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Cardio-vascular reserve index (CVRI) during exercise complies with the pattern assumed by the cardiovascular reserve hypothesis

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ABSTRACT

Objectives: The Cardio-vascular reserve index (CVRI) had been empirically validated in diverse morbidities as a quantitative estimate of the reserve assumed by the cardiovascular reserve hypothesis. This work evaluates whether CVRI during exercise complies with the cardiovascular reserve hypothesis.
Design: Retrospective study based on a database of patients who underwent cardio-pulmonary exercise testing (CPX) for diverse indications.
Methods: Patient's physiological measurements were retrieved at four predefined CPX stages (rest, anaerobic threshold, peak exercise and after 2 min of recovery). CVRI was individually calculated retrospectively at each stage.
Results: Mean CVRI at rest was 0.81, significantly higher ($p < 0.001$) than at all other stages. CVRI decreased with exercise, reaching an average at peak exercise of 0.35, significant lower than at other stages ($p < 0.001$) and very similar regardless of exercise capacity (mean CVRI 0.33–0.37 in 4 groups classified by exercise capacity, $p > 0.05$). CVRI after 2 min of recovery rose considerably, most in the group with the best exercise capacity and least in those with the lowest exercise capacity.
Conclusions: CVRI during exercise fits the pattern predicted by the cardiovascular reserve hypothesis. CVRI decreased with exercise reaching a minimum at peak exercise and rising with recovery. The CVRI nadir at peak exercise, similar across groups classified by exercise capacity, complies with the assumed exhaustion threshold. The clinical utility of CVRI should be further evaluated.

1. Introduction

The cardiovascular reserve hypothesis was proposed by Gabbay and Bobrovsky as the underlying common denominator for fitness, aerobic exhaustion, heart failure and shock, regardless of their types [1]. The hypothesized cardiovascular reserve may be described as the momentary hemodynamic capability to gain in order to adapt to increasing metabolic demand. Accordingly, cardiovascular reserve is expected to decrease during exercise as the workload increases, until a hypothesized exhaustion threshold is reached, beyond which a further increase in not sustainable. The healthy, well trained individual reaches the exhaustion threshold at high intensity exercise due to a high cardiovascular reserve at rest. As fitness decreases, cardiovascular reserve at rest decreases, and exhaustion occurs at lower levels of exercise intensity. Severely deconditioned individuals and patients with heart failure are assumed to have a morbidly low cardiovascular reserve, and accordingly reach the exhaustion threshold at low intensity exercise, which may be within the scope of daily activity. Shock, according to the hypothesis, occurs when cardiovascular reserve decreases, due to an acute insult, to a level insufficient to sustain basal metabolism and vital organ function. This activates a salvage-sacrificing physiological response. The cardiovascular reserve hypothesis, by defining the momentary cardiovascular *reserve*, rather than momentary cardiovascular *performance*, provides a unified explanation for different levels of physical fitness and performance, diverse types of heart failure (low, normal or high output) and diverse types of shock [1].

In order to quantify the assumed cardiovascular reserve, the cardiovascular reserve index (CVRI) was proposed [2,3]. It was developed by theoretical analysis of the cardiovascular Open Loop Gain (OLG) [4]. OLG is a control engineering term which indicates the robustness of a given control system [5]. OLG is proportional to the product of the

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gains of each individual element in a control loop. The cardiovascular system (CVS) control (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 the baro-receptors' sensitivity (BRS). Hence the OLG of the CVS is: $OLG_{(CVS)} = SV * SVR * BRS$.

Several studies show BRS is inversely associated with respiratory rate (RR) [6]. Thus, CVRI was proposed to be the product of SV, SVR and 1/RR, divided by Body Surface Area (BSA) (to standardize for size), and by 4 (in order to normalize CVRI of a healthy individual at rest to approximately 1.0) [2,3].

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

CVRI is given in: dyn sec/cm^4 4 $*$ 10^4

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 [2,3]:

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

CVRI in this formula is given in: 20 mm Hg min^2/m^2, which is equivalent to dyn sec/cm^4 4 $*$ 10^4).

CVP is usually very low in comparison with MABP. Therefore in the term (MAP-CVP), CVP is frequently neglected (i.e. [*MABP-CVP*] ≈ *MABP*), or approximated [10]. Accordingly the term for SVR was simplified to

$$SVR \approx 80 * MABP/CO$$

And thus the CVRI formula may be simplified to:

$$CVRI = 20 * MABP/(RR * HR * BSA) \quad (3)$$

Note that CVRI may be considered as a unit-less index for the purpose of this study.

In a previous study we empirically validated the correlation between diverse morbidities and exercise capacity groups with CVRI at rest [3].

The aim of this study was to perform a proof-of-principle empirical validation of CVRI during exercise, to test whether CVRI complies with the reserve pattern assumed by the cardiovascular reserve hypothesis [1].

2. Methods

We designed a retrospective study based on an existing database of patients who underwent cardiopulmonary exercise testing (CPX) in the Lung Institute, Sheba Medical Center (an Israeli tertiary hospital located in the Tel-Aviv metropolitan area) between 2008 and 2012. The protocol was approved by the Sheba Medical Center Institutional Review Board. The requirement for informed consent was waived as the study involved retrospective analysis of de-identified data.

Symptom-limited progressive CPX tests were performed using a cycle-ergometer and a metabolic cart. Tests were performed, analyzed and interpreted according to an internal clinical protocol based on clinical practice guidelines. The test protocol included 3 min rest, then 3 min of unloaded cycling followed by an incremental phase in which the resistance of the flywheel of the cycle ergometer gradually increased until the patient indicated he or she could no longer continue, or until the patient was unable to maintain his or her cycling cadence. The increment of the load (watts/minute) was individually determined in order to enable an incremental stage of 8–12 min.

The computerized CPX system in the Lung Institute enables storage and retrieval of test measurements during the entire CPX test. Apart from physiological measurements acquired during the test, each individual patient record contains demographic data, anthropometrics, co-morbidities (as recorded from the referral), and the CPX test interpretation. Tests are interpreted jointly by two experienced readers. For the purposes of this study we recorded: (1) Exercise capacity (EC) by category: normal (peak oxygen consumption ($pV'O_2$) > 80% predicted), mildly decreased ($pV'O_2$ 65–79% predicted), moderately decreased ($pV'O_2$ 50–64% predicted) and severely decreased ($pV'O_2$ < 50% predicted); and (2) the exercise-limiting system (cardiovascular or ventilatory).

Four hundred unselected, consecutive records of patients with diverse morbidities and exercise capacities, who underwent CPX due to diverse clinical indications, were retrieved.

Patients with incomplete physiological measurements (essential to compute CVRI) in any of the CPX stages or incomplete CPX interpretation were excluded.

Physiological measurements were retrieved at 4 predefined CPX stages: rest, anaerobic threshold, peak exercise and recovery, as defined below:

"At rest" refers to the baseline recorded with the patient connected to this system at complete rest.

"Anaerobic threshold" refers to the gas-exchange threshold, determined using the V-slope method [7].

Peak exercise" refers to the highest level of effort attained. Notably these clinical CPX tests were symptom limited, and thus peak exercise was the point at which the patient indicated (subjectively) that he or she could not continue.

"Recovery" was uniformly defined, for the purpose of this study, at 2 min into recovery after reaching peak exercise. We chose this point due to feasibility and convenience considerations as there is no standardized milestone for recovery.

CVRI was computed individually for each of the predefined CPX stages (using formula 3). For this purpose, BSA was computed individually using the Mosteller formula [8]:

$$BSA = (H * W/3600)^{0.5}$$

where '*H*' is height (in cm.) and *W* is weight (in kg.). MABP was calculated individually from systolic and diastolic blood pressure, for each of the predefined CPX stages, using the formula [9]:

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

where *DBP* is diastolic blood pressure and *SBP* is systolic blood pressure (both in mm Hg).

Statistical analysis was performed using SPSS version 2.2 2014 (IBM Inc.).

Multi-comparisons of CVRI values by CPX stage and by EC group were performed using ANOVA. Association between continuous variables was evaluated by Pearson's correlation coefficient and for non-parametric variables by Spearman's correlation coefficient. Evaluation of multivariate influence on CVRI was performed by multivariate linear regression modeling. Distribution consistency was evaluated through Chi-square analysis.

3. Results

400 consecutive patients' records were retrieved from the CPX database, of which 362 files (90.5%) contained all physiological measurements essential to compute CVRI at all exercise stages, as well as a complete CPX interpretation. The study population characteristics are presented in Table 1. The average age was 55.4 years, and 52% were males. The differences in gender and age group distribution between exercise capacity groups were not significant ($p = 0.27$ Chi-square).

The prevalence of the most common clinical diagnoses in the study population, as recorded by the referring physician, is presented in Table 2.

The exercise limiting system was dominantly cardiovascular (91%), the remainder being pulmonary limitation (7%), and combined cardio-pulmonary impairment (2%). The percentage of patients with

Table 1
Patients characteristics by exercise capacity group.

Exercise capacity group	N	Gender (% males)	Age (95% CI)
All	362	52%	55.4 (53.7–57.1)
Normal	58	34%	60.0 (55.9–64.1)
Mildly decreased	98	44%	55.4 (51.9–58.9)
Moderately decreased	91	54%	55.4 (52.0–58.8)
Severely decreased	115	67%	52.2 (49.3–55.2)

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