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Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients

E. Kupersztych-Hagege[1,2], J.-L. Teboul[1,2], A. Artigas[3], A. Talbot[1,2], C. Sabatier[3], C. Richard[1,2] and X. Monnet[1,2]*

[1] Hôpitaux universitaires Paris-Sud, Hôpital de Bicêtre, service de réanimation médicale, 78, rue du Général Leclerc, F-94270 Le Kremlin-Bicêtre, France
[2] Univ Paris-Sud, Faculté de médecine Paris-Sud, EA4533, 63, rue Gabriel Péri, F-94270 Le Kremlin-Bicêtre, France
[3] Centro de Críticos, Hospital de Sabadell, CIBER de Enfermedades Respiratorias, Corporació Sanitària i Universitària Parc Taulí, Universitat Autònoma de Barcelona, Parc Taulí, s/n, 08208 Sabadell, Spain

* Corresponding author: Service de réanimation médicale, Centre Hospitalier Universitaire de Bicêtre, 78, rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France. E-mail: xavier.monnet@bct.aphp.fr

Editor's key points

- Data are conflicting regarding the accuracy and validity of non-invasive cardiovascular monitoring devices in the critically ill.
- This study compared changes in cardiac index in response to passive leg raising (PLR) and volume expansion using the NICOM® and $PiCCO_2$™ devices.
- There was poor correlation between the two monitors after volume expansion.
- The NICOM® did not predict fluid responsiveness to PLR.

Background. Bioreactance estimates cardiac output in a non-invasive way. We evaluated the ability of a bioreactance device (NICOM®) to estimate cardiac index (CI) and to track relative changes induced by volume expansion.

Methods. In 48 critically ill patients, we measured CI estimated by the NICOM® device (CI_{Nicom}) and by transpulmonary thermodilution (CI_{td}, $PiCCO_2$™ device) before and after a 500 ml saline infusion. Before volume expansion, we performed a passive leg raising (PLR) test and measured the changes it induced in CI_{Nicom} and in pulse contour analysis-derived CI.

Results. Considering the values recorded before PLR and before and after volume expansion ($n=144$), the bias (lower and upper limits of agreement) between CI_{td} and CI_{Nicom} was 0.9 (−2.2 to 4.1) litre min^{-1} m^{-2}. The percentage error was 82%. There was no significant correlation between the changes in CI_{td} and CI_{Nicom} induced by volume expansion ($P=0.24$). An increase in CI estimated by pulse contour analysis >9% during the PLR test predicted fluid responsiveness with a sensitivity of 84% (95% confidence interval 60–97%) and a specificity of 97% (95% confidence interval 82–100%). The area under the receiver operating characteristic curve constructed to test the ability of the PLR-induced changes in CI_{Nicom} in predicting fluid responsiveness did not differ significantly from 0.5 ($P=0.77$).

Conclusions. The NICOM® device cannot accurately estimate the cardiac output in critically ill patients. Moreover, it could not predict fluid responsiveness through the PLR test.

Keywords: equipment, monitors; dobutamine; measurement, cardiac output; measurement techniques; shock

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Several new devices that monitor haemodynamics have been introduced with the aim of reducing the need for haemodynamic invasive monitoring. Bioreactance is potentially attractive since it only requires four electrodes stickers placed on the thorax.[1] This technique is based upon the measurement of frequency modulation and signal phase shift of an electrical current crossing the thorax, the variations of which are related to changes in the volume of the thoracic aorta.[2] This allows estimation of the volume of blood ejected in the thoracic aorta with each heart beat.

The validation of this technique is still ongoing and initial results are conflicting. While some studies found good agreement between bioreactance and a reference technique,[3–5] others found less promising results.[6–9] Our aim was to compare the values of cardiac output measured by a bioreactance device (NICOM®, Cheetah Medical, Tel Aviv, Israel) with the values provided by transpulmonary thermodilution. Particularly, we evaluated the capacity of the NICOM® to track the changes in cardiac index (CI) during a passive leg raising (PLR) test and to predict fluid responsiveness.

Methods

Population

This prospective study took place in the medical intensive care unit (ICU) of a university hospital. It was approved by the institutional review board of our institution (Comité pour la Protection des Personnes Ile de France VII). All patients (or next of kin) gave informed consent. The inclusion criteria were (i) the presence of an acute haemodynamic failure, as defined by a

systolic arterial pressure ≤90 mm Hg or a decrease ≥40 mm Hg compared with the usual systolic arterial pressure, skin mottling, blood lactate ≥2 mmol litre^{-1}, urine output ≤0.5 ml kg^{-1} h^{-1} for at least 2 h, tachycardia ≥100 beats min^{-1}, (ii) a decision by the clinician in charge to perform a PLR test and to administer a volume expansion, and (iii) a transpulmonary thermodilution device in place (PiCCO$_2$™, Pulsion Medical Systems, Munich, Germany). Patients were excluded if there was a contra-indication to the PLR test (intracranial hypertension, venous compression stocking).

Bioreactance and transpulmonary thermodilution measurements

Derived from the original bioimpedance technique, the NICOM® system sends a high-frequency current with known low amplitude through the thorax using four electrodes and measures the frequency-modulation and phase-modulation resulting from the changes in the thoracic blood volume through four other adjacent electrodes. After placing the electrodes and recording patients' characteristics, the NICOM® automatically calibrates and then provides a continuous CI value.

The PiCCO$_2$™ system requires a central venous catheter in the superior vena cava territory and a femoral thermistor-tipped arterial catheter (PV2024 Pulsion Medical Systems). The latter is connected to a pressure sensor (PV8115 Pulsion Medical Systems). The PiCCO$_2$ device measures CI in two different ways. First, transpulmonary thermodilution principle provides an intermittent measure of CI. After injection of a 15 ml cold bolus through the central venous line, cardiac output is computed from the blood temperature curve recorded by the arterial catheter. With this technique, if CI is calculated as the average of three consecutive thermodilution measurements, its least significant is 12%.[10] Secondly, pulse contour analysis provides a continuous and real-time estimation of CI. It is based upon the principle that the area under the systolic part of the arterial signal is physiologically proportional to stroke volume. The PiCCO$_2$™ calibrates the initial value of CI by transpulmonary thermodilution. After calibration, pulse contour analysis allows the continuous display of CI values.

Study design

At baseline, the CI values provided by the NICOM® (CI$_{Nicom}$) and PICCO$_2$™ (transpulmonary thermodilution, CI$_{td}$) devices were recorded simultaneously. A PLR test was then performed by moving the patient's bed from a semi-recumbent position to a position in which the trunk was horizontal and lower limbs raised at 45°. At the time when PLR induced its maximal haemodynamic effects (i.e. within 1 min), CI$_{Nicom}$ and CI provided by pulse contour analysis were recorded. Then, the patient was placed back into the semi-recumbent position and CI values were allowed to return to baseline. The PiCCO$_2$™ device was recalibrated and the CI$_{Nicom}$ and CI$_{td}$ were recorded.

During the next 10 min, 500 ml saline was infused to cause intravascular volume expansion. After volume expansion, CI$_{Nicom}$ and CI$_{td}$ were again recorded simultaneously.

Data analysis

The normality of data distribution was tested with the Anderson–Darling test. Data are expressed as mean [standard deviation (SD)] or median (IQR), as appropriate. Comparisons of haemodynamic variables between the different study times were assessed using a paired Student *t*-test or a Wilcoxon test, as appropriate. Comparisons between volume-responders *vs* non-volume-responders were assessed using a two-sample Student *t*-test or a Mann–Whitney *U*-test, as appropriate.

Values of CI$_{td}$ (recorded at baseline, after return to the semi-recumbent position, and after volume expansion) *vs* CI$_{Nicom}$ were compared using the Bland–Altman analysis. CI was used for analysis considering that the reliability of a device for measuring absolute variables of CI is similar than for cardiac output. The percentage error was calculated as 2SD divided by the mean of CI$_{td}$.

The percentage changes in CI$_{td}$ and CI$_{Nicom}$ induced by volume expansion were compared by linear regression analysis (for per cent change). Percentage changes were taken into account rather than the absolute changes because they take into consideration that the impact of an error in cardiac output measurement is not the same depending upon the absolute value of cardiac output measured by the reference technique. For assessing the ability of CI$_{Nicom}$ to follow trends, we constructed a four-quadrant plot, as described by Critchley and colleagues.[11]

We considered as 'volume-responders' patients responding to volume expansion by an increase of at least 15% of CI$_{td}$. The other patients were considered as 'non-volume-responders'. For testing the ability of the changes in CI$_{Nicom}$ and CI provided by pulse contour analysis induced by the PLR test to predict fluid responsiveness, we constructed receiver operating characteristics (ROC) curves. Sensitivity and specificity are expressed as median (95% confidence interval). The cut-off values of changes in CI$_{Nicom}$ and CI provided by pulse contour analysis for predicting volume responsiveness by the PLR test were considered as those providing the lowest Youden index. A *P*-value of <0.05 was considered statistically significant. The statistical analysis was performed with the MedCalc 8.1.0.0 software (Mariakerke, Belgium).

Results

Patients

Forty-eight patients were included in the study (Table 1). No patient was excluded. Sepsis was the aetiology of shock in 83% of the patients and a majority presented an acute respiratory distress syndrome. Eleven patients presented cardiac arrhythmias, spontaneous breathing activity, or both.

Comparison of absolute values of CI$_{td}$ and CI$_{Nicom}$

When considering all pairs of CI$_{td}$ and CI$_{Nicom}$ measurements (at baseline before PLR, before volume expansion, and after volume expansion, $n=144$), the bias between CI$_{td}$ and CI$_{Nicom}$ was −0.9 litre min^{-1} m^{-2}. The limits of agreement

Table 1 Patients characteristics at baseline, $n=48$. Data are expressed as mean (SD), median (IQR), or as n (%). SAPS, Simplified Acute Physiologic Score

Age (range, yr)	33–82
Gender (M/F)	28/20
SAPS II [mean (SD)]	51 (17)
Mechanical ventilation (n, %)	40 (83)
Tidal volume in ventilated patients [ml kg^{-1} of predicted body weight, mean (SD)]	7 (1)
Spontaneous breathing activity in ventilated patients (n, %)	10 (25)
Non-intubated patients (n, %)	4 (8)
Atrial fibrillation (n, %)	2 (4)
Type of shock	
Septic (n, %)	40 (83)
Hypovolaemic (n, %)	5 (10)
Cardiogenic (n, %)	3 (7)
Vasopressors	
Norepinephrine (n, %)	30 (63)
Dosage of norepinephrine [median (IQR), μg kg^{-1} min^{-1}]	0.4 (0.3–0.7)
Dobutamine (n, %)	2 (4)

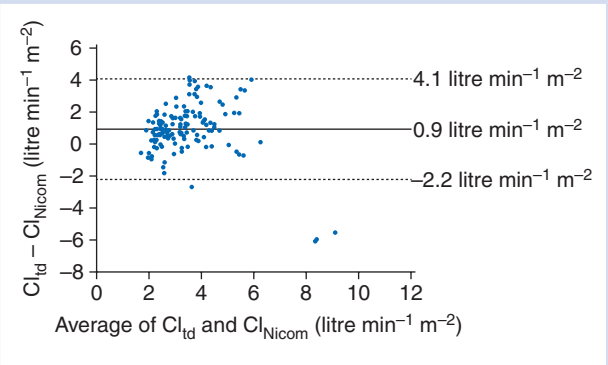

Fig 1 Bland–Altman plot for the absolute values of CI values measured by transpulmonary thermodilution (CI_{td}) and by the NICOM® device (CI_{Nicom}). $n=144$; straight line: bias, dashed line: $+2$SD/-2SD limits of agreement.

were -2.2 and 4.1 litre min^{-1} m^{-2} (Fig. 1). The percentage error was 82%.

When excluding the 11 patients with cardiac arrhythmias, spontaneous breathing activity, or both, the bias between CI_{td} and CI_{Nicom} was 1.0 litre min^{-1} m^{-2} (111 pairs of measurements). The limits of agreement were -2.2 and 4.3 litre min^{-1} m^{-2}. The percentage error (calculated with those 111 pairs of measurements) was 85%. *A posteriori*, considering an α-risk of 0.05 and a β-risk of 0.20, we could calculate that 32 patients should be required to obtain the above results.

Comparison of the changes in CI_{td} and CI_{Nicom}

As described in Table 2, pulse contour analysis-derived CI and CI_{Nicom} significantly increased during PLR and after volume expansion in volume-responders. Pulse contour analysis-derived CI did not significantly change either during PLR or after volume expansion in non-volume-responders. However, CI_{Nicom} did significantly increase during PLR in non-volume-responders.

There was no significant correlation between the changes in pulse contour analysis-derived CI_{td} and CI_{Nicom} induced by volume expansion ($P=0.24$, Fig. 2). The concordance rate between changes in CI_{td} and CI_{Nicom} induced by volume expansion was 43% (Fig. 2), meaning that in 43% of instances, CI_{td} and CI_{Nicom} changed in the same direction. When excluding changes <15%, the concordance rate was 52% (Fig. 2).

Ability of the PiCCO and Nicom devices to assess the effects of the PLR test

The area under the ROC curve constructed to assess the ability of PLR-induced changes in pulse contour analysis-derived CI was 0.87 (0.06) ($P<0.001$) (Fig. 3).

An increase in pulse contour analysis-derived CI by >9% during the PLR test allowed prediction of fluid responsiveness with a sensitivity of 84% (95% confidence interval 60–97%), a specificity of 97% (82–100%), a positive predictive value of 94% (70–100%), and a negative predictive value of 90% (74–98%).

The area under the ROC curve constructed for testing the ability of the PLR-induced changes in CI_{Nicom} did not differ significantly from 0.5 ($P=0.77$) (Fig. 3).

Discussion

Our study showed that the NICOM® device is unable to provide a reliable estimate of CI in critically ill patients. The ability of the NICOM® device to detect changes in CI was also poor. As a consequence, the NICOM® could not assess the effects of the PLR test to test fluid responsiveness.

During the last years, major efforts have been made in order to develop devices measuring and monitoring cardiac output. In particular, the aim was to obtain less-invasive or non-invasive measurements. In this context, the NICOM® device is completely non-invasive since it only requires four double electrode stickers placed on the thorax. The measure of cardiac output by the NICOM® is based upon bioreactance technology, which is an evolution of the bioimpedance principle. With bioimpedance, a constant high-frequency current with known amplitude is applied to the thorax by cutaneous electrodes. The bioimpedance devices measure the variations in tension resulting from the changes in thoracic impedance through four adjacent electrodes. At each systole, the thoracic impedance decreases in proportion of the increase in the intrathoracic iron amount and thus in proportion to the augmentation of thoracic blood volume. The variations in thoracic impedance are in fact mainly due to the variations of the aortic volume (i.e. variations of stroke volume).[12] With bioreactance, it is not the changes in the amplitude of the signal that are measured but the changes in frequency. This allows to substantially improve the signal-to-noise ratio.[3] The ability of the device to measure cardiac output might be limited by

Table 2 Evolution of haemodynamic variables. Data are expressed as mean (SD). *$P<0.05$, non-volume-responders *vs* volume-responders; **$P<0.05$, during PLR *vs* CI_{td} at Baseline 1; ***$P<0.05$, during PLR *vs* Baseline 1; ****$P<0.05$, and after volume expansion *vs* Baseline 2. CI, cardiac index; CI_{td}, CI measured by transpulmonary thermodilution; CI_{Nicom}, CI measured by the NICOM® device

	Baseline 1	During passive leg	Baseline 2	After volume expansion
Heart rate [mean (SD), beats min^{-1}]				
Volume-responders ($n=19$)	94 (22)	93 (21)	94 (23)	93 (21)
Non-volume-responders ($n=29$)	90 (20)	89 (20)	91 (18)	89 (18)
Mean arterial pressure [mean (SD), mm Hg]				
Volume-responders ($n=19$)	82 (16)	83 (14)	83 (13)	85 (13)
Non-volume-responders ($n=29$)	79 (11)	80 (11)	82 (12)	82 (12)
Central venous pressure [mean (SD), mm Hg]				
Volume-responders ($n=19$)	9 (4)	12 (4)***	11 (4)	13 (5)****
Non-volume-responders ($n=29$)	10 (5)	12 (5)***	10 (6)	13 (6)****
CI_{td} [mean (SD), litre min^{-1} m^{-2}]				
Volume-responders ($n=19$)	3.6 (0.9)	—	3.8 (0.9)	4.7 (1.1)****
Non-volume-responders ($n=29$)	3.7 (1.6)	—	3.8 (1.4)	3.9 (1.6)****,*
$CI_{derived\ from\ pulse\ contour\ analysis}$ [mean (SD), litre min^{-1} m^{-2}]				
Volume-responders ($n=19$)	—	4.1 (1.0)**	—	—
Non-volume-responders ($n=29$)	—	3.9 (1.6)**	—	—
CI_{Nicom} [mean (SD), litre min^{-1} m^{-2}]				
Volume-responders ($n=19$)	2.9 (2.2)	3.2 (2.2)***	3.3 (2.3)	3.5 (2.4)****
****Non-volume-responders ($n=29$)	2.6 (1.0)	2.9 (1.1)***	3.0 (1.1)	2.9 (0.9)****,*
Global end-diastolic volume [mean (SD), ml m^{-2}]				
Volume-responders ($n=19$)	763 (282)	—	799 (220)	844 (206)****
Non-volume-responders ($n=29$)	832 (183)	—	854 (191)	826 (206)

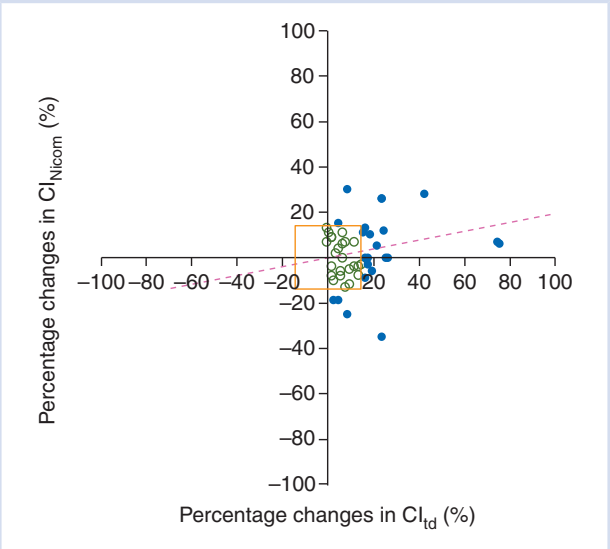

Fig 2 Four-quadrant concordance analysis between the percentage changes in CI measured by transpulmonary thermodilution (CI_{td}) and by the NICOM® device (CI_{Nicom}) induced by volume expansion. The zero-centred square corresponds to the 15% exclusion zone.

variations in thoracic impedance due to other causes (variations in the thoracic blood volume due to respiration, arrhythmias, etc.).

Comparing bioreactance with transpulmonary thermodilution, we conclude that NICOM® was not reliable to assess the cardiac output or to predict the effects on the cardiac output of a PLR or fluid responsiveness. In the Bland–Altman analysis, we found wide limits of agreement. Moreover, the percentage error was 82% for NICOM® which is largely above the 30% cut-off that is commonly considered as acceptable when using a reference method with a precision of 15%,[13] as is the case with transpulmonary thermodilution.[10] A device measuring cardiac output must not only be able to provide reliable absolute values but also to detect changes.[14] In the present study, there was no significant correlation between the volume expansion-induced changes in CI_{Nicom} and CI_{td}. Finally, bioreactance was unable to assess the effects of the PLR test. While changes in CI during PLR allowed prediction of fluid responsiveness when CI was measured by pulse contour analysis, this was not the case at all when CI was estimated by the NICOM® device. Interestingly, the results were not better when excluded patients with cardiac arrhythmias and spontaneous breathing activity, suggesting that these limitations did not explain the poor reliability of the system. There was a trend towards that

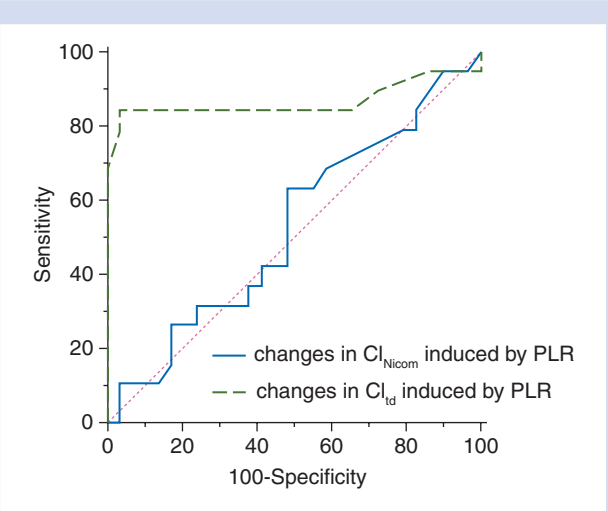

Fig 3 ROC curves testing the ability of the percentage changes in CI measured by transpulmonary thermodilution (CI_{td}) and by the NICOM® device (CI_{Nicom}) induced by the PLR test to predict fluid responsiveness.

after PLR, the NICOM® CI values failed to return to baseline. One has to suspect that lung volume changed during the PLR in a way such that it did not totally return to baseline, which could alter the bioreactance estimation of cardiac output. Furthermore, volume loading had minimal effect on the CI_{Nicom}. One could hypothesize that volume expansion would reduce haemoglobin levels and possibly alter the bioreactance reading, which is related to the iron content of the thorax.[15]

So far, only a few studies have validated bioreactance technology. Comparing bioreactance with continuous pulmonary thermodilution in a large number of measurements after cardiac surgery, Squara and colleagues[3] found that the percentage error was 30%. In this study, changes in cardiac output were not induced by systematic therapeutic interventions. The same team confirmed these previous results when comparing NICOM® with transpulmonary thermodilution during lung recruitment manoeuvres.[5] Nevertheless, in this study, the percentage error of bioreactance was >30% (33%) on average. Marqué and colleagues[16] found a good agreement between NICOM® and Vigileo, but the latter technique can hardly be considered a gold standard for measuring cardiac output.[17] In contrast to these positive results, Fagnoul and colleagues[6] recently demonstrated that the NICOM® device was unreliable compared with pulmonary thermodilution for estimating cardiac output in a population similar to ours (coefficient of correlation: 0.13). NICOM® was also found unreliable when compared with echocardiography in newborns.[8] NICOM® was used for assessing the effects of PLR and it was found reliable in two studies,[9 18 19] but importantly NICOM® was not compared with a reference technique in those studies. Taken together, these results could suggest that the reliability of the device might be different depending on the context, the positive studies being conducted in the perioperative period and the negative studies being conducted in ICUs. Interestingly, in the same context of septic patients, bioimpedance was shown to be unreliable compared with pulmonary thermodilution.[20] In animals, Critchley and colleagues[21] showed that the reliability of bioimpedance was influenced by the level of peripheral resistance. This suggests that septic shock may be a specific context where bioimpedance and thus bioreactance could be less reliable than in others, which could explain the unreliability of the NICOM® device in our population with a large majority of septic shock patients. Also, in an animal model of acute respiratory distress syndrome, the team of Critchley suggested that the unreliability of bioimpedance could be due to changes in lung fluid.[22] They confirmed later that in critically ill patients, the degree of bioimpedance unreliability was related to the extent of lung injury and fluid accumulation within the thorax.[23] Even though we could not investigate this specific issue, it could explain the poor results we obtained with bioreactance in our population in which the incidence of acute respiratory distress syndrome was high.

Our study has certain limitations. The first is that it included only ICU patients, most of whom were in septic shock. Thus, our results might not be able to be extrapolated to other contexts like the operating theatre, where artifacts limiting the bioreactance technique are less frequent. Also, we were unable to determine the reason why bioreactance performed so badly for estimating cardiac output, even though we suggest that this was not related to the presence of spontaneous breathing activity, cardiac arrhythmias, or both. Finally, we did not investigate another variable provided by the NICOM® device, the total fluid content. It was not the purpose of this study to validate this variable, which has recently demonstrated to diagnose acute decompensated heart failure in an emergency department.[24]

Conclusions

The bioreactance technique was unable to estimate absolute values or relative changes in CI in critical care patients. It was also unable to assess the effects of a PLR test to predict fluid responsiveness.

Authors' contributions

E.K.-H. performed the collection of data, contributed to analysis and interpretation of the data, and drafted the manuscript; J.-L.T. conceived the study, participated in its design, contributed to analysis and interpretation of the data, and helped to draft the manuscript; A.A. participated in the design of the study, contributed to analysis and interpretation of the data, and helped to draft the manuscript; A.T. contributed to the collection of data; C.S. participated in the design of the study, contributed to analysis and interpretation of the data, and helped to draft the manuscript; C.R. participated in the design of the study, contributed to analysis and interpretation of the data, and helped to draft the manuscript; X.M. conceived the study, contributed to analysis and interpretation of the data, and drafted the manuscript. All authors read and approved the final manuscript.

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Declaration of interest

J.-L.T. and X.M. are members of the Medical Advisory Board of Pulsion Medical Systems. The other authors have no conflict of interest to declare.

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Thirdly, we are afraid that Dr Squara did not read our methods section carefully. Indeed, we state that we assessed the effects of passive leg raising when they reached their maximum, which occurs 'within 1 minute'. This does not mean that passive leg raising was strictly limited to 1 min. Again, the study simply demonstrates that the Nicom could not be used to assess the passive leg raising test. We believe that this information is actually useful for clinicians since they may not be aware of the slow time response.

Fourthly, we strongly disagree with Dr Squara regarding the inappropriate data acquisition for the reasons stated above. Finally, we agree with Dr Squara that the study by Marik and colleagues[3] could seem positive. Nevertheless, one should emphasize that the authors did not use any cardiac output reference technique in this study. Moreover, the positivity of that study suggests that the arguments of Dr Squara regarding averaging over 10 min are not pertinent and that our negative results could not be only explained by the slow time response of the Nicom device.

To conclude, we believe that our conclusions are fully supported by the data. Indeed, they showed that the Nicom device was not reliable in our critically ill patients, especially for performing the passive leg raising test, when used in the way that is recommended for current practice. We do not claim that it would be so unreliable for monitoring stable patients over 10 min periods.

Declaration of interest

X.M. and J.-L.T. are members of the Medical Advisory Board of Pulsion Medical Systems.

X. Monnet[1]*
A. Artigas[2]
J.-L. Teboul[1]
[1]*Paris, France*
[2]*Sadabell, Spain*
**E-mail: xavier.monnet@bct.aphp.fr*

1 Kupersztych-Hagege E, Teboul JL, Artigas A, *et al*. Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients. *Br J Anaesth* 2013; **111**: 961–6

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Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients

Editor—We read with interest the study by Kupersztych-Hagege and colleagues,[1] 'Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising (PLR) in critically ill patients'. Key methods in the study differed from well known and accepted literature and also Cheetah NICOM Instructions for Use (IFU). After a detailed and careful review of the paper, we believe that issues with study execution and the manner in which previous studies are referenced lead to flawed conclusions about NICOM's capabilities.

1. Cheetah NICOM was not used in accordance with its IFU: Kupersztych-Hagege and colleagues chose a PLR challenge duration of only 1 min, although two of the authors (J.L. Teboul and X. Monnet) have published a paper, which was a clinical review of the literature, where they state the PLR needs to be performed over 30–90 s to provide real-time tracking, especially in septic patients.[2] In practice, a patient normally reaches the maximum cardiac index (CI) during the PLR challenge around the 60 s mark. The Cheetah NICOM averages its measurements every 1 min, and the maximum CI resulting from the PLR challenge is normally observed in the second minute of the PLR challenge rather than the first. Kupersztych-Hagege and colleagues performed the Cheetah NICOM measurements outside accepted and even their own group's suggested PLR protocol. Therefore, the maximum CI value measured in the study's PLR challenge by the Cheetah NICOM is unlikely to represent the true maximal change. Furthermore, the Cheetah NICOM is equipped with a PLR Wizard that automatically measures CI during a 3 min challenge and calculates the percentage change from baseline. To achieve and measure maximal change in CI due to the PLR, while allowing for a stable baseline, the authors would need to follow the IFU. This would have allowed the maximal change in CI to be determined. For this same reason, when the authors performed the back to baseline validation, the NICOM was still recording the PLR challenge (minutes 2 and 3 from initiation of the PLR challenge). Thus, comparison with the PICCO thermodilution CI value at this point is based on incorrect use of the NICOM and the subsequent measurement is not valid.

2. The manner by which the PLR threshold was selected is vague—Kupersztych-Hagege and colleagues used a threshold of 9% to differentiate responders from non-responders, while co-authors previously have reported a threshold of 10–12% as significant thresholds in reporting fluid responsiveness. We are given no indication as to why they chose the threshold of 9%. In previous PLR studies, the threshold was selected by optimization of the selected device, based on the sensitivity and specificity of that device to detect change; in the form of the Youden index, ROC, and maximum sensitivity and specificity. In the current study, the authors state only one threshold value but fail to inform the reader as to which technology the cut-off (threshold) was applicable, and to which technology the optimization was valid (PICCO or NICOM). As different technologies yield different thresholds for PLR to predict fluid responsiveness, it is imperative to inform the reader of the methodologies in selecting the PLR cut off.[2–4] If PLR predictiveness was optimized for PICCO technology, followed by testing with Cheetah NICOM, this would further flaw the results of the study, falsely undermining the reliability of the NICOM device.

3. The validation references in the article appear misleading—the authors state that validation of the bioreactance technique is still ongoing and that initial results are conflicting. To support this statement, they cite references where bioreactance is shown to perform positively (references 3–5) and then cite four publications (references 6–9) to support a premise that bioreactance, specifically Cheetah NICOM, is not reliable in estimating cardiac output. Unfortunately, there appear to be several serious issues with the interpretation of these references and the conclusions drawn from these references suggesting poor performance of the NICOM device. Our concerns are as follows:

(i) Reference 6 in the article[5] is not a peer-reviewed study but an observational letter, based on a case series, with only 11 patients.
(ii) Reference 7 in the article[6]—this is a validation study performed utilizing a bioimpedance product (BioZ by Cardiodynamics). This is not a Cheetah NICOM validation study.
(iii) Reference 8 in the article[7]—Weisz and colleagues concluded, 'Non-invasive cardiac output monitoring is feasible in neonates. Further validation studies in neo-natal animal experimental models and human neonates need to be conducted before routine clinical use'. This is a positive outcome conducted with the Cheetah NICOM monitor as the non-invasive technology. Weisz and colleagues state that further studies are required because although both NICOM and the LVO devices were highly correlated in their values (R=0.95, r<0.001), there was a consistent 30% bias between them. As neither device is accepted as gold standard, Weisz and colleagues suggested further examination.
(iv) Reference 9 in the article[8]—Marik and colleagues concluded in their study, 'Monitoring the hemodynamic response to a PLR using the NICOM provides an accurate method of assessing volume responsiveness in critically ill patients'. This is again a positive study involving the Cheetah NICOM monitor.

4. The technology referenced may confuse bioimpedance and bioreactance—in the article, Kupersztych-Hagege and colleagues state that the bioreactance technique is based on phase shifts of electrical current crossing the thorax and they refer the reader to reference 2 in the article.[9] This reference does not correctly describe the bioreactance technology but only a modification to the bioimpedance technology. The reader could be led to understand that the bioreactance and the technology commonly known as bioimpedance are actually the same. We refer the authors to the bioreactance pre-clinical publication by the bioreactance inventor Keren and colleagues[10] for an accurate and comprehensive description of the bioreactance technology.

We therefore believe that this study has several significant deficiencies, which include marked deviation from appropriate use of the Cheetah NICOM, erroneous interpretation of references citing NICOM's poor performance, and lack of adequate data presented to support the authors' conclusions.

We at Cheetah Medical welcome a robust and properly conducted evaluation of the technology, but this does not appear to have been done in this instance.

Declaration of interest

W.T.D. is the Chief Medical Officer of Cheetah Medical. C.H. is the CEO & President of Cheetah Medical. B.L. is the Chief Technology Officer of Cheetah Medical.

W. T. Denman*
C. Hutchison
B. Levy
MA, USA
**E-mail: william.denman@cheetah-medical.com*

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8 Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and Carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest* 2013; **143**: 364–70
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Contribution of oxycodone and its metabolites to the analgesic effect

Editor—Kokki and colleagues[1] published an article on central nervous system penetration of oxycodone in humans. These are the first human data available for this drug and also its metabolites. We have recently published a method to calculate

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Bioreactance for estimating cardiac output and the effects of passive leg raising in critically ill patients

Editor—I read with interest the study of E. Kupersztych-Hagege and colleagues,[1] entitled: 'Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients'. However, I believe that this conclusion is flawed for the following reasons.

First, since 83% of the patients of the study had sepsis and 'most of them' had acute respiratory distress syndrome, it would be wise to restrict the title and conclusion to these patients.

Secondly, three thermodilution boluses were averaged as reference method and unexpected results were probably removed to ensure an adequate averaging, as generally recommended. In contrast, only one instantaneous value of bioreactance was collected. In a way, this is like comparing the resolution of a carefully taken picture and a freeze video image. In other papers where acceptable concordance was observed, 10 min of bioreactance trend lines were averaged while thermodilution boluses were performed. This method has been recommended for smoothing the impacts of artifacts, differences in time responses and precisions, and comparing really the two technologies.

Thirdly, it has been well shown that the minimum time response of the bioreactance technology was 1 min. In this study, the passive leg raising (PLR) results were assessed after 1 min. The bioreactance changes were therefore necessarily underestimated. This time delay limited to 1 min is surprising since two co-authors of this paper have popularized the PLR test recommending a time frame 30–90 s, especially in septic patients.

Finally, the study showed that the agreement between bioreactance and thermodilution was below that expected from chance alone (43%). This corroborates the area under the ROC curve close to zero for predicting fluid responsiveness. These results only tell us that, in this study, the inappropriate data acquisition seemingly made the value of bioreactance close to that obtained at random.

Subsequently, four references are provided to support the so-called 'Bioreactance less promising results'. In reality, the paper from Fagnoul and colleagues[2] included 11 patients, the paper from Engoren and Barbee[3] investigated another technology (bioimpedance), the study of Weisz and colleagues[4] was done in neonates where a bioreactance calibration factor has never been calculated. Finally, the paper from Marik and colleagues[5] concluded that 'Monitoring the hemodynamic response to a PLR manoeuvre using Bioreactance provides an accurate method of assessing volume responsiveness in critically ill patients'. I think it is still true.

Declaration of interest

P.S. was a consultant for Cheetah Med from 2005 to 2010.

P. Squara
Neuilly-ur-eine, France
E-mail: pierre.squara@orange.fr

1 Kupersztych-Hagege E, Teboul J-L, Artigas A, *et al.* Bioreactance is not reliable for estimating cardiac output and the effects of passive leg raising in critically ill patients. *Br J Anaesth* 2013; **111**: 961–6
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Reply from the authors to Dr Squara

Editor—We are thankful to Dr Squara for his interest in our study[1] and for his comments. We would like to answer his criticisms point by point.

First concerning the title of the article, we did not specifically demonstrate that the unreliability of the Nicom was related to septic shock or acute respiratory distress syndrome. In the absence of any certitude about this point and to be scientifically rigorous, we chose a title that simply specified the population that was actually included, that is, critically ill patients.

Secondly, no thermodilution curve was rejected from analysis. We previously showed that, with such a method, the precision of transpulmonary thermodilution is 12%.[2] Dr Squara suggests that we should have taken the value of cardiac index averaged over 10 min rather than the instantaneous value of cardiac index displayed by the Nicom device. Of course, it is obvious that this would have reduced the influence of artifacts on cardiac index measurements. Nevertheless, the manufacturer clearly insists on the 'fast responsiveness' of the technique. What our study simply shows is that it is actually untrue, at least in critically ill patients.