demographic data, morbidity type, data source, sub-group classification and the vital signs measurement at the initial evaluation for retrospective CVRI computing.

2.2. Data processing and statistical analysis

CVRI was calculated for each record according to the vital signs based formula for CVRI (Eq. (2), above). For the purpose of this work CVRI may be considered as unit-less index.

If blood pressure measurement was reported as systolic/diastolic, MABP was calculated using the formula [10]:

$$MABP = DBP + (SBP-DBP)/3$$

where DBP is diastolic blood pressure and SBP is systolic blood pressure.

If the record lacked measurements of either CVP or BSA, the following estimation methods were used:

Missing CVP measurement—when CVP was clinically described as elevated or considerably elevated (e.g. clinical description of cervical vein distension) we imputed CVP as 10 mm Hg, and 15 mm Hg respectively. When CVP was described as decreased we imputed CVP as 3 mm Hg.

When CVP was neither reported nor clinically described, we assume that CVP may be approximated as 10% of MABP.