Bioreactance reliably detects preload responsiveness by the end-expiratory occlusion test when averaging and refresh times are shortened

Francesco Gavelli1,2*, Alexandra Beurton1, Jean‑Louis Teboul1, Nello De Vita1, Danila Azzolina3, Rui Shi1, Arthur Pavot1 and Xavier Monnet1

Abstract

Background: The end‑expiratory occlusion (EEXPO) test detects preload responsiveness, but it is 15 s long and induces small changes in cardiac index (CI). It is doubtful whether the Starling bioreactance device, which averages CI over 24 s and refreshes the displayed value every 4 s (Starling‑24.4), can detect the EEXPO‑induced changes in CI (ΔCI). Our primary goal was to test whether this Starling device version detects preload responsiveness through EEXPO. We also tested whether shortening the averaging and refresh times to 8 s and one second, respectively, (Starling‑8.1) improves the accuracy of the device in detecting preload responsiveness using EEXPO.

Methods: In 42 mechanically ventilated patients, during a 15‑s EEXPO, we measured ΔCI through calibrated pulse contour analysis (CI<sub>pulse</sub>, PICCO2 device) and using the Starling device. For the latter, we considered both CI<sub>Starling‑24.4</sub> from the commercial version and CI<sub>Starling‑8.1</sub> derived from the raw data. For relative ΔCI<sub>Starling‑24.4</sub> and ΔCI<sub>Starling‑8.1</sub> during EEXPO, we calculated the area under the receiver operating characteristic curve (AUROC) to detect preload responsiveness, defined as an increase in CI<sub>pulse</sub> ≥ 10% during passive leg raising (PLR). For both methods, the correlation coefficient vs. ΔCI<sub>pulse</sub> was calculated.

Results: Twenty‑six patients were preload responders and sixteen non preload‑responders. The AUROC for ΔCI<sub>Starling‑24.4</sub> was significantly lower compared to ΔCI<sub>Starling‑8.1</sub> (0.680 ± 0.086 vs. 0.899 ± 0.049, respectively; p = 0.027). A significant correlation was observed between ΔCI<sub>Starling‑8.1</sub> and ΔCI<sub>pulse</sub> (r = 0.42; p = 0.009), but not between ΔCI<sub>Starling‑24.4</sub> and ΔCI<sub>pulse</sub>. During PLR, both ΔCI<sub>Starling‑24.4</sub> and ΔCI<sub>Starling‑8.1</sub> reliably detected preload responsiveness.

Conclusions: Shortening the averaging and refresh times of the bioreactance signal to 8 s and one second, respectively, increases the reliability of the Starling device in detection of EEXPO‑induced ΔCI.

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Keywords: Fluid, Cardiac index, Monitoring, Passive leg raising, Fluid challenge, Heart lung interactions
Background
Over the last decade, much effort has been put into the development of methods monitoring cardiac index (CI) non-invasively [1–6]. Among them, bioreactance estimates cardiac output by analyzing the phase shift between an inward current that is sent through the thorax and the resulting outward current [1]. The principle of the technique is that this phase shift is determined by the variation of the volume of the thorax. From beat to beat, this variation is related to the variation of the volume of blood in the descending aorta and, thus, to stroke volume [7]. Bioreactance is considered as an improvement of bioimpedance which might be less sensitive to artifacts and the patient’s movements. The technique is totally non-invasive, as it only requires electrodes pasted on the thorax.

It has been shown to detect real-time changes of CI (ΔCI) induced by a passive leg raising (PLR) test and volume expansion [7]. Besides the PLR test, the end-expiratory occlusion (EEXPO) test is another test assessing preload responsiveness which can be used in mechanically ventilated patients. It consists in interrupting mechanical ventilation at end-expiration for a few seconds, which increases cardiac preload, and in observing the ΔCI which occurs in cases of preload responsiveness. Its accuracy has been established [12–14] and it is easy to perform.

Nevertheless, the duration of EEXPO is only 15 s, and the induced ΔCI are relatively small [12]. It is then uncertain whether the available commercial version of the bioreactance device, which averages the CI signal over 24 s and refreshes the displayed value every 4 s, is adequate for monitoring the effects of EEXPO (Fig. 1). Thus, the primary goal of this study was to test whether the commercial version of the bioreactance device accurately detects preload responsiveness through the EEXPO-induced ΔCI. The secondary goal was to assess whether shortening the averaging and refresh times of the device improves this detection. We hypothesized that bioreactance can monitor the EEXPO effects on CI, provided that the time over which it averages CI and after which it refreshes its displayed value is short.

Patients and methods
Patients
This prospective study was conducted in a 25-bed intensive care unit (ICU) and approved by an Institutional Review Board (No. IDRCB: 2018-A02825-50). At the time of inclusion, patients’ next of kin were informed of the study protocol and of the option to refuse participation. As soon as clinical conditions improved and patients were able to give consent, the same opportunity was given to them. All patients and/or relatives agreed to participate.

![Fig. 1 Averaging and refresh times of both the commercial (Starling-24.4—upper panel) and research (Starling-8.1—lower panel) bioreactance devices. CI: cardiac index; Starling-24.4: commercial version of the Starling device (averaging time 24 s, refresh time 4 s); Starling-8.1: research Starling device (averaging time 8 s, refresh time one second)
Patients were included if they met the following inclusion criteria: age \( \geq \) 18 years, admission to the ICU for less than 24 h, invasive mechanical ventilation, PiCCO2 device already in place (Pulsion Medical Systems, Feldkirchen, Germany) and decision by the attending clinicians to perform a PLR test. Exclusion criteria were intra-abdominal hypertension and venous compression stockings (which may decrease the PLR test reliability) [15], intracranial hypertension (which is a contraindication for PLR) and inability of the patients to sustain a 15-s EEXPO. Patients were included depending on the availability of the investigators. The study report complies with the Standards for Reporting Diagnostic Accuracy (STARD) statement [16].

Bioreactance measurements
The Starling v5.5 device (Baxter, Deerfield, IL, USA) requires 4 double-electrode sensors pasted on the thorax skin, creating a “virtual box” around the heart. The upper sensors are placed on the mid-right and mid-left clavicles and the lower sensors on the mid-right and mid-left last ribs. In each electrode pair, the outer one delivers a current with known alternating high frequency, detected by the inner electrode pair. The phase modulation between currents recorded at the inner and outer electrodes is altered by the changes in thoracic pulsatile blood volume, which allows a proprietary algorithm to derive stroke volume and CI [1, 17, 18].

The Starling v5.5 device displays a CI value which corresponds to the moving average of the raw values that have been measured over the last 24 s (Fig. 1). The displayed average is refreshed on the screen every 4 s. The CI value measured in this way will hereafter be called “CIStarling-24.4”.

We also extracted raw data from our recordings by the Starling device. In a post-hoc analysis, we changed the averaging time to 8 s, instead of 24. This duration was the shortest possible time that could be achieved, according to the technological limitations of the currently available device. We judged this interval as appropriate for estimating the effects of the 15-s EEXPO.

The refreshing delay was reduced to one second, instead of 4. The CI value obtained in this way will be called “CIStarling-8.1” (Fig. 1).

Transpulmonary thermodilution and pulse contour analysis measurements
The PiCCO2 device measures CI through transpulmonary thermodilution, which is performed by injecting three 15-mL boluses of cold saline in the superior vena cava [19, 20], and through pulse contour analysis (CI pulse), which is calibrated by transpulmonary thermodilution [21]. The value of CI pulse provided by pulse contour analysis is averaged over 12 s, with values that are refreshed every second. CI pulse was continuously recorded by the PiCCOWin software (Pulsion Medical Systems).

Other measurements
In addition to arterial pressure, heart rate and CI, we measured central venous pressure at end-expiration. Respiratory variables such as positive end-expiratory pressure, plateau pressure, respiratory rate and tidal volume (Vt) were also collected. Intra-abdominal pressure was measured through the bladder pressure as previously described [22].

Arterial, central venous and airway pressures were continuously recorded by data acquisition software (HEM3.5, Notocord, Croissy-sur-Seine, France).

Study protocol
At baseline, a set of thermodilution measurements was performed and CI pulse was calibrated. Once hemodynamic stability was observed (change in mean arterial pressure < 5% over 4 min) (EEXPO start), CI pulse, CI Starling-24.4, CI Starling-8.1 and other hemodynamic measurements were collected. A 15-s EEXPO was then initiated as previously described [12]. At the end of the EEXPO test (EEXPO end), the same variables were recorded. Subsequently, once the values of the hemodynamic variables had returned to baseline, another set of measurements were performed (PLR start). A PLR maneuver was performed as previously described [23], and, after 1 min of PLR, measurements were collected again (PLR end). If the ΔCI pulse between PLR start and PLR end was ≥ 10%, the patient was defined as a “preload responder”. This threshold corresponds to the increase in CI that has been demonstrated to indicate preload responsiveness with the best combination of sensitivity and specificity [24]. Sedative drugs, catecholamines and ventilatory settings were kept unchanged during the study period.

Statistical analysis
Based on a previous study by our group [11], to detect an increase in CI of at least 5% measured by the Starling device, expecting a baseline value of 3.1 L/min/m², we estimated that 42 pairs of measurements were required. This assessment was performed taking into account an α risk of 5% and a β risk of 20%, estimating that half of the patients would be preload responders. The minimal change of 5% was chosen, because it corresponds to the best threshold of EEXPO-induced CI changes that
detects preload responsiveness [14]. It is compatible with the least significant change of CIpulse [25].

Data are summarized as mean ± SD or median [interquartile range, IQR] as appropriate. The normality of distribution was evaluated visually. Pairwise comparisons of data were done with the paired Student’s t test or Wilcoxon test. The two-tailed Student’s t test or Mann–Whitney U test compared preload responders and non-responders.

To assess the significance of changes of variables over time during different interventions, we used a linear mixed-effect model to evaluate the group (preload responders and non-responders) and time (EEXPOstart, EEXPOend, PLRstart, PLRend) effects on hemodynamic variables. Time and groups were assumed as fixed effects, also considering the interaction component. A random intercept term was considered in patients to account for correlation among repeated measurements. The post-hoc pairwise comparison was reported by adjusting p values for multiple testing, using the Holm method [26]. Regarding our primary goal, receiver operating characteristic curves for EEXPO-induced relative ΔCIStarling-24.4 to predict preload responsiveness was built, providing sensitivity, specificity and the best threshold, and their area under the receiver operating characteristic curve (AUROC) was measured. The same analysis was performed for ΔCIStarling-8.1 to assess our secondary goal, and the AUROC were compared with the Hanley–McNeil test [27]. The ability of both ΔCIStarling-24.4 and ΔCIStarling-8.1 to detect preload responsiveness was subsequently tested in the subgroup of patients with and without norepinephrine infusion and in patients with a high and a low body mass index (BMI). “High” and “low” BMI values were defined according to the median of the variable measured in the whole population. To evaluate the overall concordance between absolute values of CIpulse and both CIStarling-24.4 and CIStarling-8.1 for EEXPO, we reported the intraclass correlation coefficient (ICC). Pearson’s correlation coefficient tested the correlations between the EEXPO-induced ΔCIpulse and both ΔCIStarling-24.4 and ΔCIStarling-8.1, and these coefficients were compared for relative changes.

We compared the absolute values of CIpulse and CIStarling-24.4 and the absolute values of CIpulse and CIStarling-8.1 recorded during EEXPOstart, EEXPOend, PLRstart and PLRend using the Bland–Altman analysis. Limits of agreement plots were defined as accounting for repeated measurements with possibly heteroscedastic measurement errors [28]. A Critchley polar plot analysis was performed [29] for assessment of the trending ability of CIStarling-24.4 and CIStarling-8.1 to compare the concordance in terms of relative ΔCIpulse vs. ΔCIStarling-24.4 and ΔCIStarling-8.1, both for EEXPO and PLR. Radial limits of agreement < 30° are considered to indicate good trending ability.

Statistical significance was set at a p value < 0.05 and statistical analysis was performed with MedCalc software 19.1 (Mariakerke, Belgium) and R 3.5.2 statistical software with lme4, MethodCompare and irr packages [30].

Results
Patients
Forty-two patients were included between April and September 2019. No patient was excluded due to inability to sustain a 15-s respiratory hold (Additional file 1: Figure S1). All patients were sedated with propofol and remifentanil (Table 1). Eight (19%) patients were paralyzed at the time of inclusion and no patient exhibited spontaneous breathing activity. No patient was in the prone position or had renal replacement therapy in place. Two patients had atrial fibrillation, whereas the others were in sinus rhythm (Table 1).

Hemodynamic changes during interventions
Twenty-six (62%) patients were defined as preload responders, according to the results of the PLR test. The

| Table 1 | Patient characteristics (n = 42) |
|---------|---------------------------------|

| Age (years) | 60 ± 9 |
| Male gender (n, %) | 21 (50%) |
| Body mass index (kg/m²) | 24 [21–27] |
| Simplified Acute Physiologic Score II on inclusion | 49 [31–55] |
| Richmond Agitation Sedation Scale score | 5 [1–5 to 19] |
| Left ventricular ejection fraction (%) | 45 ± 6 |
| Intra-abdominal pressure (mmHg) | 13 ± 4 |
| Type of shock (n, %) | |
| Septic | 36 (85.7%) |
| Cardiogenic | 4 (9.5%) |
| Hypovolemic | 1 (2.4%) |
| Distributive non-septic | 1 (2.4%) |
| Atrial fibrillation (n, %) | 2 (4.8%) |
| Cumulative fluid balance (mL) | 1035 [734–1655] |
| ICU length of stay (days) | 17 [7–44] |
| Mortality at day-28 (n, %) | 13 (31%) |
| Norepinephrine | |
| Number of patients (%) | 27 (64%) |
| Dose of norepinephrine (µg/kg/min) | 0.28 [0.13–0.43] |
| Ventilator settings | |
| Tidal volume (mL/kg of PBW) | 6.0 [5.1–6.0] |
| Respiratory rate (breaths/min) | 28 ± 5 |
| Fraction of inspired oxygen | 0.51 ± 0.16 |
| Positive end-expiratory pressure (cmH₂O) | 12 ± 3 |
| Plateau pressure (cmH₂O) | 25 ± 5 |

ICU intensive care unit, PBW predicted body weight,
changes in hemodynamic variables in both groups are shown in Table 2.

PLR induced a $\Delta \text{CI}_{\text{pulse}}$ of 16.8 [12.0–24.43%] in responders and 2.2 [1.3–4.5%] in non-responders ($p < 0.0001$). It induced a $\Delta \text{CI}_{\text{Starling-24.4}}$ of 21.7 [14.3–43.8%] in responders and 0.0 [0.0–4.1%] in non-responders ($p < 0.0001$). PLR induced a $\Delta \text{CI}_{\text{Starling-8.1}}$ of 49.7 [29.3–74.4%] in responders and 5.1 [-0.4–11.1%] in non-responders ($p = 0.0001$) (Table 2).

The EEXPO test induced a $\Delta \text{CI}_{\text{pulse}}$ of 5.3 [4.1–7.5%] in responders and 1.2 [0.5–2.4%] in non-responders ($p < 0.0001$). It induced a $\Delta \text{CI}_{\text{Starling-24.4}}$ of 5.5 [−0.2–7.1%] in responders and 0.1 [−0.1–0.1%] in non-responders ($p = 0.049$). The EEXPO test induced a $\Delta \text{CI}_{\text{Starling-8.1}}$ of 12.8 [7.8–22.2%] in responders and 0.9 [−1.1–4.8%] in non-responders ($p = 0.0001$) (Table 2).

### Table 2 Hemodynamic measurements

| Variables                      | EEXPO<sub>start</sub> | EEXPO<sub>end</sub> | PLR<sub>start</sub> | PLR<sub>end</sub> |
|-------------------------------|------------------------|---------------------|---------------------|-------------------|
| Heart rate (min<sup>−1</sup>)  |                        |                     |                     |                   |
| Preload responders (n = 26)    | 95 ± 16                | 96 ± 17             | 96 ± 17             | 93 ± 18**         |
| Preload non-responders (n = 16)| 93 ± 23                | 93 ± 23             | 93 ± 22             | 93 ± 22           |
| Systolic arterial pressure (mmHg) |                       |                     |                     |                   |
| Preload responders (n = 26)    | 120 ± 17               | 121 ± 17            | 122 ± 20            | 136 ± 16**        |
| Preload non-responders (n = 16)| 134 ± 24<sup>a</sup>   | 134 ± 24<sup>a</sup> | 132 ± 18            | 139 ± 18          |
| Diastolic arterial pressure (mmHg) |                       |                     |                     |                   |
| Preload responders (n = 26)    | 60 ± 11                | 60 ± 10             | 62 ± 11             | 67 ± 11**         |
| Preload non-responders (n = 16)| 68 ± 11<sup>a</sup>    | 68 ± 11<sup>a</sup> | 67 ± 11             | 71 ± 9            |
| Mean arterial pressure (mmHg)  |                        |                     |                     |                   |
| Preload responders (n = 26)    | 82 ± 12                | 82 ± 11             | 83 ± 13             | 93 ± 12**         |
| Preload non-responders (n = 16)| 92 ± 12<sup>a</sup>    | 92 ± 13<sup>a</sup> | 91 ± 11<sup>a</sup> | 96 ± 9            |
| Central venous pressure (mmHg) |                        |                     |                     |                   |
| Preload responders (n = 26)    | 11 ± 5                 | 11 ± 4              | 12 ± 4              | 14 ± 5**          |
| Preload non-responders (n = 16)| 14 ± 4<sup>a</sup>     | 13 ± 4              | 14 ± 4              | 15 ± 3            |
| PiCCO<sub>2</sub> Cardiac Index (L/min/m<sup>2</sup>) |             |                     |                     |                   |
| Preload responders (n = 26)    | 2.95 ± 1.05            | 3.12 ± 1.06<sup>*</sup> | 2.89 ± 0.94         | 3.40 ± 1.03**     |
| Preload non-responders (n = 16)| 3.03 ± 0.87            | 3.08 ± 0.89         | 2.97 ± 0.78         | 3.08 ± 0.89       |
| Starling-24.4 Cardiac Index (L/min/m<sup>2</sup>) |             |                     |                     |                   |
| Preload responders (n = 26)    | 2.8 ± 0.5              | 3.0 ± 0.6<sup>*</sup> | 2.8 ± 0.5           | 3.5 ± 0.7**       |
| Preload non-responders (n = 16)| 2.4 ± 0.4<sup>a</sup>  | 2.3 ± 0.4<sup>a</sup> | 2.6 ± 0.5           | 2.6 ± 0.5<sup>a</sup> |
| Starling-8.1 Cardiac Index (L/min/m<sup>2</sup>) |             |                     |                     |                   |
| Preload responders (n = 26)    | 2.83 ± 0.58            | 3.25 ± 0.71<sup>*</sup> | 2.69 ± 0.55         | 3.98 ± 0.86**     |
| Preload non-responders (n = 16)| 2.45 ± 0.41            | 2.48 ± 0.39<sup>a</sup> | 2.63 ± 0.50         | 2.79 ± 0.51<sup>a</sup> |
| Pulse pressure variation (%)   |                        |                     |                     |                   |
| Preload responders (n = 26)    | 10 ± 6                 | –                   | 11 ± 7              | 10 ± 6            |
| Preload non-responders (n = 16)| 10 ± 9                | –                   | 11 ± 8              | 10 ± 9            |
| Stroke volume variation (%)    |                        |                     |                     |                   |
| Preload responders (n = 26)    | 12 ± 6                 | –                   | 12 ± 6              | 11 ± 6            |
| Preload non-responders (n = 16)| 11 ± 8                | –                   | 11 ± 8              | 11 ± 8            |

<sup>a</sup> $p < 0.05$ vs. Preload responders
<sup>*</sup>$p < 0.05$ vs. EEXPO<sub>start</sub> **$p < 0.05$ vs. PLR<sub>start</sub>
Relative \( \Delta CI \) Starling-24.4 detected preload responsiveness, as defined by the increase in \( \Delta CI_{\text{pulse}} \geq 10\% \) during PLR, with an AUROC of 0.929 ± 0.039. The cut-off corresponding to the best Youden index was 10%. Similarly, PLR-induced relative \( \Delta CI \) Starling-8.1 detected preload responsiveness with an AUROC of 0.970 ± 0.024 and a best Youden index cut-off of 15% (Additional file 1: Table S3).

Concordance analysis
When considering all the changes observed during the study (n = 84) at Bland–Altman analysis, absolute values
of both CI\textsubscript{Starling-24.4} and CI\textsubscript{Starling-8.1} showed a regressive pattern vs. CI\textsubscript{pulse}, with the bias line moving for higher values (Additional file 1: Figure S2). The percentage error was 67% for CI\textsubscript{Starling-24.4} and 65% for CI\textsubscript{Starling-8.1}.

The ICC for absolute value comparison vs. CI\textsubscript{pulse} at the EEXPO test (n = 42) was higher for CI\textsubscript{Starling-8.1} than for CI\textsubscript{Starling-24.4} (0.60 vs. 0.48, respectively; p = 0.04). Again, when considering only the changes observed during EEXPO, a significant correlation was observed between relative ΔCI\textsubscript{pulse} and ΔCI\textsubscript{Starling-8.1} (r = 0.42; p = 0.009), but not between ΔCI\textsubscript{pulse} and ΔCI\textsubscript{Starling-24.4} (p = 0.40). When considering only the changes observed during PLR, a significant correlation was observed both between ΔCI\textsubscript{pulse} and ΔCI\textsubscript{Starling-8.1}, and between ΔCI\textsubscript{pulse} and ΔCI\textsubscript{Starling-24.4} (r = 0.70 and r = 0.60, respectively; p < 0.0001 for both).

When considering only the changes observed during EEXPO (n = 42) at polar plot analysis, after removing from the central exclusion data points for which ΔCI were less than 1.5% [25], the ability to track ΔCI was higher for CI\textsubscript{Starling-8.1} (polar concordance: 83%) than for CI\textsubscript{Starling-24.4} (polar concordance: 71%) (Fig. 3). When considering only the changes observed during PLR (n = 42), the ability to track ΔCI was similar for CI\textsubscript{Starling-8.1} (polar concordance: 81%) and for CI\textsubscript{Starling-24.4} (polar concordance: 86%) (Additional file 1: Figure S3).

Discussion

This study shows that the commercial version of the Starling device poorly detects preload responsiveness through the EEXPO test. However, when the hemodynamic effects of the EEXPO test are tracked with a modified version of the Starling device, where the averaging time is reduced to 8 s and the refresh time to one second, the ability to detect preload responsiveness is good. In addition, this study confirms that bioreactance reliably follows the PLR-induced ΔCI, whichever setting is used.

Over the years, different tests have been developed to detect preload responsiveness before deciding to infuse fluids or not [31]. However, these tests differ not only in the amplitude of ΔCI they induce, but also in the time over which these changes occur [13, 32]. In particular, the EEXPO test was performed over 12 to 30 s in the studies that tested its reliability [33, 34].

Regarding the different techniques estimating CI, the issue of averaging and refresh times is often neglected. Averaging the beat-to-beat values of CI allows the smoothing of CI changes, due either to its physiological instability or to the lack of precision of the technique that estimates it. Without any average, it would be difficult to distinguish small changes from the noise of the signal. Conversely, if the averaging period is very long, the signal could be so smoothed that small changes would be undetectable. Besides the averaging time, the frequency at which every new CI value is displayed is also crucial. If the value is refreshed at each cardiac beat, the displayed value may be very unstable, again impairing the assessment of significant changes. Conversely, in the event of infrequent refreshments, acute changes may be masked.

Our team has demonstrated that bioreactance did not reliably detect ΔCI induced by a 1-min PLR if the averaging time was 30 s [10]. A version of the NICOM device using a moving averaging period of 8 s was much better for this purpose [11]. In the present study, we investigated the ability of bioreactance to assess the EEXPO test, the duration of which is much shorter than that of the PLR test. For this purpose, we changed the averaging time and the refresh time from the raw values of CI estimated by bioreactance.

Regarding our primary goal, the EEXPO test was unable to detect preload responsiveness if assessed with the commercial version of the Starling device, which should not be used for this purpose. As a matter of fact, 11 (26%) patients were wrongly classified by Starling-24.4 at the EEXPO test. Regarding our secondary goal, we confirmed that the EEXPO test was correctly assessed if the
averaging and refresh times were reduced to 8 and one second, respectively. In the overall population, all but 5 patients were correctly defined as “preload responders” and “preload non-responders” by the Starling-8.1 device. However, among 2 of the 3 false negatives, the $\Delta C_{I,\text{Starling-8.1}}$ was close to the 5% cut-off value (respectively, 4.7% and 4.8%). This was also the case in one of the 2 false positives (5.7%). Our results suggest that bioreactance can be used to perform the EEXPO test only if the averaging and refresh times of the device are shortened, at least transiently.

Our Bland–Altman and concordance analyses showed that the estimation of the absolute value of CI by bioreactance was far from perfect. The percentage error was high, confirming previous studies [11, 35]. The Bland–Altman analysis did not provide different results for $C_{I,\text{Starling-8.1}}$ and $C_{I,\text{Starling-24.4}}$. On the contrary, the trending ability of the device was much better. In particular, the polar plot analysis of changes provided acceptable results. Interestingly, when changes were assessed during EEXPO, the trending ability of $C_{I,\text{Starling-8.1}}$ was better than that of $C_{I,\text{Starling-24.4}}$, confirming that these short-term changes were better tracked by the former version than by the latter.

Of note, the present study also contributes to the validation of the EEXPO test. The EEXPO-induced $\Delta CI$ measured by pulse contour analysis well detected preload responsiveness, which was estimated through the PLR-induced $\Delta CI$. The AUROC was above 0.900, a level achieved only by very reliable tests and indices of preload responsiveness [24, 36]. The fact that these results were obtained in patients ventilated with a $V_t \leq 6$ mL/kg confirms that low $V_t$ ventilation does not make the EEXPO test unreliable, despite studies affirming the contrary [37, 38]. In addition, it confirms that in the presence of low $V_t$, the reliability of both PPV and SVV is limited: as shown in Table 2, no significant differences were observed between preload responders and non-responders. Of note, a limitation of the EEXPO test is that the patients must be able to sustain a rather long ventilator occlusion. In the present study, the Richmond Agitation Sedation Scale score was quite high.

Limitations
First, we defined preload responsiveness by a positive PLR test and a fluid bolus was not infused in all the patients. However, the demonstration of PLR test reliability is likely strong enough today to allow one to consider it as a reliable surrogate of a fluid bolus [24]. Second, we investigated only a 15-s EEXPO test; a duration of 30 s has also been described [34]. With a longer EEXPO, the performances of $C_{I,\text{Starling-8.1}}$ and $C_{I,\text{Starling-24.4}}$ in tracking $\Delta CI$ might have differed less. Third, we included only hemodynamically stable patients who did not require changes in vasopressor dosage: we cannot, therefore, address the issue of whether the reliability of bioreactance could be influenced by short-term changes in afterload. In addition, sepsis was the cause of circulatory failure in most of the patients (86%). Thus, in theory, our results should apply only to this specific population. Finally, we investigated only ICU patients, though the best reliability of bioreactance has been demonstrated in normal subjects [39, 40] or in the peri-operative setting [8, 9].

Conclusion
The Starling bioreactance device reliably detects preload responsiveness through the EEXPO test, provided that its averaging time is reduced to 8 s and its refresh time to one second.

Abbreviations
AUROC: Area under the receiver operating characteristic curve; CI: Cardiac index; $C_{I,\text{Starling-8.1}}$: Cardiac index measured through the commercial version of the Starling device (averaging time 24 seconds, refresh time 4 seconds); $C_{I,\text{Starling-24.4}}$: Cardiac index measured through raw data analysis of the Starling device (averaging time 8 seconds, refresh time 1 second); $C_{I,\text{pulse}}$: Cardiac index measured by the pulse contour analysis method; EEXPO: End-expiratory occlusion; ICC: Intraclass correlation coefficient; ICU: Intensive care unit; PLR: Passive leg raising; $V_t$: Tidal volume; $\Delta CI$: Changes in cardiac index.

Supplementary Information
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Additional file 1. Additional tables and figures.

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Authors’ contributions
FG acquired the data, performed data analysis and interpretation and wrote the manuscript. AB acquired the data and contributed to data analysis. J-LT designed the study, participated in data analysis and interpretation and contributed to writing the manuscript. NDV acquired the data and contributed to data analysis. DA performed data analysis and interpretation and contributed to writing the manuscript. RS acquired the data. AP acquired the data. XM acquired the data, performed data analysis and interpretation and wrote the manuscript. All authors read and approved the final manuscript.

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Consent for publication
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Competing Interests
J-LT and XM are members of the medical advisory board for Pulsion Medical
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Author details
1Service de Médecine Intensive-Réanimation, Université Paris-Saclay, AP-HP, Hôpital de Bicêtre, DMU CORREVE, Inserm UMR S_999, CARMAS,
78, Rue du Général Leclerc, 94 270 Le Kremlin-Bicêtre, France. 2Emergency Medicine Unit, Department of Translational Medicine, Università degli Studi
del Piemonte Orientale, 28100 Novara, Italy. 3Research Support Unit, Depart-
ment of Translational Medicine, Università degli Studi del Piemonte Orientale,
28100 Novara, Italy.

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