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Interpreting EVERDAC: Deferring arterial cannulation in critically ill patients with shock

ABSTRACT

Patients admitted to the intensive care unit with shock do not automatically need to have an arterial catheter inserted immediately. This is the main take-away point from the Early Versus Deferred Arterial Catheterization in Critically Ill Patients With Acute Circulatory Failure (EVERDAC) trial, which found that slightly fewer patients died in a group randomly assigned to not have an arterial catheter inserted unless it was truly needed, compared with putting one in immediately. This result easily met the trial's predefined criterion for noninferiority of deferring arterial catheterization, and it challenges our standard practice.

KEY POINTS

EVERDAC compared a strategy of deferred arterial catheterization with the usual practice of early catheterization in adult patients with shock.

Patients in the deferred catheterization group did not receive an arterial catheter unless they met criteria indicating worsening shock such as needing high-dose vasopressors.

The rates of mortality at 28 days (the primary outcome of the EVERDAC trial) and organ injuries (the secondary outcome) were about the same in the 2 treatment groups.

Noninvasive blood pressure monitoring and venous blood analysis, if deemed reliable, are reasonable alternatives to guide management in lieu of invasive blood pressure monitoring and arterial blood analysis.

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Patients with shock routinely receive an arterial catheter early in their stay in the intensive care unit to monitor their blood pressure and obtain arterial blood samples. Do they really need it?

Without an arterial catheter, we can still monitor blood pressure noninvasively, but noninvasive monitoring may be less accurate in those with severe shock, and the impact of such inaccuracies is unclear. We can obtain arterial blood samples by arterial puncture, but this is painful. We can also obtain central or peripheral venous blood samples, but venous blood analysis may not be as valuable in complex acid-base disorders and cannot deliver accurate oxygenation data, and a central venous line may not be justified unless vasopressors are being given in high doses or for prolonged times, or for venous access. Peripheral venous blood sampling can be problematic.[1]

But now we have evidence that not all patients with shock need an arterial catheter right away—or ever. The Early Versus Deferred Arterial Catheterization in Critically Ill Patients With Acute Circulatory Failure (EVERDAC) trial[2] was the first randomized controlled trial to evaluate whether deferring arterial catheterization is noninferior to routine early catheterization. The findings challenge the strategy of reflexive early placement of arterial lines in the intensive care unit.

WHY CHALLENGE ROUTINE EARLY ARTERIAL CANNULATION?

Four previous observational studies compared

the outcomes of intensive-care patients with and without arterial cannulation.[3–6] No inference can be drawn regarding the timing of cannulation from these studies.

Moreover, arterial catheterization poses risks that can be justified only if important clinical outcomes are shown to be superior if it is done.

EVERDAC TRIAL DESIGN

EVERDAC was a pragmatic noninferiority trial comparing the standard invasive strategy of early arterial cannulation for all patients admitted to intensive care with shock, vs a noninvasive strategy of deferring cannulation until deterioration reached certain thresholds.

A total of 1,010 patients in 9 French hospitals were recruited. The inclusion criteria were as follows:

- Age 18 years or older
- Admitted to intensive care within the past 24 hours
- In shock (systolic blood pressure < 90 mm Hg or mean arterial pressure < 65 mm Hg for > 15 minutes or initiation of vasopressor therapy, plus at least 1 sign of tissue hypoperfusion).

They were excluded for the following reasons:

- Noninvasive blood pressure measurement was not possible or reliable
- They needed extracorporeal membrane oxygenation
- They had severe brain injury
- Their body mass index was greater than 40 kg/m^2
- They were pregnant
- They were receiving norepinephrine tartrate or epinephrine in doses higher than 2.5 µg/kg/minute. (One µg of norepinephrine tartrate equals 0.5 µg of norepinephrine base, the measure more widely used in the United States.[2])

Randomization was stratified by center, the need for invasive mechanical ventilation, and vasopressor dose (< 0.36 µg/kg/minute vs ≥ 0.36 µg/kg/minute).

Noninvasive vs invasive strategies

In the noninvasive-strategy group, arterial catheterization was not allowed from the time of randomization until 28 days had passed or the patient left the intensive care unit. If the patient already had an arterial catheter when randomized to this group, it was removed within 1 hour. However, arterial catheterization was allowed during the first 28 days in this group for the following reasons:

- Oximetry or noninvasive blood pressure measurements became unreliable
- Arterial blood gas measurements were absolutely needed after 5 attempts at arterial puncture had failed
- Extracorporeal membrane oxygenation was needed
- Vasopressors (norepinephrine, epinephrine, or both) were given in doses higher than 2.5 µg/kg/minute
- Surgery was needed within the following 4 hours, in which case the catheter had to be withdrawn within 4 hours postoperatively.

In the invasive-strategy group, an arterial catheter was inserted within 4 hours of randomization. Noninvasive blood pressure monitoring was not allowed unless there was an arterial line infection or thrombosis.

In both groups, the arterial line, once inserted, was maintained for 28 days or until discharge or death or its use was considered futile (though futility was not defined).

Outcomes

The primary outcome was the number of patients who had died of any cause at 28 days. The secondary outcomes were as follows:

- Evolution over the first 7 days of the Sequential Organ Failure Assessment (SOFA) score (a measure of respiratory, cardiovascular, coagulatory, renal, hepatic, and neurologic dysfunction; scores range from 0 [no organ failure] to 24 [most severe organ failure])
- Number of days free from ventilator support, dialysis, and vasopressor therapy from day 1 to day 28
- Number of infections related to arterial or central venous catheters while in the intensive care unit.

The investigators also recorded pain related to blood pressure measurements (invasive or noninvasive) in patients who were able to communicate, at a time "sufficiently distant from any vascular puncture procedure unrelated to the arterial puncture." How much time was considered sufficiently distant was not defined.

RESULTS

The average age of the patients was 66.5 years. The 2 treatment groups were similar in terms of demographics, comorbidities before admission, types of shock, need for mechanical ventilation, and proportion on vasopressors. About 67% of patients were mechanically ventilated when randomized, and most were receiving vasopressors: 87% in the noninvasive-strategy group and 90% in the invasive-strategy group.

A criticism: the investigators did not present enough information about hemodynamics, acid-base disorders, and lactate levels on randomization, which reflect the degree of shock. Given the known inaccuracies of noninvasive blood pressure measurement in severe hypotension, a better picture of how "sick" the patients truly were at enrollment should have included acid-base data.

In the noninvasive-strategy group, 504 patients were included in the primary intention-to-treat analysis. Of these, 2 were excluded because they had arterial catheters in place at randomization that were not removed, leaving 502 in the first and second per-protocol analyses.

In the invasive-strategy group, 502 patients were included in the intention-to-treat analysis. Of these, 10 were removed, 1 because of brain injury, 1 because of catheterization beyond the 24-hour window, and 8 because no catheterization attempts were made, leaving 492 patients in the first per-protocol analysis. Two further patients underwent unsuccessful catheterization attempts, leaving 490 patients in the second per-protocol analysis.

Primary outcome

The primary outcome, mortality at 28 days, was analyzed first by intention to treat and then by 2 per-protocol analyses.

Intention-to-treat analysis. By 28 days after randomization, 173 (34.3%) of the 504 patients in the noninvasive-strategy group and 185 (36.9%) of the 502 patients in the invasive-strategy group had died (absolute risk difference with adjustment for stratification in favor of deferral –3.2 percentage points, 95% confidence interval [CI] –8.9 to 2.5, $P = .006$ for noninferiority, $P = .2$ for superiority).

Also at 28 days, 74 (14.5%) of the patients in the noninvasive-strategy group had undergone arterial cannulation as prespecified because of high vasopressor requirements in 33, high-risk surgery (with prompt removal of the arterial line postoperatively) in 20, unreliable noninvasive blood pressure measurements in 15, failing pulse oximetry in 7, more than 5 consecutive arterial blood gas samples in 6, and extracorporeal membrane oxygenation in another 6. These reasons clearly overlapped in some of the 74 patients.

Per-protocol analyses. The results of the per-protocol analyses were similar to those of the intention-to-treat analysis.

Secondary outcomes

The median SOFA score at randomization was 10 points (interquartile range [IQR] 7–12) in the noninvasive-strategy group and 10 points (IQR 8–12) in the invasive-strategy group, decreasing to 5 points (IQR 3–9) on day 7 in both groups.

The mortality rate at 90 days was 42.7% in the noninvasive group and 44% in the invasive group (absolute risk difference adjusted for stratification –1.7 percentage points, 95% CI –7.0 to 3.5).

The median number of days free of ventilator treatment, vasopressor treatment, and dialysis at day 28 and intensive care unit length of stay were also similar in the 2 groups.

Hematomas and hemorrhages. In the noninvasive-strategy group, 74 patients (14.7%) had to have an arterial catheter inserted, and 5 (6.8%) of the 74 had a catheter-related hematoma or hemorrhage. In the invasive-strategy group, 41 patients (8.2%) had a similar complication. These incidence rates were similar. However, the overall incidence of hematoma or hemorrhage was 5 of 504 (1%) in the noninvasive-strategy group vs 41 of 502 (8.2%) in the invasive-strategy group ($P < .001$).

Infections. The number of arterial catheter–related bloodstream infections per 1,000 intensive care unit days was 0.6 in the noninvasive-strategy group and 2.7 in the invasive-strategy group (difference favoring noninvasive strategy 0.18, 95% CI 0.06–0.54). The average duration of arterial catheters remaining in place can safely be assumed to be longer in the invasive-strategy group. For comparison, a 2014 meta-analysis reported that when arterial catheters were cultured in suspected bloodstream infection, the incidence of arterial catheter–related bloodstream infections was 0.96 per 1,000 catheter days.[7]

Pain. Patients in the noninvasive-strategy group endured 742 arterial puncture attempts for blood sampling (not including catheter placement) per 1,000 intensive care unit days, vs 269 in the invasive group (incidence ratio 2.76, 95% CI 2.41–3.16). It is unclear whether the arterial punctures in the invasive-strategy group were necessitated by arterial line–sampling difficulties. Although the pain specific to arterial puncture and topicalization was not reported, the difference between the number of punctures between cohorts (742 in the noninvasive group vs 502 arterial cannulations plus 269 arterial puncture attempts for blood sampling in the invasive group) is not large.

More patients in the noninvasive-strategy group (66/504, 13.1%) than in the invasive-strategy group (45/502, 9%) complained of serious blood pressure–related discomfort on at least 1 day ($P = .05$, 95% CI 0.3–8.0). A larger proportion of patients were coherent enough to answer questions in the noninvasive group (22.8%, 66 patients) than in the invasive group (15.4%, 45 patients; $P = .02$), although more in the invasive group were not interviewed for undisclosed reasons; the risk difference was 7.5 ($P = .02$, 95% CI 0.0–13.9). In short, noninvasive blood pressure monitoring caused pain.

Post hoc safety and subgroup analyses

In the noninvasive-strategy group, 65 patients (12.9%) reached the predefined upper vasopressor dose limit of 2.5 µg/kg/minute at a median time of 1 day (IQR 1–2), including 34 patients who received the dose over a period of 2 or more consecutive hours. In the invasive-strategy group, 72 patients (14.3%) reached the vasopressor-dose threshold at a median time of 1 day (IQR 1–2).

Reaching such extraordinarily high vasopressor doses suggests severe shock. Their 28-day mortality rate was accordingly much higher: 49 (75.4%) of these 65 patients in the noninvasive group died, as did 54 (75%) of the 72 patients in the invasive group.

DID EVERDAC SHOW DEFERRED CANNULATION AS NONINFERIOR TO EARLY CANNULATION?

EVERDAC has moderately high internal validity.

There was central randomization with allocation concealment, although there was no way to blind the attending clinicians and patients to the treatment. Arterial cannulation was allowed under pragmatic circumstances in the noninvasive-strategy group. Exclusions after randomization were minimal. Protocol adherence was excellent, with 493 (98.2%) of the 502 patients undergoing arterial cannulation in the invasive-strategy group, 479 within 4 hours. Only 74 (14.7%) of the 504 in the noninvasive-strategy group received arterial cannulation according to rescue protocol, at a median time of 22 hours (IQR 6–141). The low per-protocol conversion to invasive blood pressure monitoring in the noninvasive-strategy group suggests that most of the patients did not need arterial cannulation.

However, the population was heterogeneous in regard to the causes of shock: sepsis in 54.1%, cardiogenic in 11.3%, postcardiac arrest in 9.2%, hemorrhagic in 6%, obstructive in 0.8%, and other in 18.3%. Grouping diverse shock states and evaluating mortality as the primary outcome poses the risk of obscuring potential benefits of invasive monitoring in selected situations.

What does 'noninferior' actually mean?

The primary outcome—mortality—was objective. However, "noninferiority" is a nuanced concept.

Citing the possible catheterization-related complications (ischemia, hematoma, pseudoaneurysm, bloodstream infections, and possibly more frequent blood sampling), before the trial the investigators decided that the noninvasive strategy would be "noninferior" if the upper limit of the difference between the mortality rate in the noninvasive group (presumed higher) and that in the invasive group was no more than 5 percentage points (a *noninferiority margin* of 5%).

This prespecified definition of noninferiority—a noninferiority margin of 5 percentage points—was "fairly large."[8] The investigators did not describe how they arrived at this noninferiority margin, only that it was based on consensus, taking into account that noninvasive treatment would avoid vascular injury and infection.[2,9,10]

Such lack of transparency on how noninferiority is statistically and mathematically derived is common.[11] In superiority trials, the hypothetical change in outcome that renders a statistically significant difference ($P \leq .05$) nonsignificant ($P > .05$) is called the *fragility index*.[12] A low fragility index suggests that the results may not be robust and that examination of the number of dropouts and protocol violations is warranted.

The concept of fragility index has never been applied to noninferiority studies, in part because statistical significance depends predominantly on the noninferiority margin. Had the EVERDAC noninferiority margin been preset at 2.6%, the noninvasive strategy would not have been found noninferior. The fragility index for intention-to-treat in EVERDAC can be calculated to be 8 (meaning 8 more deaths in the noninvasive group compared with only 2 dropouts in that group) or more than 12 (meaning all 12 dropouts in the invasive group would have survived if they had not dropped out). In the per-protocol analysis (recommended for noninferiority trials), the fragility index is 7. These fragility indices are not low, considering that randomized controlled trials are powered (and sometimes halted) for a type-1 (false-positive) error of 0.05 or less, ie, a 5% or lower chance of incorrectly rejecting a true null hypothesis.

Based on a noninferiority margin of 5%, the EVERDAC mortality results are trustworthy, further reinforced by the fact that there were actually relatively fewer deaths in the noninvasive group.

Did the investigators turn to central venous catheterization more often to make blood sampling easier in the noninvasive-strategy group, thus defeating the purpose of deferring or avoiding arterial cannulation? No: the rate of central venous catheterization was actually lower in the noninvasive group (45 vs 53 per 1,000 intensive care unit days; incidence ratio 0.84, 95% CI 0.66–1.06).

CAN THE EVERDAC RESULTS BE GENERALIZED TO ALL INTENSIVE-CARE PATIENTS?

EVERDAC offers good to excellent external validity. However, the results should not be generalized to chil-

dren, pregnant women, patients with unusually high vasopressor requirements, or those with intracranial hypertension.

The protocol included a realistic safety net such that cannulation was allowed in the noninvasive group if there was clinical need. The exclusion of patients with severe shock did not skew the results in favor of deferral because in this pragmatic trial, of the 4,183 patients recruited, only 57 (1.36%) were excluded for requiring epinephrine or norepinephrine in doses of 1.25 µg/kg/minute or higher.

All aspects of intensive care unrelated to management of the arterial catheter were at the discretion of the clinical teams using "established international guidelines."[13] Such a pragmatic protocol likely contributed to the high compliance rate.

The inclusion criteria of systolic arterial blood pressure lower than 90 mm Hg or mean arterial pressure lower than 65 mm Hg for more than 15 minutes or initiation of vasopressor therapy, plus at least 1 sign of tissue hypoperfusion did not include sufficient context. In real-world practice, a favorable clinical response to 1 or 2 fluid boluses in a relatively robust and interactive patient may not lead to immediate arterial cannulation. For the one-third of EVERDAC patients who were not on mechanical ventilation when randomized, arterial cannulation might not be a priority. Relatively broad inclusion criteria recruiting less unstable or critical patients might increase the chance of finding no difference (noninferiority). While this may be a study "limitation," it conveys the message that prioritizing arterial cannulation is not always necessary.

Forced removal of an arterial line in situ in the noninvasive-strategy group and disallowance of noninvasive blood pressure monitoring after arterial cannulation in the invasive-strategy group do not reflect real-world practice but were necessary for clear separation of the variables.

There is no mention of maximal barrier precautions to reduce line sepsis,[14] in keeping with the fact that this was a pragmatic trial.

Two cases of ischemia or necrosis of digits occurred in the noninvasive group, and 7 cases in the invasive group; these could have been due to shock, vasopressors, vascular disease, or arterial trauma. Use of ultrasonography guidance is associated with high first-pass success rates (in one study, 83.3% vs 55.6% with palpation guidance [$P = .02$], fewer attempts, and shorter procedure time[15]), and far less pain and vascular injuries.[15–17] In EVERVAC, use of ultrasonography guidance was left to the discretion of clinicians.

To minimize line sepsis and thrombosis, arterial lines should be removed when no longer needed, and not necessarily kept in for 28 days or until discharge, death, or determination of futility, as reported. The investigators provided no additional details about deescalating.

EVERDAC SHOULD CHANGE PRACTICE

EVERDAC should be of great interest to intensivists. The objective of this study was to answer whether arterial catheterization can be deferred instead of being automatically prioritized.

Notwithstanding the shortcomings and limitations, this study provides the only good evidence to date that deferring arterial catheterization in intensive-care patients with shock does not compromise care if a pragmatic cannulation protocol is in place. Given that 85.3% of the noninvasive-strategy group never received an arterial catheter, one can infer that patients who have a stable or improving trajectory can be managed with noninvasive blood pressure monitoring, venous blood analysis, oximetry, electrocardiography, and clinical judgment. In this regard, EVERDAC should change practice.

When should we insert a catheter, apart from cases of deteriorating shock? Worth reiterating is that 14.7% of patients in the noninvasive-strategy group did receive an arterial catheter, at a median of 22 (IQR 6–141) hours after randomization. In real-world practice, arterial cannulation is but one step beyond an arterial puncture and is efficient under ultrasonography guidance. Given the high number of arterial punctures recorded in the noninvasive-strategy group, and the pain associated with it and with noninvasive blood pressure monitoring, I would argue that deferring arterial cannulation may not be prudent if multiple blood samplings and frequent noninvasive blood pressure cycling (from hemodynamic lability) are required.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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