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# The approximated cardiovascular reserve index complies with haemorrhage related hemodynamic deterioration pattern: A swine exsanguination model

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## HIGHLIGHTS

- Cardiovascular reserve index (CVRI) estimates the assumed cardiovascular reserve.
- CVRI is computed by routinely measured physiological parameters.
- Criteria for haemodynamic deterioration prediction were preset.
- CVRI met preset criteria (correlation, detecting threshold and indicative range).

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## ABSTRACT

*Background:* To estimate the cardiovascular reserve we formulated the Cardiovascular Reserve Index (CVRI) based on physiological measurements. The aim of this study was to evaluate the pattern of CVRI in haemorrhage-related haemodynamic deterioration in an animal model simulating combat injury.

*Methods:* Data were collected retrospectively from a research database of swine exsanguination model in which serial physiological measurements were made under anesthesia in 12 swine of haemorrhagic injury and 5 controls. We calculated the approximated CVRI ($CVRI_A$). The course of haemodynamic deterioration was defined according to the cumulative blood loss until shock. The ability of heart rate (HR), mean arterial blood pressure (MABP), stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) and the $CVRI_A$ to predict haemodynamic deterioration was evaluated according to three criteria: strength of association with the course of haemodynamic deterioration ($r^2 > 0.5$); threshold for haemodynamic deterioration detection; and range at which the parameter remained consistently monotonous course of deterioration.

*Results:* Three parameters met the first criterion for prediction of haemodynamic deterioration: HR ($r^2 = 0.59$), SV ($r^2 = 0.57$) and $CVRI_A$ ($r^2 = 0.66$). Results were negative for MABP ($r^2 = 0.27$), CO ($r^2 = 0.33$) and SVR ($r^2 = 0.02$). The detection threshold of the $CVRI_A$ was 200–300 ml blood loss whereas HR, SV and CO showed a delay in detection, MABP and CVRI exhibited a wide indicative range toward shock.

*Conclusions:* The $CVRI_A$ met preset criteria of a potential predictor of haemorrhage-related haemodynamic deterioration. Prospective studies are required to evaluate use of the CVRI in combat medicine.

*Level of evidence:* Level III.



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## 1. Introduction

Haemorrhage is the leading underlying cause of preventable death in trauma, accounting for approximately 90% of all combat-associated preventable deaths [1–3]. Early control of haemorrhage, whether mechanical or surgical, coupled with haemodynamic stabilization by replacement of fluids and blood improves outcome dramatically [4,5]. However, the window of opportunity for successful intervention is very narrow, as deterioration to haemorrhagic shock and death may be very rapid [3,6,7]. Therefore, early and precise detection is crucial [8,9]. Occult haemorrhage in the field poses a particular challenge even to trained personnel, because it may be overlooked during the initial clinical assessment [6,10].

There are as yet no accurate and practical methods for detecting haemorrhage and predicting haemodynamic deterioration [11], either in the battlefield or in non-combat (e.g., postoperative) settings. Although blood pressure and heart rate (HR) are traditionally measured, their predictive value for the haemodynamic state is equivocal [12,13]. Oxygen saturation has become a crucial measure in emergency medicine, but its yield for the detection of haemorrhage is limited, at least in the early stages [14]. Several studies have suggested noninvasive tools for estimating cardiac output (CO), the classic measure of cardiovascular performance [15], but they have not yet become an accepted part of the initial evaluation [16]. Furthermore, CO may be preserved even in progressive haemorrhage due to compensatory mechanisms [17], especially in young and otherwise healthy individuals, such as military combatants. Pulmonary capillary wedge pressure, introduced by Swan and Ganz [18] as a reliable measure of heart failure, requires invasive means of measurement, and its significance in haemorrhage detection has not been established [19,20]. Central venous pressure (CVP) was traditionally considered a sensitive measure of hypovolemia, but questions regarding its predictive role have arisen in recent years [21]. Others have suggested using diagnostic algorithms such as the Shock Index [22] and the Compensatory Reserve Index [23], but these have not become a standard of care.

The cardiovascular reserve hypothesis suggests that haemodynamic deterioration is associated with decreased (momentary) cardiovascular reserve. The cardiovascular reserve may be described as the momentary haemodynamic capability to comply with an increasing metabolic demand by increasing CO. During exercise, CO rises, and the cardiovascular reserve decreases accordingly, until it reaches an assumed threshold at which dyspnea and exhaustion limit further effort. In healthy well-trained individuals, the threshold is reached following intensive exercise. However in individuals with an acute morbidity or injury that causes haemodynamic deterioration (e.g. myocardial infarction, haemorrhage, sepsis, etc.), the cardiovascular reserve may drop below the exhaustion threshold to an assumed sustainability limit which leads to shock [24]. In military combatants, reduced cardiovascular reserve may be associated with heat, physical exhaustion, dehydration, and haemorrhage.

In 2015, Gabbay and Bobrovsky [25] formulated the Cardio-Vascular Reserve Index (CVRI) for estimation of the assumed cardiovascular reserve. The CVRI index is based on principles of control theory in general and open loop gain (OLG) in particular. OLG which defines the robustness of the control loop, is proportional to the product of each of the individual gains in the system. The control loop of the cardiovascular system, also termed the cardiovascular feedback mechanism, is composed of three main elements. These include the heart, in which gain is represented by stroke volume (SV), the vasculature, in which gain is represented by systemic vascular resistance (SVR), and baro-receptor sensitivity (BRS), yielding the formula for the OLG of the cardiovascular system OLGcv: OLGcv ~ SVxSVRxBRS.

Several studies have indicated that BRS is reciprocally associated with respiratory rate (RR). Accordingly, the CVRI was proposed as a product of SV by SVR by 1/RR, divided by body surface area (BSA) for standardization of body size and by 4 in order to normalize the CVRI of healthy individuals to about 1 [25–27]. The basic CVRI formula is thus represented as:

$$CVRI = SVxSVR/(RRxBSAx4) \quad (1)$$

where SV = stroke volume, SVR = systemic vascular resistance, RR = respiratory rate, and BSA = body surface area.

Thus, a low CVRI may indicate a lesser adaptation capability due, for example, to acute volume loss and consequent haemodynamic deterioration.

As neither SV nor SVR can be reliably measured noninvasively, the CVRI formula shown above was converted to an equivalent clinical formula using conventional haemodynamic equations, namely, SV=CO/HR and SVR = 80*x*[(MABP−CVP)/CO]. Accordingly, CVRI=(CO/HR) *x*(80*x*(MABP−CVP)/CO)/(RR*x*BSA) *x*4, yielding the formula:

$$CVRI = 20(MABP-CVP)/(HRxRRxBSA), \quad (2)$$

where MABP = mean arterial blood pressure, CVP = central venous pressure, HR = heart rate, RR = respiratory rate and BSA = body surface area.

Previous studies have demonstrated an association of the CVRI with diverse morbidities and exercise capacity levels. A high CVRI of around 1 was associated with normal exercise capacity, a lower CVRI with a decreased exercise capacity, and an even lower CVRI, with morbidity. The lowest CVRI of around 0.2 was associated with shock of any type [26]. Others found that the CVRI decreased with increasing exercise, reaching a minimum of about 0.35 at peak exercise, regardless of the exercise capacity [27].

The aim of the present study was to determine if the pattern of the approximated CVRI ($CVRI_A$) complies with the course of haemorrhage-related haemodynamic deterioration in an experimental model simulating combat injury.

## 2. Methods

The original study was conducted at the Center for Innovative Surgery of the Hadassah Medical Center, Jerusalem with the Institute for Research in Military Medicine and the Trauma and Combat Medicine Branch of the Medical Corps of the Israel Defense Forces to study haemorrhage-related haemodynamic deterioration in the combat setting using a swine model. Swine were selected owing to their size and physiological similarity to humans [28,29]. The original study included 17 white domestic female pigs (Laboratory Animals Farm, Lahav, Israel) aged 12.4 months and weighing 41–50 kg. Twelve swine were randomly selected to undergo controlled haemorrhage and 5 served as controls. Animals in both groups were anesthetized and monitored according to an identical protocol. Serial measurements of a range of physiologic parameters were made during the course of haemodynamic deterioration, and each was documented with a time stamp. The cumulative blood loss was also monitored continuously, and each measurement was documented with a respective time stamp. In the experimental arm, controlled bleeding was stopped when MABP dropped to 30 mmHg, indicating shock. The findings were stored on a computerized spreadsheet in the Trauma Branch of the Surgeon General's Headquarters of the Israel Defense Forces.

Data of all 17 swine were used in the present study. Because both the physiologic parameters and the cumulative blood loss of

each animal were documented over time, we were able to integrate the serial physiological measurements on a haemodynamic-deterioration scale based on the cumulative blood loss until shock. The following physiological parameters and vital signs were considered relevant to our study: CO, MABP, CVP and HR. CO was measured indirectly using the delusion method. In brief, a solution with different characteristics from blood was injected into one end of the cardiovascular system, and the characteristics of the blood-solution at the other end were analyzed. A simple algorithm was then applied to determine CO. MABP was measured invasively via an arterial line, and CVP was measured via a central vein catheter. HR was measured by electrocardiography. As the animals were of the same age and gender and of similar weight (about 40 kg) and length (about 70 cm), the BSA of each was considered equal to $\approx 1\ m^2$ [30].

CVRI, SV, and SVR were calculated at every time point.

The restored measurements did not include RR. Moreover, the animals were artificially ventilated (around 14 RPM throughout the study), so the CVRI could only be approximated ($CVRI_A$). On the assumption of a linear association between RR and HR during bleeding in otherwise healthy animals, with an estimated RR:HR ratio of 1:5,. (i.e., RR ~ HR/5), we derived the following formula [25]:

$$CVRI_A = 100(MABP-CVP)/(HR^2*BSA) \quad (3)$$

where $CVRI_A$ = an approximation of CVRI, MABP = mean arterial blood pressure, CVP = central venous pressure, HR = heart rate and BSA = body surface area.

SV was computed as SV=CO/HR, where CO is cardiac output and HR is heart rate, and SVR was computed as SVR = 80*(MABP−CVP)/CO, where MABP is mean arterial blood pressure, CVP is central venous pressure and CO is cardiac output.

Blood loss was cumulatively measured, stratified in increments of 100 ml (1–100 ml, 101–200 ml, 201–300 ml, etc.), up to over 800 ml until reaching shock when active bleeding was stopped. Animals were not treated for shock yet continuously monitored.

The theoretical haemodynamic deterioration process proceeds from healthy uninjured pre-haemorrhage baseline, through progressive hypovolemia, and toward the inevitable deterioration to hemorrhagic shock. A schematic representation is shown in Fig. 1. According to the cardiovascular reserve hypothesis, the pattern of the assumed cardiovascular reserve is expected to consistently follow the process of the haemodynamic deterioration.

To test this hypothesis, measurements of the physiologic parameters and the $CVRI_A$ were correlated to predefined stages of haemodynamic deterioration, as follows: pre-bleeding, defined as the state before bleeding was initiated; hypovolemia, defined as continuous cumulative blood loss of 100 ml–800 ml; pending shock, defined as blood loss of more than 800 ml until MABP reached 30 mmHg; and shock. The latter stage was further divided into early shock, defined as the first hour after reaching shock, and late shock, as the period thereafter.

Each of the physiological parameters and the $CVRI_A$ was evaluated as a potential predictor of haemorrhage-related haemodynmic deterioration in terms of three predefined criteria.

1) *Strength of association*, evaluated by the Spearman correlation coefficient between the parameter evaluated and the stage of haemodynamic deterioration, with an acceptance limit of $r^2 > 0.5$.
2) *Threshold of hypovolemic detection*, defined as the minimal cumulative blood loss at which the parameter evaluated significantly decreased (to at least 15% of the baseline value).
3) *Indicative range*, defined as the range within which the parameter consistently and monotonously decreased in accordance with the expected haemodynamic deterioration (as shown in Fig. 1).

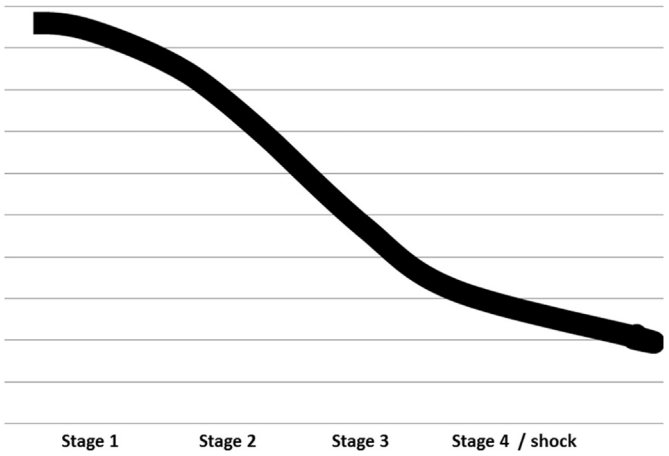


**Fig. 1.** Schema of the expected pattern of haemorrhage-related haemodynamic deterioration.

Bias and confounders were minimized by our use of existing research data to which the researchers were blinded. The use of accepted formulas to calculate the relevant variables at each documented time point assured high repeatability. The evaluation and comparison of measured physiological parameters with the severity of blood loss assured standardization of the process of haemodynamic deterioration.

### 2.1. Statistical analysis

Statistical analysis was performed with SPSS software, version 22 (IBM Inc., 2014). We performed multiple comparisons, and 95% confidence intervals (CI) were computed for each average. Multiple comparisons of means were evaluated by analysis of variance. The association between each potential predictor and the haemodynamic deterioration stage was analyzed with Spearman correlation coefficient ($P < 0.05$).

### 2.2. Ethics approval

The original study was approved by the Animal Ethics Committees of the Israel Ministry of Defense and Hebrew University. Permission was granted to perform the haemorrhage study with a minimal number of control animals; hence, the 5:2 ratio between the two arms. As the present study was based on the retrospective data documented in the original study, the Medical Corps, Academy Branch of the Israel Defense Forces waived the need for additional ethical approval.

## 3. Results

The preliminary analysis of the retrospective data of the experimental arm revealed an average duration of pre-bleeding anesthesia of 25 min (95% CI 22,27), of active bleeding, 60 min (95% CI 55,65), and of post-bleeding monitoring, 420 min (95% CI 370,490). The average cumulative blood loss was 960 ml (95% CI 905,1019). In the control group, the average duration of monitoring was 480 min.

On analysis of the compliance of the parameters evaluated with the prediction criteria (Table 1), HR had a high association with haemodynamic deterioration ($r^2 = 0.59$) with a low maximum-to-

minimum ratio (2.1). Its detection threshold was delayed until a blood loss of 600–700 ml, and it remained indicative to shock. The association of MABP with haemodynamic deterioration was lower than the acceptance limit ($r^2 = 0.27$) with a low maximum-to-minimum ratio (2.3). MABP had a detection threshold of 100–200 ml blood loss and an indicative range up to 700–800 ml blood loss. The association of CO with haemodynamic deterioration was low ($r^2 = 0.33$) with a low maximum-to-minimum ratio (1.9). Its detection threshold was delayed until a blood loss of 500–600 ml, and it remained indicative up to 800 ml blood loss. SV had a high association with haemodynamic deterioration ($r^2 = 0.57$) with a fair maximum-to-minimum ratio (3.2). Its detection threshold was delayed until a blood loss of 500–600 ml blood loss, and it remained indicative thereafter until shock. SVR had an extremely low association with haemodynamic deterioration ($r^2 = 0.02$), and practically SVR had no predictive capability. The association of the $CVRI_A$ with haemodynamic deterioration was high ($r^2 = 0.66$) with a high maximum-to-minimum ratio (5.2). The $CVRI_A$ had a detection threshold of 200–300 ml blood loss and remained indicative along the entire range of hypovolemia toward shock (Fig. 2).

Although CO had a low correlation coefficient with haemodynamic deterioration, it considered the best potential parameter for haemodynamic assessment. We found that CO values were preserved with some fluctuations in the range between pre-bleeding and hypovolemia of 400–500 ml cumulative blood loss (Fig. 3). CO had a detection threshold of 500–600 ml blood loss in a stairwise pattern. Its indicative range persisted thereafter only to 700–800 ml cumulative blood loss.

The study and control arms were compared for selected physiological parameters, vital signs, and the $CVRI_A$ at four consecutive 30-min intervals (0–29 min, 30–59 min, 60–89 min, 90–119 min) (Table 2). In the control arm, the average HR and MABP values remained stable over time. Unexpectedly, CO increased by 30% and CVP, by 120%. CVRI decreased by 30% in inverse proportion to the increase in CO.

## 4. Discussion

This study examined the ability of mean arterial blood pressure (MABP), heart rate (HR), stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) and the $CVRI_A$ to predict haemorrage-related haemodynamic deterioration in a swine model according to three preset criteria. The results showed that MABP had a high threshold of detection and a wide indicative range, but its strength of association with haemodynamic deterioration was lower than the acceptance limit. HR and SV met the criterion of strength of association, but their detection threshold was delayed and, accordingly, their indicative range was narrow. SVR had almost no predictive capability. The finding that CO, SV and HR values remained unchanged even during progressive haemorrhage is especially relevant for the evaluation of young and otherwise healthy combat casualties [17].

The $CVRI_A$ was the only parameter that met all three criteria for predicting haemorrhage-related haemodynamic deterioration. There was a high correlation coefficient between the CVRI and the haemodynmic deterioration process ($r^2 = 0.66$, $P < 0.001$). The detection threshold of the $CVRI_A$ was slightly lower than that of MABP, but its indicative range was wider. Therefore, the $CVRI_A$ appears to be a better predictor of haemodynamic deterioration than the other parameters evaluated.

Most of the other physiological parameters evaluated are measures of performance, whereas the CVRI is a measure of the cardiovascular reserve. As such, while CO is preserved early in the course of haemodynamic deterioration owing to compensatory physiological mechanisms, the CVRI, an estimate of the cardiovascular reserve, decreases already in the early stages.

We observed an unexpected abnormal 30% increase in CO in the control arm. We cannot explain this finding. It may have been due to the anesthesia, a hydration state, an unexplained increase in metabolic needs, or other unrecognized confounders. Surprisingly, the $CVRI_A$ decreased by 30%, in inverse proportion to the increase in CO. According to the cardiovascular reserve hypothesis, cardiac reserve is expected to decrease with an increase in CO.

This study was limited by the small size of the sample and the retrospective design. The CVRI has not been previously validated in animals, and its calculation on the basis of data derived from a previous animal study poses a risk of bias. Furthermore, the database lacked RR measurements, so we were able to calculate only the approximated CVRI ($CVRI_A$), which has not been validated in animals or humans. The $CVRI_A$ may be sufficient for the prediction of haemorrhage-related haemodynamic deterioration in otherwise healthy animals but could be less conclusive in the presence of multiple trauma or diverse co-morbidities or under combat-specific conditions such as dehydration, exposure to extreme climate, and physical exhaustion. Although swine are a popular model for human physiology, unlike humans, they are very sensitive to anesthesia [31], and swine blood pressure is far more sensitive to hypovolemia than human blood pressure. Finally, it should be noted that the level of evidence is Level III.

## 5. Conclusions

The $CVRI_A$ is a promising potential predictive measure of haemorrhage-related haemodynamic deterioration, but further validation is needed. It is easily computed from routinely measured vital signs (MABP, CVP, HR, RR and BSA) and does not require special medical devices or a specialized facility. Because it is a continuous measure, the trade-off between sensitivity and specificity may be optimally determined through receiver operating characteristic analysis.

Indirectly, the results of this study support the cardiovascular reserve hypothesis, although they do not by any means prove it. Further studies in animal models are warranted, preferably with

**Table 1**
Compliance with predefined criteria for haemorrhage-related hemodynamic deterioration prediction by each potential predictor.

| Criterion | HR | MABP | CO | SV | SVR | CVRI |
|---|---|---|---|---|---|---|
| Spearman Correlation coefficient $r^2$ with the hemodynamic deterioration proceedings | 0.59<br>$P < 0.001$ | 0.27<br>$P < 0.001$ | 0.33<br>$P < 0.001$ | 0.57<br>$P < 0.001$ | 0.02<br>$P = 0.007$ | 0.66<br>$P < 0.001$ |
| Threshold of Hypovolemic Detection (ml blood loss) | 600–700 ml | 100–200 ml | 500–600 ml | 500–600 ml | 500–600 ml | 200–300 ml |
| Indicative Range | 600–700 ml to shock | 100–200 ml to 700 –800 ml | 500–600 ml to 700 –800 ml | 500–600 ml to shock | Practically none | 200–300 ml to shock |
| Maximum to minimum ratio | 2.1 | 2.3 | 1.9 | 3.2 | 2.0 | 5.2 |

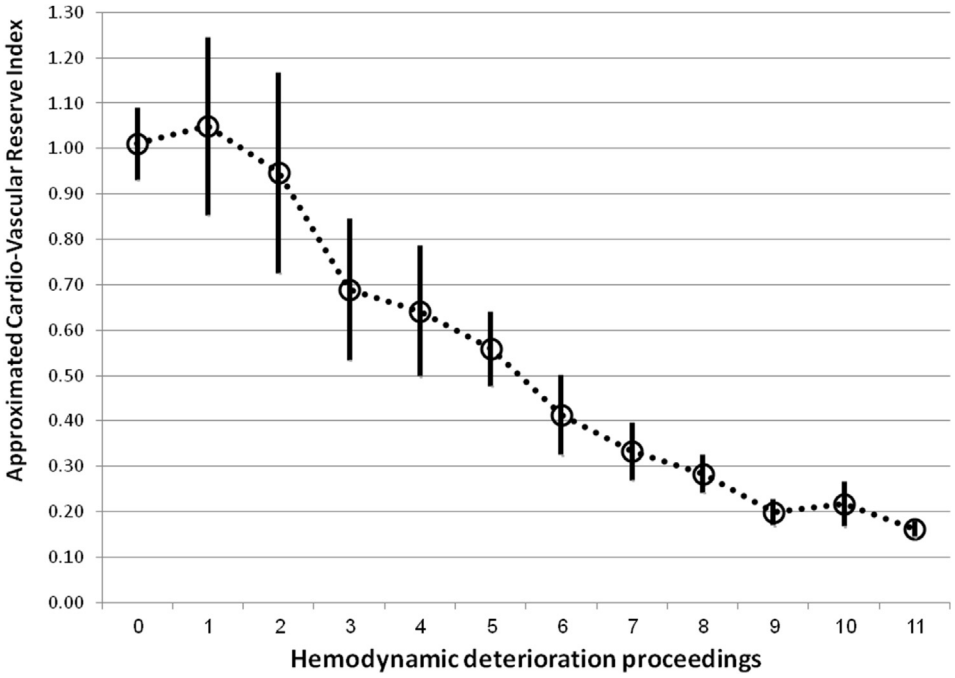


**Fig. 2.** Approximated cardiovascular reserve index ($CVRI_A$) in relation to the process of haemorrhage-related haemodynamic deterioration. 0- Pre-haemorrhage baseline; 1- 1–100 ml blood loss; 2- 101–200 ml blood loss; 3- 201–300 ml blood loss; 4- 301–400 ml blood loss; 5- 401–500 ml blood loss; 6- 501–600 ml blood loss; 7- 601–700 ml blood loss; 8- 701–800 ml blood loss; 9- Pending shock (>800 ml cumulative blood loss until MABP reaches <30 mmHg (shock), in which active bleeding is stopped); 10- Early shock (Within 1 h of reaching shock); 11- Late shock (>1 h after reaching shock).

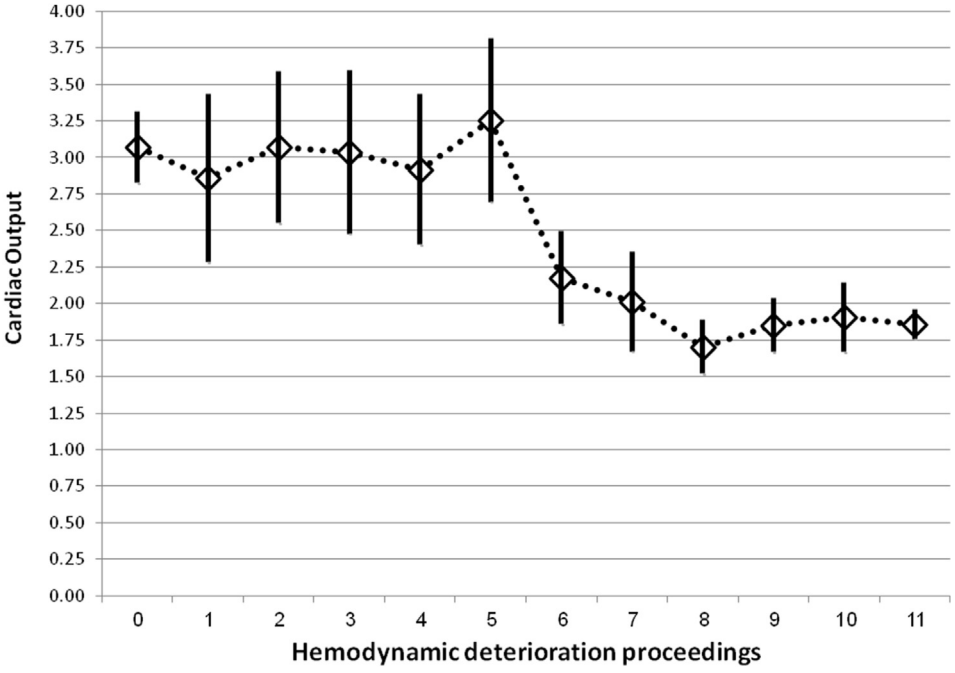


**Fig. 3.** Cardiac output (CO) in relation to the expected process of haemorrhage-related haemodynamic deterioration. 0- Pre-haemorrhage baseline; 1- 1–100 ml blood loss; 2- 101–200 ml blood loss; 3- 201–300 ml blood loss; 4- 301–400 ml blood loss; 5- 401–500 ml blood loss; 6- 501–600 ml blood loss; 7- 601–700 ml blood loss; 8- 701–800 ml blood loss; 9- Pending shock (>800 ml cumulative blood loss until MABP reaches <30 mmHg (shock), in which active bleeding is stopped); 10- Early shock (Within 1 h of reaching shock); 11- Late shock (>1 h after reaching shock).

the use of sedation that allows for spontaneous respiration. This will provide real-time RR measurements, making it possible to calculate the true CVRI rather than the approximated CVRI ($CVRI_A$). Ultimately, clinical and field studies will be needed to determine if the cardiovascular reserve is an effective means for detecting and monitoring haemodynamic deterioration in combat casualties.

**Table 2**
Physiological parameters averages by research arm and by monitoring period.

| Measure | Research arm | Monitoring period | | | |
|---|---|---|---|---|---|
| | | 0–29 min | 30–59 min | 60–89 min | 90–119 min |
| Blood loss | Control | 0 | 0 | 0 | 0 |
| | Haemorrhage | 33 | 231 | 731 | 898 |
| CO | Control | 2.5 | 3.0 | 3.2 | 3.3 |
| | Haemorrhage | 3.1 | 2.9 | 2.0 | 1.8 |
| CVP | Control | 6.6 | 12.3 | 14.9 | 13.6 |
| | Haemorrhage | 10.3 | 10.3 | 8.1 | 7.9 |
| HR | Control | 75 | 74 | 78 | 76 |
| | Haemorrhage | 78 | 79 | 97 | 114 |
| MABP | Control | 62 | 59 | 58 | 61 |
| | Haemorrhage | 67 | 57 | 34 | 31 |
| CO | Control | 2.5 | 3.0 | 3.2 | 3.3 |
| | Haemorrhage | 3.1 | 2.9 | 2.0 | 1.8 |
| CVRI | Control | 1.05 | 0.85 | 0.78 | 0.83 |
| | Haemorrhage | 1.01 | 0.80 | 0.33 | 0.23 |

## Ethical approval

The study was based on existing data base.

## Sources of funding

None.

## Author contribution

Roy Nadler contributed in (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article and (3) final approval of the version to be submitted.

Elon Glassberg contributed in (1) the conception and design of the study, analysis and interpretation of data, (2) drafting the article and (3) final approval of the version to be submitted.

Note that the above authors share equivalent contribution as the primary investigators and authors.

Itay E Gabbay contributed in (1) the analysis and interpretation of data, (2) drafting the article and (3) final approval of the version to be submitted.

Linn Wagnert-Avraham contributed in (1) performing the study, (2) acquisition of data, and (3) final approval of the version to be submitted.

Gal Yaniv contributed in (1) performing the study, (2) acquisition of data, and (3) final approval of the version to be submitted.

David Kushnir contributed in (1) performing the study, (2) acquisition of data, and (3) final approval of the version to be submitted.

Arik Eisenkraft contributed in (1) performing the study, (2) acquisition of data, and (3) final approval of the version to be submitted.

Ben-Zion Bobrovsky contributed in (1) the analysis and interpretation of data, (2) revising the article critically for important intellectual content (3) final approval of the version to be submitted.

Uri Gabbay contributed in (1) the analysis and interpretation of data, (2) drafting the article and (3) final approval of the version to be submitted.

## Conflicts of interest

Gabbay and Bobrovsky had applied for a patent on CVRI.

## Guarantor

Roy Nadler.
Elon Glassberg.
Arik Eisenkraft.
Uri Gabbay.

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