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 colleagues1 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.

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3 Marik PE, Levitov A, Young A, Andrews L. The use of NICOM (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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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 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—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—Weisz and colleagues concluded, 'Non-invasive cardiac output monitoring is feasible in neonates. Further validation studies in neonatal 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—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. 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 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.

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**Contribution of oxycodone and its metabolites to the analgesic effect**

Editor—Kokki and colleagues 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