Published in Journal of Applied Physiology, 24 May 2018
https://doi.org/10.1152/japplphysiol.01009.2017


# RESPIRATORY PUMP MAINTAINS CARDIAC STROKE VOLUME DURING HYPOVOLEMIA IN YOUNG HEALTHY VOLUNTEERS

[1]Maria Skytioti, [2, 3]Signe Søvik, [1]Maja Elstad

[1]Division of Physiology, Institute of Basic Medical Sciences, University of Oslo, P.O. Box 0317, Blindern, 0317 Oslo, Norway

[2]Dept. of Anaesthesia and Intensive Care, Akershus University Hospital, P.O. Box 1000, 1478 Lørenskog, Norway

[3]Institute of Clinical Medicine, University of Oslo
P.O. Box 1171 Blindern, 0318 Oslo, Norway

**Corresponding author:**

M. Skytioti, Univ. of Oslo, Institute of Basic Medical Sciences, Division of Physiology;
P.O. Box 1103, Blindern, 0317 Oslo, Norway.
**E-mail:** maria.skytioti@medisin.uio.no
Phone number: 0047-22845575

**Author contributions:** Literature search: MS, SS, ME, Data collection: MS, ME, Study design: ME, Analysis of data: MS, SS, ME, Manuscript preparation: MS, ME, Review of manuscript: MS, SS, ME

**Funding:** The study was funded by the University of Oslo and the Research Council of Norway (Grant 230354).

No conflict of interest is declared

**Short Title:** Respiratory pump maintains stroke volume in hypovolemia

**Abstract**

Spontaneous breathing has beneficial effects on the circulation, since negative intrathoracic pressure enhances venous return and increases cardiac stroke volume. We quantified the contribution of the respiratory pump to preserve stroke volume during hypovolemia in awake, young, healthy subjects. Non-invasive stroke volume, cardiac output, heart rate and mean arterial pressure (Finometer) were recorded in 31 volunteers (19 females), 19-30 years old, during normovolemia and hypovolemia (approximating 450-500 ml reduction in central blood volume) induced by lower body negative pressure. Control-mode non-invasive positive pressure ventilation was employed to reduce the effect of the respiratory pump. The ventilator settings were matched to each subject's spontaneous respiratory pattern. Stroke volume estimates during positive pressure ventilation and spontaneous breathing were compared with Wilcoxon matched-pairs signed-rank test. Values are overall medians. During normovolemia, positive pressure ventilation did not affect stroke volume or cardiac output. Hypovolemia resulted in an 18% decrease in stroke volume and a 9% decrease in cardiac output ($p<0.001$). Employing positive pressure ventilation during hypovolemia decreased stroke volume further by 8% ($p<0.001$). Overall, hypovolemia and positive pressure ventilation resulted in a 26% reduction in stroke volume ($p<0.001$) and 13% in cardiac output ($p<0.001$), compared to baseline. Compared to the situation with control-mode positive pressure ventilation, spontaneous breathing attenuated the reduction in stroke volume induced by moderate hypovolemia by 30% (i.e., -26% vs. -18%). In the critically ill patient with hypovolemia or uncontrolled hemorrhage, spontaneous breathing may contribute to hemodynamic stability, while controlled positive pressure ventilation may result in circulatory decompensation.

**Keywords**: cardiac output, cardiac stroke volume, hypovolemia, respiratory pump

Published in Journal of Applied Physiology, 24 May 2018
https://doi.org/10.1152/japplphysiol.01009.2017


48 **New and Noteworthy**

49 Maintaining spontaneous respiration has beneficial effects on hemodynamic compensation,
50 which is clinically relevant for intensive care patients. We have quantified the contribution of
51 the respiratory pump to cardiac stroke volume and cardiac output in healthy volunteers during
52 normovolemia and central hypovolemia. The positive hemodynamic effect of the respiratory
53 pump was abolished by non-invasive low-level positive pressure ventilation. Compared to
54 control-mode positive pressure ventilation, spontaneous, negative-pressure ventilation
55 attenuated the fall in stroke volume by 30%.

56

57

58

## Introduction

Spontaneous respiration has important beneficial effects on circulatory homeostasis (26, 32), aside from its vital role in gas exchange and acid-base balance (33). Importantly, favorable effects on the circulation by spontaneous respiration have been demonstrated in both patients and healthy individuals (36, 45). The negative intrathoracic pressure generated during inspiration enhances venous return and increases cardiac preload, stroke volume (SV), and cardiac output (CO) (8, 41, 46). During severe dehydration or acute hypovolemia due to hemorrhage, preserving spontaneous respiration can delay hemodynamic decompensation (32). In a randomized study, paced slow breathing of 6 breaths per minute with increased tidal volumes ($V_T$) resulted in improved tolerance to orthostatic stress induced by head-up tilt and lower body negative pressure, compared to spontaneous breathing with a mean respiratory rate (Rf) of 20 breaths per minute (26). Analogously, hyperventilation with both increased Rf and $V_T$ has been observed experimentally in response to progressive hypovolemia (6) and is a common clinical finding in hemodynamically unstable patients, e.g. those with severe sepsis (38) or hemorrhage (13). The effects of the respiratory pump on the circulation have also been indirectly demonstrated with the use of an impedance threshold device, used as a therapeutic measure in hypovolemia and hypotension (8, 36, 37, 45). The impedance threshold device enhances the physiological effects of the respiratory pump by applying resistance during spontaneous inspiration, thus augmenting the decrease in intrathoracic pressure. The use of this device during hemodynamic instability maintained cardiac SV and arterial blood pressure and delayed presyncope by optimizing the physiological effects of spontaneous respiration on the circulation (7, 35, 36). In normovolemic and hypovolemic anesthetized pigs, continuous application of negative intrathoracic pressure via an intrathoracic pressure regulator increased mean arterial blood pressure and improved cerebral and coronary perfusion pressures; the effects were more pronounced during severe hypovolemia (47).

Mechanical positive pressure ventilation, on the other hand, can result in hemodynamic decompensation, particularly during hypovolemia (30, 31). In the intensive care unit (ICU), pressure or volume controlled ventilatory modes delivering tidal breaths at a predetermined rate are usually changed to supported modes as soon as patient pathophysiology allows. In supported, or assisted, ventilatory modes the patient's spontaneous inspiratory effort triggers the delivery of each positive pressure tidal breath, and importantly, the patient's diaphragmatic and intercostal muscle contractions contribute to filling the lungs. As a result, intrathoracic positive pressures are often lower in supported modes (20). Modern ICU ventilators can be triggered by a patient's inspiratory effort also during controlled modes, thus assisting additional, spontaneous breaths (5). This is in contrast to most ventilators used in the operating room, where the anaesthetic doses necessary during surgery usually abolish spontaneous breathing efforts.

The use of positive pressure ventilation abolishes the negative intrathoracic pressure during inspiration, thus the beneficial circulatory effects of the respiratory pump are reduced (41). Moreover, positive end expiratory pressure (PEEP) is often applied to expand the lung, prevent atelectasis, and recruit alveoli for oxygenation. The use of PEEP, however, further impedes venous return (3, 27, 41). The negative effects of positive pressure ventilation on venous return and cardiac preload are more pronounced during hypovolemia (30, 31). Positive pressure ventilation is thus an additional challenge for already hemodynamically compromised patients. In a clinical setting, the anaesthetic agents necessary to make the patient accept orotracheal intubation will further impede the circulation through their sympatholytic, vasodilatatory and cardiodepressant effects (1). Critical care and trauma patients who received early prehospital intubation and mechanical ventilation were more prone to circulatory collapse with poor outcomes (32).

We aimed to investigate the isolated effect of mechanical ventilation on cardiac SV, and to quantify the contribution of the respiratory pump to preserving cardiac SV during hypovolemia, in awake, young healthy subjects. To this end we used a lower-body negative-pressure (LBNP) chamber to induce central hypovolemia, and controlled non-invasive ventilation (NIV) to reduce the effect of the respiratory pump. We hypothesized that the reduction in SV and CO induced by hypovolemia would be more pronounced during concomitant NIV due to a reduction of the beneficial circulatory effects of the respiratory pump.

## Materials and Methods

### *Subjects*

Thirty-seven young healthy volunteers (nineteen females), aged 19–30 years, were recruited and gave written, informed consent to participate. All procedures conformed to the Declaration of Helsinki. The regional ethics committee (ref.no: 2012/2251 and 2014/2228, January 2015) approved the protocol and procedures.

This study is a combined side-analysis of two previous experimental series with the exact same experimental protocol, performed in the same laboratory. Output variables were collected and processed in the same way and with the same equipment. Twenty-two subjects were recruited for the first experimental series (2012) and fifteen for the second (2015). The first experimental series examined if heart rate variability and SV variability could be used to detect central hypovolemia during spontaneous breathing and positive pressure ventilation (11). The second experimental series assessed the effects of positive pressure ventilation and hypovolemia on cerebral blood flow (39) and tested a possible role of respiratory sinus arrhythmia as a regulatory mechanism for cerebral perfusion (40). The outcome variables were variability in HR and SV and internal carotid artery blood flow respectively in the previous studies. Descriptive statistics were however reported for SV estimates separately for these datasets.

None of the subjects had any cardiovascular or respiratory disorder or any other known pathology, none smoked or used any other nicotine or tobacco products, and none used any medication (except contraceptive pills). All undertook weekly exercise (median 5 hours, range 2–10 hours). The subjects were instructed to abstain from coffee, tea and exercise on the day of experiments and to have a light meal two hours prior to each experiment. All reported that they

had consumed fluids as usual prior to arrival in the laboratory. They abstained from alcohol for at least 24 hours prior to the experiment.

*Experimental protocol*

The subjects visited the laboratory twice before the experimental day. During these visits they were acclimatized to the laboratory and practiced using the non-invasive ventilator. On the experimental day before the beginning of the experiment, the subjects rested supine for a few minutes and practiced with the ventilator to determine their spontaneous breathing pattern (Rf, $V_T$, inspiratory time, need for PEEP). During the experiment, the subjects lay supine in the LBNP chamber (17), which was sealed on the level of the iliac crest to prevent air leakage. The LBNP chamber induced a pressure drop to -30 mmHg within a heartbeat (0.3 s) and achieved an equalization of pressure at the same rate. A NIV face mask (Respireo Primo F Non Vented, Air Liquide Medical Systems, Italy), adjusted to each subject's face, was used throughout the procedure. The subjects took breaths of normal depth and rate when breathing spontaneously; the tidal volume during spontaneous breathing was however not recorded. During control-mode NIV, the subjects passively accepted the tidal volume and respiratory rate provided by the ventilator (VIVO50, Diacor a/s, Oslo, Norway), pre-set to just exceed each individual's values during spontaneous breathing. The ventilator settings (median (range)) were: inspiration time: 1.3 sec (1.2–1.8); respiratory frequency: 15 breaths per min (11–17); target tidal volume: 750 ml (500–1050); PEEP: 2.5 $cmH_2O$ (1-4). Maximum and minimum inspiratory pressures were set to 14 $cmH_2O$ and 4.5 $cmH_2O$ respectively. Medians and 95% Confidence Intervals (95% CI) of recorded peak inspiratory pressure (PIP), mean inspiratory pressure (Pmean), PEEP, and $V_T$ are presented in Table 1.

The experimental protocol started with a baseline recording of ten minutes. Immediately after this baseline period, we abruptly induced central hypovolemia by LBNP of -30 mmHg in all

subjects. After ten minutes of central hypovolemia, the chamber pressure was abruptly returned to atmospheric pressure and a ten-minute recovery recording was made. All three experimental situations (baseline, LBNP, and recovery) included five minutes of spontaneous breathing and five minutes of NIV. The initial ventilation mode (spontaneous or NIV) was randomized. Figure 1 shows one sequence of the experimental states.

The LBNP was terminated if the subject experienced any presyncopal symptoms (dizziness, nausea, vision loss) or signs (reduction of mean arterial blood pressure >15 mmHg or increase in heart rate to >120 beats per minute).

*Instrumentation and Recordings*

Respiratory movements were registered using a belt around the upper abdomen (Respiration and Body position Amplifier, Scan-Med a/s, Drammen, Norway). Instantaneous HR was obtained from the duration of the R-R interval from a three-lead ECG signal (SD-100, Vingmed, Horten, Norway). Non-invasive finger arterial pressure was recorded continuously from the left middle finger, positioned at heart level (Finometer, Finapres Medical System, Amsterdam, The Netherlands). The pressure output was transferred to the recording computer, and beat-by-beat mean arterial blood pressure (MAP) was calculated by numerical integration. The Finometer also provided SV calculated by the ModelFlow algorithm (4). A capnograph incorporated in the VIVO50 registered the partial pressure of end-expiratory $CO_2$ levels ($PETCO_2$).

ECG recordings were originally sampled at 300 Hz, respiratory movements and SV were sampled at 100 Hz. The instantaneous arterial pressure output was sampled at 100 Hz, transferred to the recording computer, and beat-to-beat MAP was calculated by numerical integration. The signals were recorded via a dedicated data collection and analysis program (Program for real time data acquisition: Morten Eriksen, Oslo, Norway).

*Signal processing and Analysis*

All recorded signals from each experimental run were visually inspected, and all time intervals with technically successful recordings from each subject were included in the subsequent analyses. All data were resampled at 4 Hz and beat-to-beat CO was calculated from SV and HR. The total peripheral resistance (TPR) was calculated from MAP divided by CO. Medians were calculated along 2-minute intervals of continuous, technically successful recordings. Comparisons were performed in the four different experimental states: normovolemia with spontaneous breathing (Baseline), normovolemia with NIV (NIV), LBNP with spontaneous breathing (LBNP) and LBNP combined with NIV (LBNP + NIV). For each experimental state, the median of all observations in the same state for each subject was used in the subsequent statistical analysis. The median was preferred as it was a better measure of central tendency in our dataset than the mean value.

*Statistics*

Non-parametric statistical analyses were chosen because SV in our dataset was not normally distributed. Reported values are medians and 95%CI calculated by Hodges-Lehmann's estimate. The Friedman test for four related samples was used to test the difference in SV across the four experimental states, and the Wilcoxon matched-pairs signed-rank test against a two-sided alternative (18) was used for the pairwise comparisons (StatExact, Cytel Studio 7; Cytel Inc., Cambridge, MA, USA). Cardiovascular variables during NIV and spontaneous breathing were compared, both during normovolemia and hypovolemia. For SV, our main outcome variable, the Wilcoxon test p-values were Bonferroni-corrected; the level of statistical significance was set to $p=0.01$ before analyses.

## Results

Thirty-one of the 37 subjects (fourteen females, median age 22 years (range: 19–30)) completed the protocol without any subjective discomfort or other termination criteria. Three females were excluded due to technical problems (one subject), pre-syncope immediately at induction of LBNP (one subject), and frequent extrasystoles invalidating Finometer measurements (one subject). The last three excluded subjects (one male and two females) were unable to tolerate the ventilator. The thirty-one subjects included in the present analysis completed all six experimental states (baseline, LBNP, recovery with and without NIV) at least once. Figure 1 shows recordings from one representative subject. Group values of SV and CO during the various experimental states are shown in Figure 2, values of HR, MAP, Rf and $PETCO_2$ are shown in Table 2.

Overall, during normovolemia, NIV did not induce changes in HR, SV, CO or MAP. Induction of central hypovolemia (LBNP) during spontaneous ventilation caused a reduction in SV and CO. A concurrent, transient reduction in MAP was rapidly restored, thereafter both MAP and HR increased. The combination of LBNP and NIV reduced SV and CO even more, MAP did not change while HR increased further (Table 2).

### *Effect of LBNP and NIV on cardiovascular variables*

Employing NIV during normovolemia did not alter SV (–0.6% corresponding to –0.5 ml (–1.5%, –0.4%, p=0.4)) and did not induce changes in HR, CO or MAP (Table 2, Figure 2). In contrast, even during spontaneous ventilation, hypovolemia resulted in a marked decrease in SV (–18.3% corresponding to –15.6 ml (–20.5%, –15.3%, p<0.001) and an increase in HR of +11% (+8%, +13%, p<0.001) that however did not fully counteract the reduction in SV. As a result, CO decreased by 9.4% (–12.2%, –7.3%) during LBNP (p<0.001, Figure 2). The added

use of NIV during hypovolemia resulted in an additional decrease in SV (–8.2% corresponding to –5.8 ml (–10%, –6.1%, p<0.001) and an additional increase in HR by 5% (+2%, +6%, p<0.001) compared to values observed during LBNP alone. Again, the HR increase did not fully compensate for the reduced SV, causing CO to decrease by an additional 3.3% (–7.5%, –2%, p=0.001). Overall, the combined challenge of LBNP and NIV resulted in a large reduction in SV (–26% corresponding to –23 ml (–29.5%, –22.7%, p<0.001) and in CO (–13.2% (–17.8%, –12%, p<0.001) compared to baseline (Figure 2).

Friedman test for related samples confirmed that SV was different among the experimental states (p<0.0001).

MAP increased by 4% (+3%, +6%) from baseline to LBNP (p<0.001) due to an increase in TPR, but did not change further from LBNP alone to LBNP + NIV (Table 2).

*Effect of LBNP and NIV on $PETCO_2$*

$PETCO_2$ as expected decreased slightly with the use of control-mode NIV, both during normovolemia and hypovolemia (p<0.001, Table 2). Also during spontaneous ventilation, a decrease in $PETCO_2$ was observed during hypovolemia induced by LBNP (p=0.001). The combination of LBNP and NIV decreased $PETCO_2$ the most (p<0.001). The reduction in $PETCO_2$ may have been caused by an increase in $V_T$, since overall respiratory rate was unchanged between normovolemia and hypovolemia. However, $V_T$ was not directly measured during spontaneous breathing.

## Discussion

In this study we experimentally assessed the effect of combined abrupt central hypovolemia (via lower body negative pressure, LBNP) and control-mode positive pressure ventilation (NIV) on central cardiovascular variables in young healthy subjects. Our aim was to examine how respiration-induced negative intrathoracic pressure contributes to preserve cardiac SV and CO during hypovolemia. Our findings show that spontaneous respiration contributed to the maintenance of SV and CO during LBNP of -30 mmHg, which corresponds to a moderate hemorrhage of 450-500 ml of blood loss (16). When normal, spontaneous negative-pressure respiration was replaced with control-mode NIV during LBNP, SV decreased and the concomitant increase in HR was insufficient to maintain the CO observed during LBNP alone.

NIV elevates the intrathoracic pressure during inspiration to positive values and thus reduces the efficacy of the respiratory pump, which normally increases the venous return of blood to the right heart via the decrease in intrathoracic pressure (10, 41). From a circulatory viewpoint, hemodynamically unstable patients both in the prehospital setting and after hospital admission may thus benefit from preserving spontaneous respiration as long as they are able to generate sufficient reductions in intrathoracic pressure with inspiration (32). Respiratory depression due to cerebral pathology, pulmonary pathology resulting in hypoxia and hypercapnia, and muscular fatigue may however limit this option. Early tracheal intubation and control-mode positive pressure ventilation may however precipitate hemodynamic compromise in such patients (32), by abolishing the respiratory pump and through the necessary use of anaesthetic agents, which to varying degrees are sympatholytic, cardiodepressant and vasodilatory (25) .

The use of NIV usually impedes the circulation less, since the patient remains awake or only lightly sedated and contributes muscularly to each breath (33). Negative circulatory effects are more pronounced in anesthetized and intubated patients, especially when high inspiratory

pressures and high levels of PEEP are imposed to restore oxygenation (28). Controlled ventilation with the use of muscle paralytic medication, mostly used in the operating room, completely abolishes the respiratory pump (21). In contrast, supported ventilator modes use the inspiratory pressure deflection or the electrical activity of the diaphragm (Neurally Adjusted Ventilatory Assist mode) to trigger the ventilator, thus synchronising the delivery of inspiratory positive pressure from the ventilator with the patient's breathing efforts. This maintains diaphragmatic ventilation and attenuates the reduction in venous return and right ventricular performance, producing a respiratory pattern that resembles spontaneous breathing (2, 42). In ventilated pigs, applying a negative airway pressure during expiration reduced intrathoracic pressure and enhanced venous return, similar to during spontaneous inspiration (47). In intubated patients with brain injury, a decrease in intracranial pressure and improved cerebral perfusion pressure was demonstrated during short periods of using this device producing negative intrathoracic pressure during expiration (24).

The effects of positive intrathoracic pressure on SV and CO are mainly mediated by the reduction in venous return. Though it is a hemodynamic variable receiving considerable attention and discussion in the ICU and the operating room, venous return is not easily quantified in a clinical setting. One study assessed the driving pressure for venous return in patients on controlled mechanical ventilation by estimating the mean systemic filling pressure during repeated 12-second end-inspiratory hold maneuvers (29). This method can be used to evaluate conditions for venous return in ventilated patients (22, 29), although limited to patients on controlled modes. In the present study, we showed that NIV reduced SV and CO in hypovolemic, otherwise healthy humans. This finding provides evidence that even low-level positive-pressure ventilation can produce negative hemodynamic effects on compromised intensive care patients, via reduction in venous return. Careful titration of the applied airway

pressure against the driving pressure for venous return may attenuate the negative circulatory effects of mechanical ventilation.

An LBNP of –30mmHg is clinically similar to an early stage of an uncontrolled hemorrhage. At this stage the cardiovascular changes may be subtle, as traditional vital signs such as arterial blood pressure, HR, and arterial oxygen saturation are either insensitive or non-specific to mild-moderate blood loss (9). This may delay diagnosis and treatment. Particularly in a prehospital setting and during transport of traumatized or critically ill patients, the detection of a compensated hypovolemia may be difficult. The very slight increase in HR and the actual increase in MAP observed during LBNP in our study subjects demonstrate how the well-functioning compensatory abilities of young healthy individuals might easily disguise an uncontrolled hemorrhage. SV and CO are more sensitive to changes in blood volume (39), but monitoring of these variables is not usually available outside the operating theater or ICU. Additionally, the wide range of normal SV and CO would make interpretation of absolute values difficult, particularly without continuous monitoring. Close attention to symptoms and signs of hypoperfusion, e.g. altered mentation and reduced skin perfusion, is therefore key in the handling of critically ill patients. Adding controlled ventilation to an unrecognized hypovolemia, albeit compensated, could hasten circulatory collapse.

In ICU patients, supported rather than controlled ventilator modes are generally aimed for. Maintaining and augmenting spontaneous respiration in ICU patients with the use of supported ventilatory methods result in improved organ perfusion and hemodynamics (14, 15, 33). In contrast, controlled mechanical ventilation must override the patient's spontaneous respiratory efforts and often involves deeper sedation. Establishing spontaneous respiration and early ventilator weaning was related to improved ICU outcomes and lower morbidity (12, 43).

322 *Importance of the respiratory pump*

323 LBNP has been extensively used to simulate central hypovolemia. LBNP has been validated as
324 an experimental model of hemorrhage as it has been shown to evoke similar cardiovascular
325 responses (16, 23). Changes in SV, central venous pressure, and MAP during LBNP and during
326 actual blood loss were closely correlated (16, 23).

327 Previous studies have examined the increased tolerance to progressive degrees of LBNP until
328 presyncope (6, 26, 36). Amplification of the respiratory pump with an impedance threshold
329 device or by using slow, deep breathing increased LBNP tolerance and delayed presyncopal
330 symptoms (7, 26, 35, 36). In our study, a decrease in $PETCO_2$ was observed during LBNP. Rf
331 was unchanged, thus the implied increase in $V_T$ may reflect an attempt to optimize the
332 respiratory pump effect during hypovolemia.

333 In our study, LBNP of -30 mmHg generated an 18.3% decrease in SV and a 9.4% decrease in
334 CO, similar to previous studies (16, 19). Combined with NIV however, LBNP decreased SV
335 by 26% and CO by 13.2%. Thus, even the modest use of the respiratory pump observed during
336 hypovolemia in our experimental setting was able to attenuate the reduction in SV by 30%,
337 compared to a situation with control-mode NIV in hypovolemia. The demonstrated respiratory
338 augmentation of the circulation likely was small compared with that often observed in critically
339 ill, hemodynamically compromised patients, who may hyperventilate with an Rf of 20–40
340 breaths/min (13). In such patients induction of anaesthesia and institution of mechanical
341 ventilation must be performed with utmost care to avoid circulatory collapse. Also, ventilation
342 modes that allow spontaneous breathing efforts are often preferable (33).

343 During LBNP, the reduction in SV and CO caused baroreceptor unloading and sympathetic
344 activation, leading to an increase in HR and a concurrent slight increase in TPR and MAP (Fig.

1; Table 2). The addition of NIV to LBNP further increased HR. However, with or without NIV, the HR increase did not fully compensate for the induced hypovolemia, and CO remained reduced. Our subjects did not however experience any presyncopal symptoms.

*Methodological considerations*

SV and CO measurements were obtained from non-invasive finger arterial pressure by ModelFlow (Finometer) (4). SV measured by ModelFlow has been shown to correlate well with SV measured by Doppler ultrasound (19, 44). ModelFlow has also been compared to electrical bioimpedance cardiography and tracked the changes of SV and CO during progressive LBNP (19, 34).

The absence of tidal volume measurements during spontaneous breathing is a limitation of this study. Tidal volume was measured during NIV states but not while the subjects breathed spontaneously. During hypovolemia, spontaneously breathing humans may increase their tidal volume in order to amplify the effect of the respiratory pump (6).

The results of this study could be expanded by progressively increasing the degree of LBNP to find the level of hypovolemia where the addition of NIV would result in presyncope. Evaluating the respiratory pump effect on SV at this point would be clinically relevant, as it could indicate the degree of hypovolemia when the induction of anesthesia and mechanical ventilation in a bleeding patient result in circulatory decompensation.

*Conclusion*

We quantified the contribution of the respiratory pump to the preservation of SV during moderate hypovolemia in healthy subjects by employing control-mode NIV to reduce spontaneous respiration. Compared to the situation during NIV, spontaneous negative-pressure ventilation ameliorated the reduction in SV induced by hypovolemia by 30%. In the critically

ill patient with hypovolemia or uncontrolled hemorrhage, spontaneous ventilation may contribute to hemodynamic stability. Sedation, intubation and controlled positive pressure ventilation may accelerate the onset of circulatory collapse.

372 **Acknowledgements**

373 Professor Lars Walløe contributed with valuable discussions on design and statistical analysis.

374 **Grants**

375 The study was funded by the University of Oslo and the Research Council of Norway (Grant

376 230354).

377 **Disclosures**

378 No conflict of interest is declared

379

## References


1. **Barker SJ, Gamel DM, and Tremper KK**. Cardiovascular effects of anesthesia and operation. *Critical care clinics* 3: 251-268, 1987.
2. **Berger D, Bloechlinger S, Takala J, Sinderby C, and Brander L**. Heart-lung interactions during neurally adjusted ventilatory assist. *Critical care (London, England)* 18: 499, 2014.
3. **Berger D, Moller PW, Weber A, Bloch A, Bloechlinger S, Haenggi M, Sondergaard S, Jakob SM, Magder S, and Takala J**. Effect of PEEP, blood volume, and inspiratory hold maneuvers on venous return. *American journal of physiology Heart and circulatory physiology* 311: H794-806, 2016.
4. **Bogert LW, and van Lieshout JJ**. Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. *Experimental physiology* 90: 437-446, 2005.
5. **Chatburn RL, El-Khatib M, and Mireles-Cabodevila E**. A taxonomy for mechanical ventilation: 10 fundamental maxims. *Respir Care* 59: 1747-1763, 2014.
6. **Convertino VA, Rickards CA, Lurie KG, and Ryan KL**. Hyperventilation in response to progressive reduction in central blood volume to near syncope. *Aviation, space, and environmental medicine* 80: 1012-1017, 2009.
7. **Convertino VA, Ryan KL, Rickards CA, Cooke WH, Idris AH, Metzger A, Holcomb JB, Adams BD, and Lurie KG**. Inspiratory resistance maintains arterial pressure during central hypovolemia: implications for treatment of patients with severe hemorrhage. *Critical care medicine* 35: 1145-1152, 2007.
8. **Convertino VA, Ryan KL, Rickards CA, Glorsky SL, Idris AH, Yannopoulos D, Metzger A, and Lurie KG**. Optimizing the respiratory pump: harnessing inspiratory resistance to treat systemic hypotension. *Respir Care* 56: 846-857, 2011.
9. **Convertino VA, Ryan KL, Rickards CA, Salinas J, McManus JG, Cooke WH, and Holcomb JB**. Physiological and medical monitoring for en route care of combat casualties. *The Journal of trauma* 64: S342-353, 2008.
10. **Duiverman ML, Arellano-Maric MP, and Windisch W**. Long-term noninvasive ventilation in patients with chronic hypercapnic respiratory failure: assisting the diaphragm, but threatening the heart? *Current opinion in pulmonary medicine* 22: 130-137, 2016.
11. **Elstad M, and Walloe L**. Heart rate variability and stroke volume variability to detect central hypovolemia during spontaneous breathing and supported ventilation in young, healthy volunteers. *Physiological measurement* 36: 671-681, 2015.
12. **Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, and Ely EW**. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 371: 126-134, 2008.
13. **Gutierrez G, Reines HD, and Wulf-Gutierrez ME**. Clinical review: hemorrhagic shock. *Critical care (London, England)* 8: 373-381, 2004.
14. **Hachenberg T**. [Augmented spontaneous breathing]. *Der Anaesthesist* 45: 839-855, 1996.
15. **Hering R, Peters D, Zinserling J, Wrigge H, von Spiegel T, and Putensen C**. Effects of spontaneous breathing during airway pressure release ventilation on renal perfusion and function in patients with acute lung injury. *Intensive care medicine* 28: 1426-1433, 2002.
16. **Hinojosa-Laborde C, Shade RE, Muniz GW, Bauer C, Goei KA, Pidcoke HF, Chung KK, Cap AP, and Convertino VA**. Validation of lower body negative pressure as an experimental model of hemorrhage. *Journal of applied physiology (Bethesda, Md : 1985)* 116: 406-415, 2014.
17. **Hisdal J, Toska K, and Walloe L**. Design of a chamber for lower body negative pressure with controlled onset rate. *Aviation, space, and environmental medicine* 74: 874-878, 2003.

18. **Hollander M, and Wolfe DA**. *Nonparametric statistical methods*. New York: Wiley, 1999.
19. **Holme NL, Rein EB, and Elstad M**. Cardiac stroke volume variability measured non-invasively by three methods for detection of central hypovolemia in healthy humans. *Eur J Appl Physiol* 116: 2187-2196, 2016.
20. **Hummler H, Gerhardt T, Gonzalez A, Claure N, Everett R, and Bancalari E**. Influence of different methods of synchronized mechanical ventilation on ventilation, gas exchange, patient effort, and blood pressure fluctuations in premature neonates. *Pediatric pulmonology* 22: 305-313, 1996.
21. **Hunter JM**. New Neuromuscular Blocking Drugs. *New England Journal of Medicine* 332: 1691-1699, 1995.
22. **Jansen JR, Maas JJ, and Pinsky MR**. Bedside assessment of mean systemic filling pressure. *Current opinion in critical care* 16: 231-236, 2010.
23. **Johnson BD, van Helmond N, Curry TB, van Buskirk CM, Convertino VA, and Joyner MJ**. Reductions in central venous pressure by lower body negative pressure or blood loss elicit similar hemodynamic responses. *Journal of applied physiology (Bethesda, Md : 1985)* 117: 131-141, 2014.
24. **Kiehna EN, Huffmyer JL, Thiele RH, Scalzo DC, and Nemergut EC**. Use of the intrathoracic pressure regulator to lower intracranial pressure in patients with altered intracranial elastance: a pilot study. *J Neurosurg* 119: 756-759, 2013.
25. **Lonjaret L, Lairez O, Minville V, and Geeraerts T**. Optimal perioperative management of arterial blood pressure. *Integrated blood pressure control* 7: 49-59, 2014.
26. **Lucas SJ, Lewis NC, Sikken EL, Thomas KN, and Ainslie PN**. Slow breathing as a means to improve orthostatic tolerance: a randomized sham-controlled trial. *Journal of applied physiology (Bethesda, Md : 1985)* 115: 202-211, 2013.
27. **Luecke T, and Pelosi P**. Clinical review: Positive end-expiratory pressure and cardiac output. *Critical care (London, England)* 9: 607-621, 2005.
28. **Luecke T, Pelosi P, and Quintel M**. [Haemodynamic effects of mechanical ventilation]. *Der Anaesthesist* 56: 1242-1251, 2007.
29. **Maas JJ, Geerts BF, van den Berg PC, Pinsky MR, and Jansen JR**. Assessment of venous return curve and mean systemic filling pressure in postoperative cardiac surgery patients. *Critical care medicine* 37: 912-918, 2009.
30. **Michard F**. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 103: 419-428; quiz 449-415, 2005.
31. **Morgan BC, Crawford EW, and Guntheroth WG**. The hemodynamic effects of changes in blood volume during intermittent positive-pressure ventilation. *Anesthesiology* 30: 297-305, 1969.
32. **Pepe PE, Roppolo LP, and Fowler RL**. The detrimental effects of ventilation during low-blood-flow states. *Current opinion in critical care* 11: 212-218, 2005.
33. **Putensen C, Muders T, Varelmann D, and Wrigge H**. The impact of spontaneous breathing during mechanical ventilation. *Current opinion in critical care* 12: 13-18, 2006.
34. **Reisner AT, Xu D, Ryan KL, Convertino VA, Rickards CA, and Mukkamala R**. Monitoring non-invasive cardiac output and stroke volume during experimental human hypovolaemia and resuscitation. *British journal of anaesthesia* 106: 23-30, 2011.
35. **Rickards CA, Ryan KL, Cooke WH, Lurie KG, and Convertino VA**. Inspiratory resistance delays the reporting of symptoms with central hypovolemia: association with cerebral blood flow. *Am J Physiol Regul Integr Comp Physiol* 293: R243-250, 2007.
36. **Ryan KL, Cooke WH, Rickards CA, Lurie KG, and Convertino VA**. Breathing through an inspiratory threshold device improves stroke volume during central hypovolemia in humans. *Journal of applied physiology (Bethesda, Md : 1985)* 104: 1402-1409, 2008.
37. **Segal N, Yannopoulos D, Truchot J, Laribi S, Plaisance P, and Convertino VA**. [Improving vital organs perfusion by the respiratory pump: physiology and clinical use]. *Annales francaises d'anesthesie et de reanimation* 32: 572-579, 2013.

38. **Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, and Angus DC**. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 315: 801-810, 2016.
39. **Skytioti M, Sovik S, and Elstad M**. Internal carotid artery blood flow in healthy awake subjects is reduced by simulated hypovolemia and noninvasive mechanical ventilation. *Physiological reports* 4: 2016.
40. **Skytioti M, Sovik S, and Elstad M**. Respiration-related cerebral blood flow variability increases during control-mode non-invasive ventilation in normovolemia and hypovolemia. *Eur J Appl Physiol* 2017.
41. **Soni N, and Williams P**. Positive pressure ventilation: what is the real cost? *British journal of anaesthesia* 101: 446-457, 2008.
42. **Stewart NI, Jagelman TA, and Webster NR**. Emerging modes of ventilation in the intensive care unit. *British journal of anaesthesia* 107: 74-82, 2011.
43. **Thille AW, Richard JC, and Brochard L**. The decision to extubate in the intensive care unit. *American journal of respiratory and critical care medicine* 187: 1294-1302, 2013.
44. **van Lieshout JJ, Toska K, van Lieshout EJ, Eriksen M, Walloe L, and Wesseling KH**. Beat-to-beat noninvasive stroke volume from arterial pressure and Doppler ultrasound. *Eur J Appl Physiol* 90: 131-137, 2003.
45. **Wampler D, Convertino VA, Weeks S, Hernandez M, Larrumbide J, and Manifold C**. Use of an impedance threshold device in spontaneously breathing patients with hypotension secondary to trauma: an observational cohort feasibility study. *The journal of trauma and acute care surgery* 77: S140-145, 2014.
46. **Wieling W, van Dijk N, Thijs RD, de Lange FJ, Krediet CT, and Halliwill JR**. Physical countermeasures to increase orthostatic tolerance. *Journal of internal medicine* 277: 69-82, 2015.
47. **Yannopoulos D, Metzger A, McKnite S, Nadkarni V, Aufderheide TP, Idris A, Dries D, Benditt DG, and Lurie KG**. Intrathoracic pressure regulation improves vital organ perfusion pressures in normovolemic and hypovolemic pigs. *Resuscitation* 70: 445-453, 2006.

Published in Journal of Applied Physiology, 24 May 2018
https://doi.org/10.1152/japplphysiol.01009.2017


**Table 1. Ventilator readings in healthy humans during controlled non-invasive ventilation, with and without central hypovolemia induced by lower-body negative pressure**

| | Controlled NIV | |
|---|---|---|
| | **Normovolemia** | **Hypovolemia** |
| **PIP ($cmH_2O$)** | 9.2 (8.0, 10.0) | 9.7 (8.8, 10.7) |
| **Pmean ($cmH_2O$)** | 4.6 (4.1, 5.1) | 4.7 (4.0, 5.0) |
| **PEEP ($cmH_2O$)** | 2.3 (1.8, 2.6) | 2.2 (1.9, 2.6) |
| **$V_T$ (ml)** | 733 (667, 787) | 754 (683, 799) |

Data are medians and 95% confidence intervals calculated by Hodges Lehmann's estimate. NIV: non-invasive ventilation, PIP: peak inspiratory pressure; Pmean: mean airway pressure; PEEP: positive end expiratory pressure, $V_T$: tidal volume. (n=31)

511

512

Published in Journal of Applied Physiology, 24 May 2018
https://doi.org/10.1152/japplphysiol.01009.2017


**Table 2. Changes in cardiovascular and respiratory variables in healthy humans challenged with hypovolemia and controlled non-invasive ventilation**

| | Normovolemia | | Hypovolemia | |
|---|---|---|---|---|
| | **Spontaneous breathing** | **NIV** | **Spontaneous breathing** | **NIV** |
| **HR (bpm)** | 57.8 (54.5, 59.7) | 56.5 (52.7, 58.5) | 63.8* (60.1, 66.3) | 67.1*† (63.0, 69.6) |
| **MAP (mmHg)** | 72.7 (69.5, 75.0) | 72.7 (69.4, 75.0) | 75.5* (72.2, 78.4) | 75.4* (72.4, 77.7) |
| **$PETCO_2$ (kPa)** | 5.0 (4.7, 5.2) | 4.7* (4.4, 4.9) | 4.9* (4.6, 5.1) | 4.3*† (4.0, 4.6) |
| **Rf (breaths/min)** | 13.7 (12.2, 14.3) | 14.7 (13.8, 15.3) | 12.6 (11.7, 13.5) | 14.4 (13.7, 15.0) |
| **TPR ($dynes/cm^5$)** | 1208 (1080, 1320) | 1216 (1096, 1336) | 1416* (1240, 1536) | 1448* (1264, 1544) |

Data are medians and 95% confidence intervals calculated by Hodges Lehmann's estimate. Hypovolemia was induced by LBNP. NIV: controlled non-invasive ventilation; LBNP: lower body negative pressure; CO: cardiac output; SV: stroke volume; HR: heart rate; bpm: beats per minute; MAP: mean arterial pressure; $PETCO_2$: end-tidal $CO_2$; Rf: respiratory rate. TPR: total peripheral resistance. Wilcoxon signed rank test was used for pairwise comparisons. *$p \leq 0.001$ compared to normovolemia and spontaneous breathing; † $p \leq 0.001$ compared to hypovolemia with spontaneous breathing. (n=31)

513

514 **Figure legends**

515 **Figure 1:** Recordings of heart rate (HR), cardiac stroke volume (SV) and cardiac output (CO)
516 from one subject. The upper panel shows the pressure in the lower body negative pressure
517 (LBNP) chamber. The induction of LBNP of -30mmHg corresponds to a moderate
518 hemorrhage of 450-500 ml blood loss. SB: spontaneous breathing, NIV: controlled non-
519 invasive ventilation

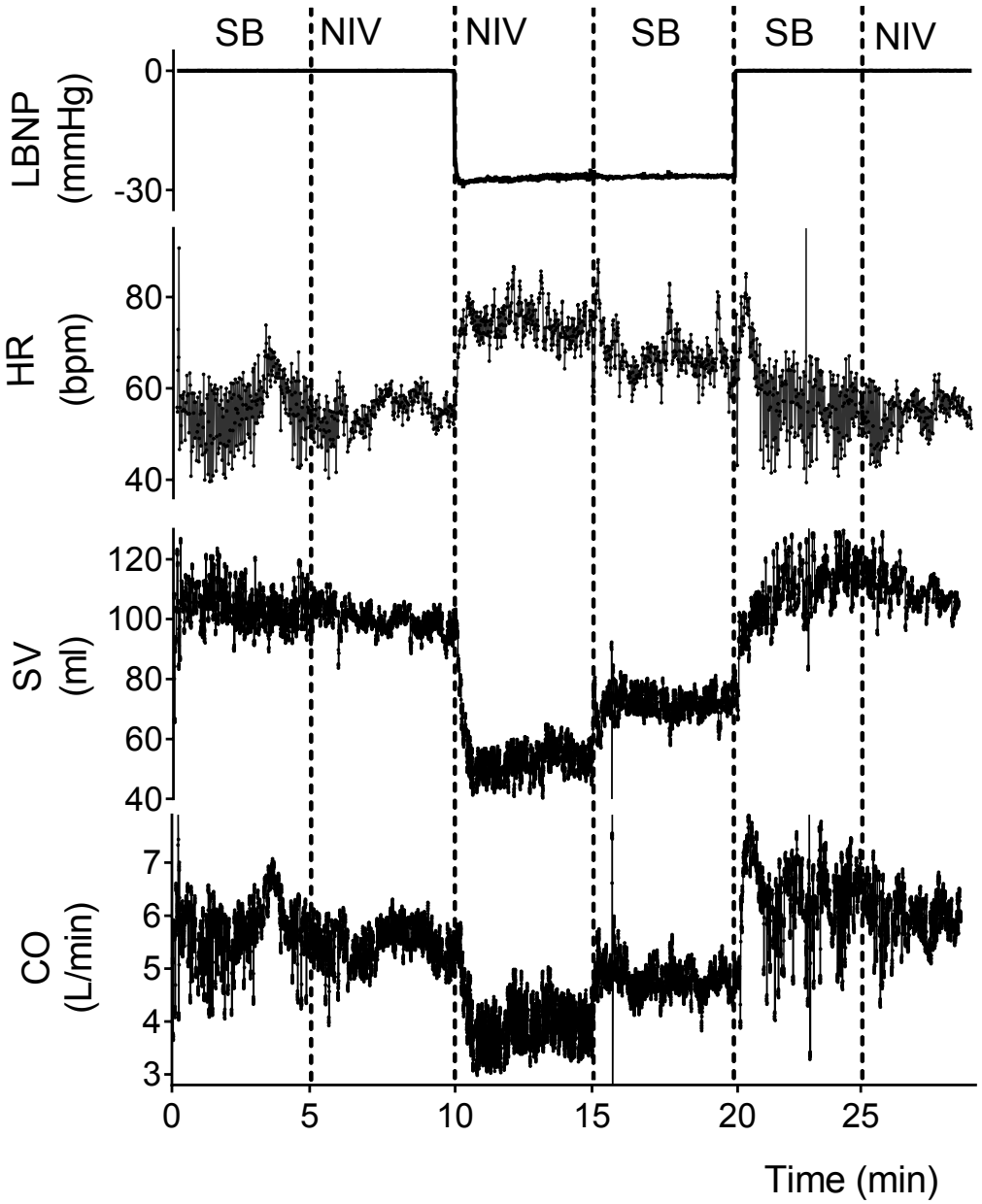
520

521 **Figure 2:** Medians and 95% CI of cardiac stroke volume (SV) and cardiac output (CO) in the
522 four different experimental states. *$p \leq 0.001$ compared to baseline. *† $p \leq 0.001$ compared to
523 lower body negative pressure (LBNP) alone. NIV: controlled non-invasive ventilation

524

Published in Journal of Applied Physiology, 24 May 2018
https://doi.org/10.1152/japplphysiol.01009.2017

**Figure 1:**



Published in Journal of Applied Physiology, 24 May 2018
https://doi.org/10.1152/japplphysiol.01009.2017

**Figure 2:**