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To cite this article: Frank C Bennis *et al* 2017 *Physiol. Meas.* **38** 1791

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# A machine-learning based analysis for the recognition of progressive central hypovolemia

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Received 18 March 2017, revised 23 June 2017

Accepted for publication 3 July 2017

Published 21 August 2017



## Abstract

**Objective:** Traditional patient monitoring during surgery includes heart rate (HR), blood pressure (BP) and peripheral oxygen saturation. However, their use as predictors for central hypovolemia is limited, which may lead to cerebral hypoperfusion. The aim of this study was to develop a monitoring model that can indicate a decrease in central blood volume (CBV) at an early stage. **Approach:** Twenty-eight healthy subjects (aged 18–50 years) were included. Lower body negative pressure (−50 mmHg) was applied to induce

central hypovolemia until the onset of pre-syncope. Ten beat-to-beat and four discrete parameters were measured, normalized, and filtered with a 30 s moving window. Time to pre-syncope was scaled from 100%–0%. A total of 100 neural networks with 5, 10, 15, 20, or 25 neurons in their respective hidden layer were trained by 10, 20, 40, 80, 160, or 320 iterations to predict time to pre-syncope for each subject. The network with the lowest average slope of a fitted line over all subjects was chosen as optimal. *Main results:* The optimal generalized model consisted of 10 hidden neurons, trained using 80 iterations. The slope of the fitted line on the average prediction was  $-0.64$  (SD 0.35). The model recognizes in 75% of the subjects the need for intervention at  $>200$  s before pre-syncope. *Significance:* We developed a neural network based on a set of physiological variables, which indicates a decrease in CBV even in the absence of HR and BP changes. This should allow timely intervention and prevent the development of symptomatic cerebral hypoperfusion.

Keywords: machine learning, prediction, hypovolemia, cerebral perfusion, pre-syncope, neural networks

(Some figures may appear in colour only in the online journal)

## Introduction

Anesthetized patients are prone to the development of undetected central hypovolemia, which is a shortage of blood volume directly available to the left ventricle of the heart. Central hypovolemia affects cardiac output (CO) and may jeopardize cerebral perfusion (van Lieshout *et al* 2003). A decrease in central blood volume (CBV) may occur due to a variety of causes, ranging from bleeding and spinal anesthesia to preoperative fasting and the compression of major veins (Joshi *et al* 2016).

Traditional patient monitoring during surgery includes the monitoring of heart rate (HR), blood pressure (BP) and peripheral oxygen saturation. However, the value of these monitored parameters as an indicator for central hypovolemia is insufficient (Hamilton-Davies *et al* 1997, Orlinsky *et al* 2001), as exemplified during World War II in which air raid victims suffered from major blood loss with relative bradycardia rather than the expected tachycardia (Grant and Reeve 1941). Faced with central hypovolemia, cardiovascular control mechanisms maintain BP despite reductions in CBV of up to 30%. A decrease beyond approximately 30% of the CBV marks the second phase of hypovolemic shock. In this phase, a Bezold–Jarisch-like reflex ceases sympathetic activity together with the development of vagal activation (Jarisch and Richter, 1939, Kinsella and Tuckey 2001, Secher and van Lieshout 2016). As a result, HR and/or systemic vascular resistance (SVR) decline, followed by a decrease in BP (Barcroft and Edholm 1945, Warren *et al* 1945, Schadt and Ludbrook 1991, van Lieshout *et al* 1991). The late development of changes in HR and BP explains the clinical delay in recognizing the occurrence of central hypovolemia. As a result, the development of cerebral hypoperfusion during surgery may pass unnoticed, resulting in brain hypoxemia with the risk of developing postoperative neurological impairment (Casati *et al* 2005).

Although cardiovascular parameters such as thorax impedance (TI) and variation in pulse pressure ( $P_{\text{pulse}}$ ) relate to CBV (Cai *et al* 2000, van Lieshout *et al* 2005, Convertino *et al* 2006, Bronzwaer *et al* 2014, 2015) and thus may contain valuable information related to central hypovolemia in an early stage, each is unable to indicate central hypovolemia by itself. However, combining several of these parameters may provide a better prediction. To interpret

the complex relationship between numerous continuous cardiovascular parameters for early or even hidden information, machine learning may offer new opportunities for complex biomedical signal analysis to support perioperative monitoring. Among machine learning models, neural networks are used to create a prediction based on the complex and non-linear relationships between parameters (Mitchell 1997). We evaluated whether a neural network approach using a large set of biomedical parameters can add in diagnosing a decrease in CBV at an early stage. Therefore, the aim of this study was to develop a neural network using beat-to-beat physiological parameters and static parameters (age, gender, weight, and height) to diagnose a decrease in CBV at an early stage.

## Methods

### *Subject population*

Healthy, non-smoking subjects aged between 18 and 50 years were recruited by advertisement in the Academic Medical Centre in Amsterdam (AMC), excluding any subject with a history of and/or treatment for cardiovascular disease, diabetes, and fainting. The measurements were performed between 6 January 2015 and 11 June 2015. Prior to inclusion, a full medical history was obtained, followed by physical examination and oscillometric BP as well as ECG measurements to assess the presence of cardiovascular contra-indications for the procedure. The study was approved by the Medical Ethics Committee of the AMC. Written informed consent was obtained from all subjects before any measurement.

### *Study design*

Measurements were performed in a quiet room. Subjects were informed about the procedures involved and instructed to empty their bladder prior to the start of testing. They abstained from coffee, tea, sports, and fatty foods the day before measurement. With the subject in the supine resting position a lower-body negative pressure (LBNP) box was placed over the lower body. The LBNP box sealed the subject from hip to toes, enabling the buildup of a pressure difference between the upper and lower body. It was verified whether the box created and maintained a subatmospheric pressure of  $-50$  mmHg. A baseline of 5 min, consisting of the same parameters obtained during LBNP, was measured after 25 min of supine rest. A LBNP of  $-50$  mmHg was induced after the baseline and maintained for 30 min or terminated earlier in the case of the development of signs or symptoms of pre-syncope such as lightheadedness, nausea, or blurry vision. Pre-syncope was additionally defined as a sudden consistent reduction of  $>25$  mmHg in systolic blood pressure ( $P_{sys}$ ), of  $>15$  mmHg in diastolic blood pressure ( $P_{dia}$ ), or of  $>15$  beats  $min^{-1}$  in HR, as these parameters will change with a large ( $>30\%$ ) decrease of CBV (Secher and van Lieshout 2016). The start and end of the baseline and LBNP was indicated by markers. Data from the subjects not experiencing pre-syncope within 30 min were excluded from the analysis.

### *Measurement parameters*

BP was measured by plethysmography at the middle finger of the left hand (Nexfin, Edwards Lifesciences BMEYE, Amsterdam, The Netherlands) during the entire experiment. The signal was stored at 200 Hz. TI (Model AI-601G, Nihon Kohden, Japan) was measured by placing electrodes in the neck and on the upper body at the level of the xiphoid process. TI measures conduction through the chest as a gauge of CBV. The analog TI signal and a marker device

were sampled at 200 Hz and stored on disk. The raw BP curve was extracted from the Nexfin. All signals were resampled at 100 Hz using Matlab (2016A, The MathWorks, Natick, MA, USA). Nine beat-to-beat parameters were extracted directly from the Nexfin. These parameters consist of  $P_{\text{sys}}$ ,  $P_{\text{dia}}$ , mean arterial pressure ( $P_{\text{mean}}$ ),  $P_{\text{pulse}}$ , HR, SV, CO, SVR, and left ventricular ejection time (LVET). Corresponding beat-to-beat values of TI were added as a parameter. Age, gender, height, and weight were entered as static parameters.

### Analysis

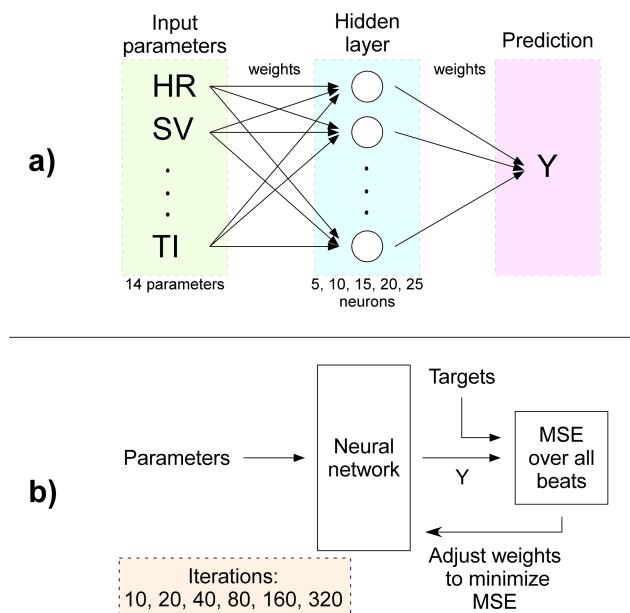
Analysis was performed off-line using a custom-made Matlab algorithm combined with the neural network toolbox in Matlab. The LBNP period was selected based on the manually defined markers. A 30 s baseline period containing few or no artifacts was selected out of the recorded baseline to accurately reflect the resting state of the subject. Recordings during the first 120 s of LBNP were removed to discard the sudden hemodynamic changes that occur at the start of LBNP. Data was visually inspected for artifacts in the raw BP curve and in the beat-to-beat parameters HR, SV, SVR, and TI. Artifacts were removed with subsequent interpolation of the remaining data.

All beat-to-beat parameters were normalized to their median value within the selected baseline period. Thereafter, these were smoothed using an averaging filter with a moving 30 s window. Because time to pre-syncope and HR varied between subjects, the amount of beat-to-beat parameter values estimated for each subject differed between subjects. To ensure that each subject contributed an equal number of samples to the model, subject data were resampled to the median number of beat-to-beat parameter values over all subjects.

**Model design and statistics.** The input to the neural network for the prediction at the time point of each heartbeat contained ten beat-to-beat parameters measured at that single heartbeat, as well as static data on age, sex, height, and weight (figure 1). Time to pre-syncope was scaled from 100%–0%, with 100% defined as 120 s after initiation of LBNP and 0% as the onset of pre-syncope. Time to pre-syncope was the desired output of the model for each training instance.

Data was divided into a training set and test set. The training set consisted of all but one subject. The test set consisted of the remaining subject. Each subject served once as a test set. For each test set, 100 neural networks were trained using the training set, as more neural networks did not increase performance, while it did increase computation time. All neural networks were initialized randomly. Thereafter, models were trained using the Levenberg–Marquardt algorithm for backpropagation. Each of the 100 neural networks predicted the time to pre-syncope for the selected test subject. These 100 predictions were averaged to create a single average prediction of the selected test subject. We assumed normovolemia at the initiation of LBNP and therefore the average predicted time to pre-syncope was set equal to 100% at the start. Each of the tested subjects served once as a test set (leave-one-out cross-validation) in the above-described procedure, finally resulting in an average prediction for each subject. These predictions ideally start at 100% when the true time remaining is also 100%, and indicate 0% when the true time remaining is also 0%. Therefore, when plotting the true time remaining versus the predicted time remaining, the ideal slope would be  $-1$ .

The above-mentioned model was created with a variable number of nodes in the hidden layer and a variable number of iterations during the training phase (figure 1), influencing the complexity of the model and the amount of training on the data. The number of hidden nodes were 5, 10, 15, 20, or 25 (figure 1(a)) and the number of iterations 10, 20, 40, 80, 160, or 320 (figure 1(b)). This resulted in a total of 30 combinations of hidden neurons and training



**Figure 1.** (a) Overview of the neural network. A total of 14 input parameters are connected by weights to the hidden layer with a variable number of neurons. The hidden layer neurons are connected by weights with the output ( $Y$ ). (b) Overview of a single iteration of the training model. Parameters enter the neural network, which generate a certain output for each beat. The mean squared error (MSE) of all predicted outputs compared with the actual output is generated. After this, the weights are altered to minimize the MSE.

iterations. Because each combination leads to an average prediction over 100 neural networks, the result was a grid of average predictions for each subject. A straight line was fitted to each of the 30 average predictions, the slope of which should be ideally  $-1$ , i.e. equal to the expected target slope. For each combination of hidden nodes and number of iterations, the slopes were subsequently averaged over all subjects. Each averaged slope can be interpreted as the expected slope of the prediction on a new subject. The least complex combination of hidden nodes and iterations that led to a slope closest to  $-1$  with the lowest standard deviation (SD) was considered the optimal model. Using the outcome on the test set to select the optimal model may introduce an optimistic outlook. However, no contamination between the training and test set is expected, because the data are already trained and tested at the moment of optimal model selection, thus reducing the possibility of an overly optimistic outlook. The fitted line on a prediction is used to evaluate the quality of the neural network, while the actual predictions by the model assess the quality of the model-prediction in an individual subject.

## Results

A total of 28 subjects (12 male, aged  $25 \pm 5$  years, weight  $71 \pm 10$  kg, height  $174 \pm 11$  cm) were included and experienced pre-syncope. The procedure was stopped, because of a decline in BP ( $n = 2$ ), symptoms such as dizziness, lightheaded and impaired vision ( $n = 10$ ), or a combination of symptoms and a decline in BP or HR ( $n = 14$ ). The reason for discontinuation of the procedure was not documented for two subjects.

**Table 1.** Mean slopes with standard deviation for each combination of iterations and number of neurons in the hidden layer. Four models have a slope of  $-0.64$ , which is the closest to the target slope of  $-1$ . The least complex model with the lowest standard deviation is displayed in bold.

Iterations	Neurons in hidden layer				
	5	10	15	20	25
10	$-0.49 (0.24)$	$-0.58 (0.30)$	$-0.60 (0.32)$	$-0.60 (0.34)$	$-0.61 (0.36)$
20	$-0.55 (0.28)$	$-0.62 (0.34)$	$-0.61 (0.37)$	$-0.62 (0.38)$	$-0.62 (0.41)$
40	$-0.56 (0.29)$	$-0.62 (0.36)$	$-0.62 (0.37)$	$-0.64 (0.40)$	$-0.63 (0.44)$
80	$-0.57 (0.28)$	<b><math>-0.64 (0.35)</math></b>	$-0.61 (0.35)$	$-0.62 (0.37)$	$-0.62 (0.44)$
160	$-0.57 (0.28)$	$-0.64 (0.35)$	$-0.59 (0.36)$	$-0.58 (0.34)$	$-0.57 (0.41)$
320	$-0.57 (0.28)$	$-0.64 (0.35)$	$-0.59 (0.35)$	$-0.59 (0.34)$	$-0.57 (0.37)$

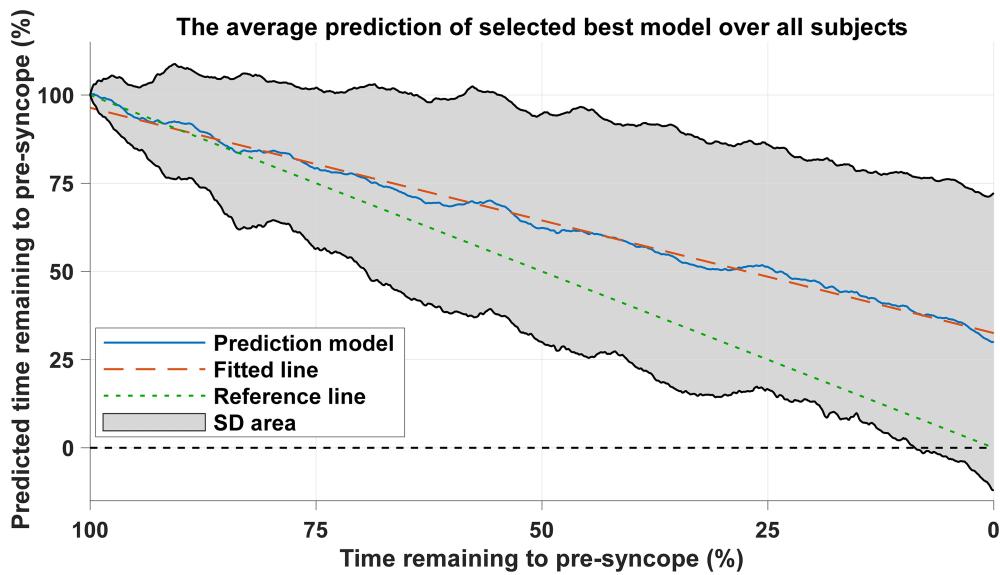
The model with 80 iterations and ten hidden neurons was found to be the least complex model where the slope was closest to  $-1$  with the lowest SD (table 1). The average prediction with the SD of this model shows how the model would predict on average on new subjects (figure 2). The median SD of the residuals of the prediction of each subject minus the corresponding fitted line is 7.2, indicating that the predictions differ up to plus minus 7.2% from the fitted line in two-thirds of the predictions.

The prediction of the model was compared to the evolution of BP and HR level of an individual (figure 3). The model indicated a decrease in time remaining to pre-syncope from the start of LBNP with a slope of 0.76 for this particular subject, whereas the parameters BP and HR, respectively, did not show any change or changed in a later phase. A decrease in time remaining to pre-syncope indicated by the model was not just seen for this subject but for each subject, as the fitted line on the prediction displayed a negative slope for each subject (not shown).

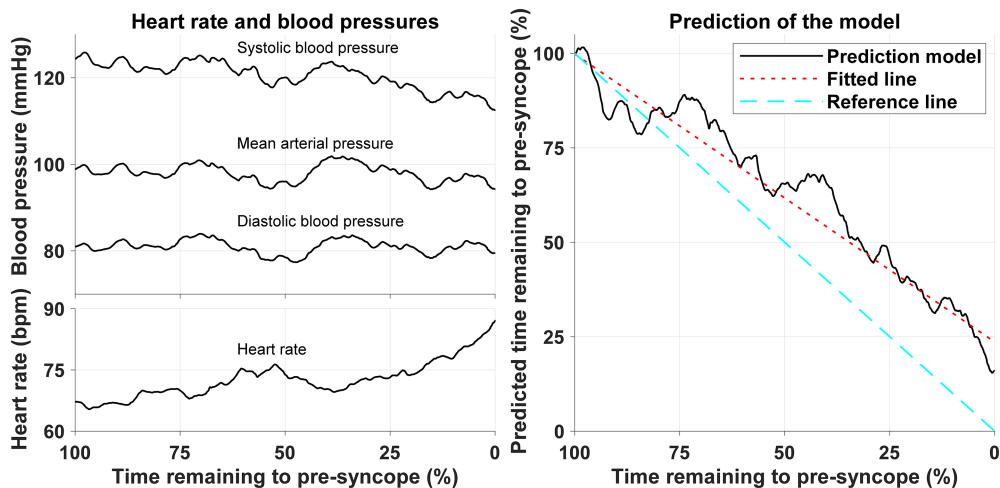
Ideally (slope =  $-1$ ), the model predicts 0% time remaining to pre-syncope with 0 s remaining. If the model-predicted slope is steeper than in reality ( $< -1$ ), the model predicts 0% time remaining to pre-syncope, while in reality there is time remaining to pre-syncope. If the model-predicted slope is less steep than in reality ( $> -1$ ), the model does not reach 0% before pre-syncope occurs, resulting in an overestimation of the remaining part. In this study, the model predicted 0% time remaining to pre-syncope for six subjects, with on average 253 s remaining (figure 4). For a total of 14 subjects, the model predicted 25% time remaining to pre-syncope, with on average 225 s remaining. The 50% time remaining to pre-syncope level is predicted for 21 subjects, with on average 342 s remaining, while for all but one subject the model predicted 75% time remaining to pre-syncope with on average 439 s remaining. If we assume that intervention is needed when the predicted time remaining is  $\leq 75\%$ , the model recognizes the need for intervention more than 200 s before pre-syncope in 75% ( $n = 21$ ) of the subjects.

## Discussion

The created neural network recognized a decrease in CBV as evoked by LBNP in an early stage using beat-to-beat cardiovascular parameters and information on age, weight, height, and sex. In individual patients, the measured downward trend may be seen before BP and HR show any noticeable changes (figure 3). As the procedure was discontinued in ten subjects, due to symptoms indicated by the subject, while during anesthesia the subject is not able to



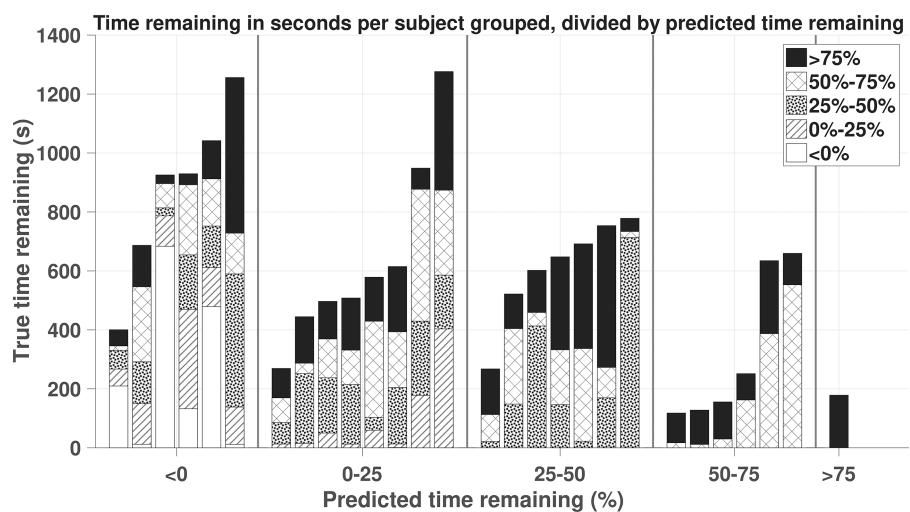
**Figure 2.** Average prediction of the selected best model on the test subjects. At 100% the test starts, at 0% pre-syncope occurs. This prediction shows how the model would predict on average on new subjects. The average prediction shows a stable decline with a slope less steep than the actual slope.



**Figure 3.** Left: commonly measured parameters  $P_{\text{sys}}$ ,  $P_{\text{dia}}$ ,  $P_{\text{mean}}$ , and HR. Blood pressures remain stable, while HR shows a clear increase the moment less than 25% of time is remaining. Right: the predicted time remaining to pre-syncope in % for this subject. A decreasing trend for CBV can be seen from the beginning of the experiment.

indicate these symptoms, pre-syncope as a serious expression of central hypovolemia will not be recognized until in a later stage.

As soon as a decrease in BP or HR was recognized, the procedure was discontinued. We showed that our model indicated a decrease well before discontinuation of the procedure (figure 4) and thus before a decrease in BP or HR (figure 3), with >200 s remaining in 75%



**Figure 4.** Total time in seconds remaining to pre-syncope versus the predicted time remaining for each subject. Subjects are divided into groups based on the lowest value of the time remaining predicted by the model. Lower predicted times remaining at 0 s remaining reflect a steeper slope, with a predicted time remaining of 0% as ideal. Each bar represents one subject, of which the top corresponds to a predicted time of 100% with the number of seconds remaining as displayed on the y-axis. As the subject progresses in time, the true time remaining in seconds decreases, while the predicted time remaining also decreases. This is visualized by the different segments in one bar.

of the subjects at the 75% level. The SD of the residuals shows that while fluctuations are present, the prediction is on average relatively stable compared to the fitted line. It has to be noted that of the seven subjects in which prediction did not reach 75% with more than 200 s remaining, the time spent in LBNP without the initial 120 s was <200 s for four persons and between 200 and 300 s for the remaining three. It is possible that the procedure was stopped too early in these cases, due to false symptom recognition. If we exclude subjects in whom pre-syncope occurred before 300 s, the model reaches the 75% threshold for every subject and 50% for 19 out of 21 subjects. These results indicate that because the model can recognize a decrease in CBV in an early stage, it may assist the anesthesiologist in decision-making. Starting treatment for central hypovolemia at low values of predicted time remaining results in treating few subjects, but may prevent pulmonary and/or peripheral edema due to overfilling. The model was able to detect pending pre-syncope and subsequent cerebral hypoperfusion, while none of the parameters used measured cerebral perfusion. Incorporating parameters that measure cerebral perfusion may further improve the recognition of decreased CBV. The two commonly used parameters to measure cerebral perfusion, near-infrared spectroscopy and transcranial Doppler ultrasound, may both be able to show changes in cerebral perfusion before other hemodynamic parameters (Albina *et al* 2004, Plachky *et al* 2004).

#### Comparison with the literature

Machine learning techniques were also used to develop the compensatory reserve index (CRI), indicating the amount of reserve before pre-syncope will occur in a subject on a scale from one to zero (Convertino *et al* 2011, Moulton *et al* 2013). The CRI is shown to be more predictive for hypovolemia than the commonly used shock index, which is the ratio of HR to  $P_{sys}$  (van Sickle

*et al* 2013). Furthermore, a decrease in CRI is seen when a small amount of blood (450 ml) is withdrawn from a subject (Nadler *et al* 2014, Stewart *et al* 2014). However, when withdrawing an average of 1.2 l in 20 subjects, the CRI decreased on average by 33%. This small decrease in CRI suggests that the CRI underestimates larger amounts of blood loss (Convertino *et al* 2015).

An important difference between our model and the CRI is the collected data on which to train the respective models. The CRI model is trained on subjects who underwent a stepwise LBNP protocol in which LBNP is lowered after every 5 min by 5 mmHg, until pre-syncope occurs. The CRI is based on the prediction of the current level of LBNP and the predicted level of LBNP at which pre-syncope will occur. During a 5 min period at a certain level of LBNP, both the predicted current and final level of LBNP will be constant if the algorithm is correct. Therefore, during this 5 min period, the CRI will be stable. This is also seen in the outcome, as the predicted levels of LBNP show a stepwise fashion, with high correlation to the actual level of LBNP ( $r = 0.94$ ) (Convertino *et al* 2011). When estimating the CRI out of these levels of LBNP, the result is a stepwise CRI (Moulton *et al* 2013). However, even though LBNP is constant between two steps, there is still a change in CBV, which is not taken into account by the CRI. In our study, a constant level of LBNP was used, resulting in a continuous change in CBV during the procedure. Therefore, our model is trained to detect a change in CBV without the effect of the change in LBNP, which may be closer to the real-life situation of central hypovolemia. Furthermore, our study is to be applied in the operating room (OR). As the CRI is developed for the battlefield, our model can take more parameters into account. The difference in the model as well as the target group makes this a good addition for use in the OR.

#### Limitations

First, the number of subjects in our neural network is relatively small. Although this drawback is partially compensated for by the low number of parameters, increasing the number of subjects may increase the accuracy of the prediction. Furthermore, increasing the number of subjects opens the possibility of creating more diversity in the models by subset selection of the subjects, leading to possible better predictions. Due to the low number of subjects, no validation set was used in this study. This may introduce an overly optimistic outlook for the selected optimal model. In this study, however, a clear downward trend was found for all possible combinations of hidden neurons and iterations (table 1). This suggests that a good prediction model would have been found for all possible combinations tested. For future studies, the inclusion of a validation set together with more subjects is recommended. Second, measurements were discontinued if the vasovagal response developed or if a subject indicated symptoms of pre-syncope. Because the onset of symptom occurrence is not by definition equal to the moment of pre-syncope, some measurements might have been interrupted early. Although this fact warrants subgroup analysis based on stopping criteria, this cannot be performed due to the low number of subjects. Third, we set the average prediction at the start equal to 100%, because we assumed normovolemia at the initiation of LBNP. It is realistic that the subjects were slightly hypovolemic, setting the true initial value below 100%. This decreases the slope of the reference line and may indicate that the calculated slope for the subjects may be closer to the reference slope than stated previously. Finally, the model requires measurement of a baseline period, which may not be available in acute cases. In these cases, baseline values may be estimated based on patient characteristics. A different approach would be to abandon normalization of parameters to the baseline, though possibly at the expense of prediction accuracy. The possibly lower prediction accuracy when using non-normalized parameters might be counteracted by the inclusion of trend parameters.

## Conclusion

We developed a neural network based on a set of physiological variables that can diagnose decreases in CBV at an early stage even in the absence of HR and BP changes. This should allow for more timely intervention and may prevent cerebral hypoperfusion.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Conflict of interest

The authors declare that there is no conflict of interest.

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