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Ultrasound to Detect Central Venous Catheter Placement Associated Complications

A Multicenter Diagnostic Accuracy Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Catheter malposition and pneumothorax are known complications of central line placement. Earlier recognition of these complications can lead to reduced morbidity and mortality. Chest x-ray film is typically used to evaluate for appropriate central line positioning and potential pneumothorax.

What This Article Tells Us That Is New

- This prospective multicenter diagnostic accuracy study found that ultrasound can detect central line malposition with moderate sensitivity and high specificity.
- This study found that there is moderate agreement between chest x-ray film and ultrasound detection of central line–related pneumothorax.

ABSTRACT

Background: Mechanical complications arising after central venous catheter placement are mostly malposition or pneumothorax. To date, to confirm correct position and detect pneumothorax, chest x-ray film has been the reference standard, while ultrasound might be an accurate alternative. The aim of this study was to evaluate diagnostic accuracy of ultrasound to detect central venous catheter malposition and pneumothorax.

Methods: This was a prospective, multicenter, diagnostic accuracy study conducted at the intensive care unit and postanesthesia care unit. Adult patients who underwent central venous catheterization of the internal jugular vein or subclavian vein were included. Index test consisted of venous, cardiac, and lung ultrasound. Standard reference test was chest x-ray film. Primary outcome was diagnostic accuracy of ultrasound to detect malposition and pneumothorax; for malposition, sensitivity, specificity, and other accuracy parameters were estimated. For pneumothorax, because chest x-ray film is an inaccurate reference standard to diagnose it, agreement and Cohen's κ-coefficient were determined. Secondary outcomes were accuracy of ultrasound to detect clinically relevant complications and feasibility of ultrasound.

Results: In total, 758 central venous catheterizations were included. Malposition occurred in 23 (3.3%) out of 688 cases included in the analysis. Ultrasound sensitivity was 0.70 (95% CI, 0.49 to 0.86) and specificity 0.99 (95% CI, 0.98 to 1.00). Pneumothorax occurred in 5 (0.7%) to 11 (1.5%) out of 756 cases according to chest x-ray film and ultrasound, respectively. In 748 out of 756 cases (98.9%), there was agreement between ultrasound and chest x-ray film with a Cohen's κ-coefficient of 0.50 (95% CI, 0.19 to 0.80).

Conclusions: This multicenter study shows that the complication rate of central venous catheterization is low and that ultrasound produces a moderate sensitivity and high specificity to detect malposition. There is moderate agreement with chest x-ray film for pneumothorax. In conclusion, ultrasound is an accurate diagnostic modality to detect malposition and pneumothorax.

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Insertion of a central venous catheter is associated with a variety of potential serious complications. They can be roughly divided by etiology into mechanical, infectious, or thrombotic origins.[1,2] The risk of developing a complication with a hazardous outcome is increased by malposition of the central venous catheter.[3] It is therefore considered important that a misplaced catheter is readily identified and reinserted correctly before its use.[4]

Since Werner Forssman cannulated his own left antecubital vein and detected the tip of the catheter in his right atrium *via* chest x-ray film, this imaging modality has been the reference standard to confirm catheter position.[5] However, disadvantages of chest x-ray film are that its accuracy is debated—especially with regard to pneumothorax and intraatrial tip position—and performance is time-consuming; replacing or omitting chest x-ray film could, therefore, minimize delay until catheter use and reduce healthcare costs.[6]

The preliminary results were reported as a poster at the annual LIVES congress of the European Society of Intensive Care Medicine in Paris, France, October 22, 2018.

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Using ultrasound to aid cannulation was first reported in 1982.[7] Since then, ultrasound-guided cannulation is considered best practice.[8] In addition, to verify central venous catheter position and detect pneumothorax, an ultrasound-only method has already been proposed and researched by various studies.[9–15] However, to date, consensus is not reached and contradictory findings about the suitability of ultrasound emerged. Previously published studies showed large heterogeneity, were underpowered, had methodologic limitations, and used small groups of operators.[16] Therefore, a large multicenter study using multiple operators with different levels of experience was needed.

The primary aim of this study was to investigate the diagnostic accuracy of ultrasound to detect catheter malposition and iatrogenic pneumothorax as compared to chest x-ray film as reference standard. Secondary outcomes were diagnostic accuracy of ultrasound to detect clinically relevant adverse events and feasibility of the protocol. Based on previous research, we hypothesized that bedside ultrasound would be highly feasible (at least 85%) and would produce a good sensitivity (at least 90%) and very good specificity (at least 95%) for malposition and a substantial agreement (κ-coefficient: 0.61 to 0.80) for pneumothorax.[14,17]

Materials and Methods

Study Design

This was a Dutch multicenter, prospective, observational diagnostic accuracy study conducted at the Amsterdam University Medical Center, VU University (Amsterdam, The Netherlands), Rijnstate Hospital (Arnhem, The Netherlands) and Groene Hart Hospital (Gouda, The Netherlands). Approval was given by the medical Ethics Review Committee (Amsterdam University Medical Center, VU University; 2016.053), and the need for written informed consent was waived. Participants or legal representatives were, instead, informed about the study by a brochure provided at intensive care unit or postanesthesia care unit (PACU) admission, attached with an opt-out card that could be completed by the patient or legal representative in case of unwillingness to participate. Patients were enrolled between April 2016 and December 2017 at the intensive care unit or PACU. The study was registered at ClinicalTrials.gov (NCT02959203). Standards for Reporting Diagnostic Accuracy Studies (STARD) guidelines were followed (appendix 1).[18]

Study Population

The study population consisted of adult patients who underwent central venous cannulation of the internal jugular vein or subclavian vein. They were included in the study if they received a catheter on the intensive care unit, were admitted to the intensive care unit or PACU after surgery and received a central venous catheter in advance, or were admitted from the emergency department and had central venous catheter placed just before intensive care unit admission. Patients were excluded if they were younger than 18 yr, no postcannulation chest x-ray film was available within 6 h, or more than 3 h passed between ultrasound and chest x-ray film examination. Sex, age, body mass index, reason for intensive care unit or PACU admission, insertion site, and use of ultrasound guidance were registered. If a patient received more than one central line, patient characteristics were duplicated in the analyses.

Central Venous Cannulation

To cannulate the right or left side (internal jugular vein or subclavian vein), a 16- or 20-cm-length Triple or Quad-Lumen Blue Flextip (Arrow International, Inc., USA) was placed, respectively. Placement of the central venous catheter was performed according to the Seldinger technique. According to local intensive care unit protocol, use of ultrasound guidance was mandatory. At the emergency department or in the operating theater, use of ultrasound guidance was not mandatory, but at the discretion of the treating physician. Position of the central venous catheter and presence of pneumothorax were evaluated by chest x-ray film. Images were interpreted by a radiologist blinded for the results of ultrasound examination. Postprocedural ultrasound examination was performed within 6 h after central line insertion by either the physician who inserted it or a distinct study team member. All ultrasound operators were blinded for the results of chest x-ray film examination. The performing operators (N = 36) were trained according to the principles of the same intensive care ultrasound course and were able to perform basic cardiac, lung, and venous ultrasonography.[19,20] If any difficulties were encountered with image acquisition, a second operator could be consulted, which is common practice in the participating centers for performing point-of-care ultrasound. If the primary and secondary operator both were unable to acquire all ultrasound images in the protocol, the ultrasound evaluation was deemed infeasible. Ultrasound evaluation was performed with the Phillips CX50 (Koninklijke Philips NV, The Netherlands) or SonoSite Edge II (FUJIFILM SonoSite, Inc., USA).

Ultrasound Evaluation for Malposition and Pneumothorax

The ultrasound protocol consisted of three parts. The first part consisted of a bilateral ultrasound examination of the internal jugular vein and subclavian vein. The central venous catheter was considered to be malpositioned if the tip did not progress into the superior vena cava and was detected in any other vein than that of the insertion site. The second part consisted of an examination of the right atrium and ventricle. Visualization of the catheter tip was facilitated by contrast-enhanced ultrasound. This was done by flushing the catheter with 5 ml of agitated saline, which

causes a laminar flow of microbubbles to appear in the right atrium within 2 s. If the flow of microbubbles appeared after 2 s or was not seen at all, the central venous catheter was considered to be malpositioned.[10] Intraatrial position of the catheter tip was in essence not considered to be a malposition due to the fact that chest x-ray film does not accurately identify it.[21] Therefore, only deep intraatrial positioning that was unlikely to be missed on chest x-ray film was considered as such. The third part consisted of an ultrasound examination for pneumothorax, performed according to the Bedside Lung Ultrasound in Emergency (BLUE)-protocol.[22] The upper and lower BLUE points were evaluated for lung sliding and B-lines, and, if both were absent, the lung point was searched for. Identification of the lung point proved pneumothorax, whereas presence of lung sliding ruled it out. If the lung point could not be identified, presence of the lung pulse was evaluated. Presence of lung pulse ruled out pneumothorax, whereas absence ruled it in.[23] Figure 1 gives an overview of the complete protocol. For a more detailed description of the ultrasound protocol, consult appendix 2.

Chest X-ray Film Evaluation for Malposition and Pneumothorax

All chest x-ray films were assessed by a radiologist blinded for ultrasound results. According to the Dutch Society of Intensive Care Medicine (Utrecht, The Netherlands), a central venous catheter is to be situated in a large vein, ideally in the lower third part of the superior vena cava. This correlates with carina height on chest x-ray film, but is not 100% sensitive for anatomic position and pneumothorax.[24] A central line was regarded malpositioned if the tip was situated in any other location than the superior vena cava or upper right atrium as assessed by the radiologist. Usually, deep intraatrial placement occurs when the catheter tip projects more than 55 mm below the carina.[21] If a visceral pleural line was seen without distal lung markings near or at the ipsilateral site of catheter insertion, pneumothorax was diagnosed.[24,25]

Outcomes

Our primary aim was to evaluate the accuracy of bedside ultrasound in detecting central venous catheter malposition and pneumothorax. Accuracy outcome parameters for malposition were sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratio, and area under the curve. A "true positive" result was defined as an ultrasound-suggested aberrant position of the central venous catheter confirmed by chest x-ray film. If ultrasound examination ruled out an aberrant position of the catheter tip correctly, it was considered a "true negative" result. Pneumothorax is often missed by chest x-ray film, and it has already been proved by several studies that ultrasound is a better alternative.[26,27] Therefore, instead of calculating the sensitivity and specificity based on an "imperfect" reference standard, we determined the interobserver and overall percent agreement between ultrasound and chest x-ray film.[17]

Secondary outcomes were the incidence of clinically relevant catheter malposition and pneumothorax. Malposition was considered to be clinically relevant if it required retraction, replacement, or removal of the central line within 24 h after placement. Pneumothorax was considered to be clinically

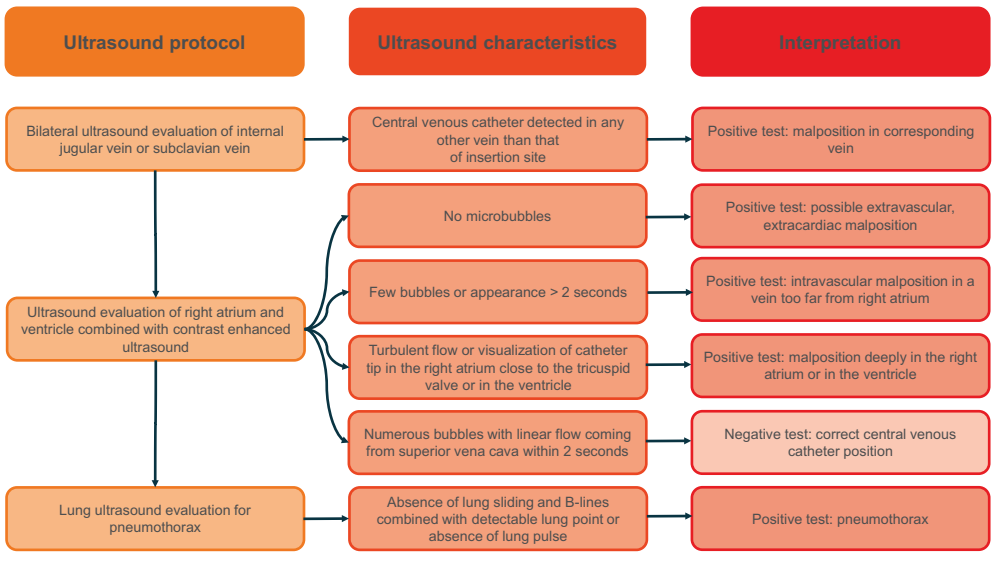

Fig. 1. Ultrasound protocol with its potential characteristics and interpretation. Flow diagram depicting the ultrasound protocol with characteristics that could be detected during examination and how they should be interpreted.

relevant if it required intervention, *e.g.*, thoracic drainage. To determine diagnostic accuracy of ultrasound in detecting clinically relevant malposition, the area under the curve was estimated. Finally, feasibility was determined. If all views in the protocol could be obtained, ultrasound was considered feasible. A comparison between feasibility and individual patient characteristics was made to investigate which characteristics affected ultrasound feasibility. Furthermore, to assess the diagnostic performance of ultrasound in different circumstances, two *post hoc* sensitivity analyses were performed. To assess for clustering of data due to potential similar anatomy within a patient, the first sensitivity analysis determined diagnostic accuracy of ultrasound for only the first catheter placement. The second sensitivity analysis was performed to determine the diagnostic accuracy of ultrasound when it was applied to all cases intended to be tested (*i.e.*, infeasible ultrasound examinations were taken into account). Results for infeasible ultrasound examinations were imputed.

Statistical Analysis

A sample size of 730 central venous catheterizations was calculated, but to account for data loss, we aimed to include 750.[28,29] Sample size calculation was based on an estimated incidence of malposition of 0.07 and a sensitivity of 0.93 with a margin of error of 0.07.[14] Categorical variables were expressed as numbers and percentages. Data were expressed as mean (± SD) or as median (± interquartile range) when appropriate. To identify distribution, histograms and Q-Q plots were evaluated. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under the curve were estimated separately with their 95% exact CI. Cohen's κ test was used to evaluate the agreement between ultrasound and chest x-ray film concerning pneumothorax. All analyses were performed in SPSS Statistics for Windows, version 22.0 (IBM Corp., USA). To determine what patient characteristics affected ultrasound feasibility, an independent two-tailed *t* test was used to compare means of continuous variables and chi-square test for categorical variables. A *P* value less than 0.05 was considered statistically significant. For the second *post hoc* sensitivity analysis, infeasible ultrasound examinations were regarded as missing data, and a fully conditional specification method (SPSS 22) was used for multiple imputation. Missing data were assumed to be missing at random, and 10 imputations were performed. Rubin's rules were used for pooling of data. Pooled sensitivity and specificity were estimated separately with their 95% CI.[30]

Results

Between April 2016 and December 2017, 758 central venous catheters in 727 patients were included. One patient signed the opt-out card and was excluded from the study (appendix 1). Baseline characteristics, central venous catheter insertion site, reason for admission, setting, and use of ultrasound guidance are described in table 1.

The incidence of catheter malposition was 3.3% (N = 25). Malposition was detected by chest x-ray film in the brachiocephalic vein (n = 7), subclavian vein (n = 6), internal jugular vein (n = 2), azygos vein (n = 3), left superior intercostal vein (n = 3), deep intraatrial/ventricular position (n = 3), and curling of the catheter (n = 1). A schematic overview of the central venous system, and detected tip locations are displayed in figure 2. Appendix 3 shows an example of a malpositioned catheter.

In 70 cases, cardiac ultrasound was infeasible, and they were excluded from the malposition accuracy analysis. Consequently, two cases of malposition were not included in the analysis and were only detected by chest x-ray film. Ultrasound correctly detected 16 out of 23 cases of malposition. There were seven false-negative cases, of which chest x-ray film showed catheter malposition in the brachiocephalic vein (n = 5), internal jugular vein (n = 1), and azygos vein (n = 1). In all those cases, ultrasound did not reveal any abnormalities during the vascular examination, and a laminar flow of microbubbles was seen within 2 s after injection during the cardiac examination. There were five false-positive cases. In three cases, microbubbles were not visible after injection of the saline flush, and in two cases, a laminar flow of microbubbles was seen after the 2-s mark, but chest x-ray film showed a correct position of the central venous catheter in the superior vena cava. Table 2 shows a contingency table of ultrasound and chest x-ray film results. Sensitivity and specificity of ultrasound to detect catheter malposition

Table 1. Patient Characteristics

Patient Characteristic	
Male sex	519 (68.5)
Age, yr	66 ± 12
Body mass index, kg/m^2	27.1 ± 4.8
Reason for ICU or PACU admission	
Elective surgery	449 (59.2)
Emergency surgery	19 (2.5)
Medical	270 (35.6)
Trauma	20 (2.6)
Setting of central venous catheterization	
Emergency department	16 (2.1)
ICU	250 (33.0)
Preoperative	492 (64.9)
Insertion site	
Right internal jugular vein	666 (87.9)
Left internal jugular vein	60 (7.9)
Right subclavian vein	16 (2.1)
Left subclavian vein	16 (2.1)
Ultrasound guided central venous catheterization,*	269 (57.4)

Values are presented as N (%) or mean ± SD. Patient characteristics including sex, body mass index, reason for intensive care unit (ICU) or postanesthesia care unit (PACU) admission, in which setting the central venous catheter was inserted, what central vein was cannulated (insertion site), and if ultrasound was used to guide cannulation.

*In 469 out of 758 central venous catheter insertions, data were available regarding ultrasound guidance during insertion. In 289 cases, it was unclear whether the landmark technique or ultrasound guidance was used during insertion.

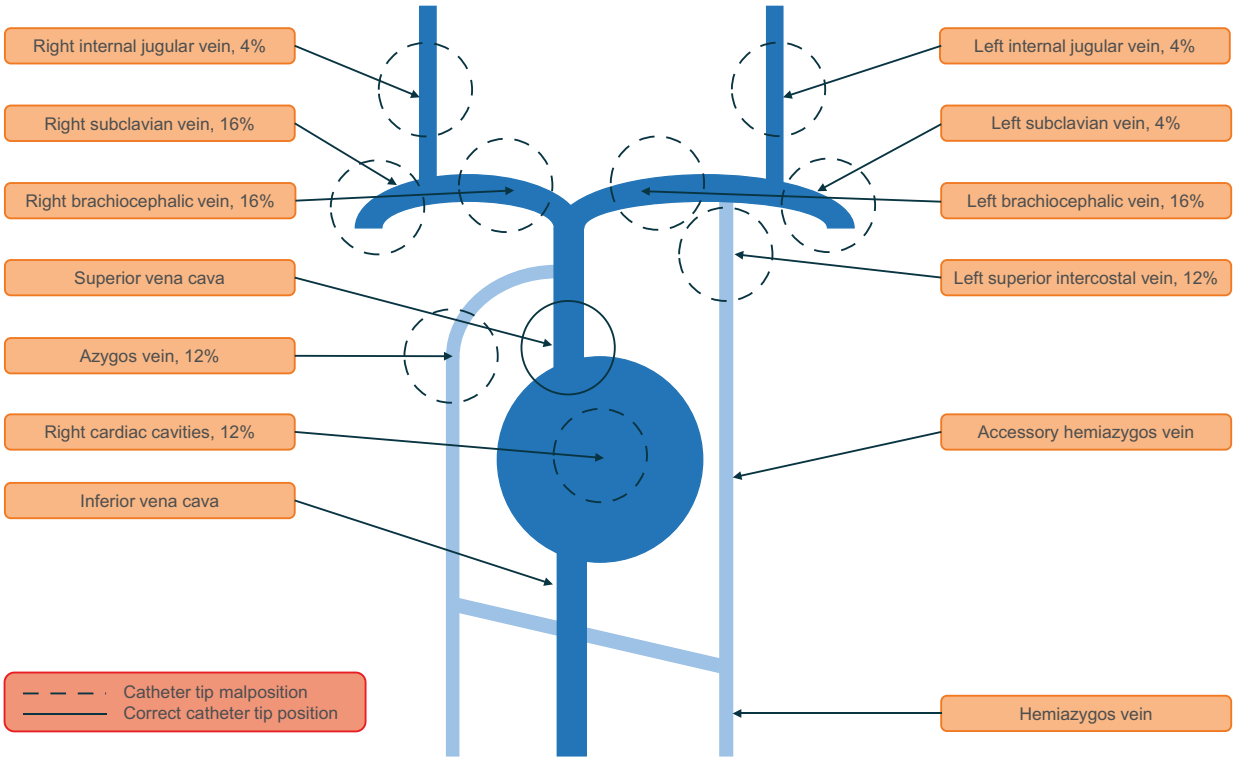

Fig. 2. Central venous catheter tip positions as determined by chest x-ray film. A schematic overview of the central venous system of the upper body and possible central venous catheter tip locations as determined by chest x-ray film. Dashed circles denote aberrant central venous catheter tip position, whereas the continuous circle denotes correct tip position in the superior vena cava or upper right atrium. A total of 25 malpositions occurred. All aberrant tip positions are shown with their respective percentage of total malposition incidence. One case (4%) of extravascular curling is not shown.

Table 2. Results of Chest X-ray Film Examination Compared to Results of Ultrasound Examination

		Ultrasound Examination					
		Superior Vena Cava or Upper Right Atrium	Internal Jugular Vein	Subclavian Vein	Deep Right Atrium or Right Ventricle	Positive Test Contrast Enhanced Ultrasound	Total
Chest X-ray Film Examination	Superior vena cava or upper right atrium	660	0	0	0	5†	665
	Brachiocephalic vein	5*	0	0	0	1	6
	Internal jugular vein	1*	1	0	0	0	2
	Subclavian vein	0	0	5	0	0	5
	Azygos vein	1*	0	0	0	2	3
	Left superior intercostal vein	0	0	0	0	3	3
	Deep right atrium or right ventricle	0	0	0	3	0	3
	Curling of catheter	0	0	0	0	1	1
	Total	667	1	5	3	12	688

Contingency table portraying central venous catheter tip position as detected on chest x-ray film compared to results of ultrasound examination. Ultrasound correctly detected 16 out of 23 cases of malposition.

*False-negative cases. †False-positive cases.

were 0.70 (95% CI, 0.49 to 0.86) and 0.99 (95% CI, 0.98 to 1.00), respectively. Diagnostic accuracy results are summarized in table 3.

In two cases, data were missing, and they were subsequently excluded from the pneumothorax accuracy analysis. Incidence of pneumothorax according to chest x-ray film and ultrasound was 0.7% (N = 5) and 1.5% (N = 11), respectively. In 748 out of 756 cases (98.9%), ultrasound and chest x-ray film showed agreement for pneumothorax. It was detected by both in four cases. In one case, radiographic examination showed a potential apical pneumothorax of the right lung, which was not detected by ultrasound and multiple subsequent chest x-ray films. In 22 out of 756 cases (3%), ultrasound examination showed absence of lung sliding and B-lines. In eight cases, a lung point could be identified. The lung pulse was identified in 11 out of the remaining 14 cases. As follows, pneumothorax was diagnosed in 11 cases (1.5%).

The incidence of clinically relevant malposition was 0.7% (N = 5). It was detected in the subclavian vein (n = 1), internal jugular vein (n = 1), azygos vein (n = 2), and deep intraatrial/ventricular position (n = 1). Clinically relevant malposition was detected by ultrasound in four out of five cases. One case, in which the catheter tip migrated into the internal jugular vein, was missed. Pneumothorax was clinically relevant in three cases; all required thoracic drainage. In two cases it occurred after resuscitation and in one case after esophageal surgery. All three cases were detected by both ultrasound and chest x-ray film.

Bilateral vascular examination of the internal jugular vein and subclavian vein was feasible in 100% (N = 758) of the cases, whereas examination of the right atrium and ventricle was feasible in 90.8% (N = 688). Lung ultrasound was performed in 99.7% of the cases (N = 756). In two cases, lung ultrasound was performed, but data were not recorded. There was a significant association between body mass index and ultrasound-feasibility (mean = 28.6, SD = 4.7 *vs.* mean = 26.9, SD = 4.8, $t(735) = 2.75$, $P = 0.006$). Other patient characteristics were not associated with ultrasound feasibility. Consult appendix 4 for a comprehensive overview.

Table 3. Diagnostic Accuracy of Ultrasound to Detect Central Venous Catheter Malposition and Pneumothorax

Malposition

	Chest X-ray Film +	Chest X-ray Film –	Chest X-ray Film Total
Ultrasound +	16	5	21
Ultrasound –	7	660	667
Ultrasound total	23	665	688
Sensitivity	0.70 (95% CI, 0.50–0.86)		
Specificity	0.99 (95% CI, 0.98–1.00)		
Positive predictive value	0.76 (95% CI, 0.56–0.91)		
Negative predictive value	0.99 (95% CI, 0.98–1.00)		
Positive likelihood ratio	92.5 (95% CI, 37.1–230.8)		
Negative likelihood ratio	0.31 (95% CI, 0.17–0.57)		
Area under the curve	0.85 (95% CI, 0.74–0.96)		

Pneumothorax

	Chest X-ray Film +	Chest X-ray Film –	Chest X-ray Film Total
Ultrasound +	4	7	11
Ultrasound –	1	744	745
Ultrasound total	5	751	756
Cohen's κ test	κ = 0.50 (95% CI, 0.19–0.80)		
Overall agreement	98.9%		

Clinically Relevant Malposition

	Chest X-ray Film +	Chest X-ray Film –	Chest X-ray Film Total
Ultrasound +	4	17	21
Ultrasound –	1	666	667
Ultrasound total	5	683	688
Area under the curve	0.89 (95% CI, 0.68–1.00)		

Two-by-two contingency tables of malposition, pneumothorax, and clinically relevant malposition are shown with their respective accuracy outcome parameters. A malposition is defined as positive outcome (+), whereas correct central venous catheter position is considered to be a negative outcome (–). Detection of pneumothorax on chest x-ray film or ultrasound is considered to be a positive test (+), whereas absence of pneumothorax is regarded a negative test (–). A malposition was considered to be clinically relevant if it required adjustment, replacement, or removal of the central venous catheter within 24 h after placement.

Post hoc sensitivity analysis, when only the first central venous catheterization was included, showed a sensitivity and specificity of ultrasound to detect malposition of 0.73 (95% CI, 0.52 to 0.88) and 0.99 (95% CI, 0.98 to 1.0), respectively. In total, 659 patients were included in the analysis. In 16 cases, ultrasound correctly detected malposition. There were six false-negative cases. In 632 cases, ultrasound correctly ruled out malposition, and there were five false-positive cases. *Post hoc* sensitivity analysis to determine the diagnostic accuracy for malposition in all cases intended to be tested showed a pooled sensitivity and specificity of 0.67 (95% CI, 0.51 to 0.86) and 0.99 (95% CI, 0.98 to 1.0), respectively. Consult appendix 5 for an overview of the analyses.

Discussion

The main findings of this prospective observational multicenter study, comparing ultrasound to chest x-ray film to detect catheter malposition, are a sensitivity of 0.70 (95% CI, 0.49 to 0.86) and specificity of 0.99 (95% CI, 0.98 to 1.00). Ultrasound and chest x-ray film showed agreement in 98.9% concerning pneumothorax. Malposition occurred in 3.3% (N = 25) of all central line placements, of which 0.7% (n = 5) were considered clinically relevant. One clinically relevant malposition out of 758 placements (0.0013%) was missed by ultrasound. Ultrasound and chest x-ray film detected all clinically relevant pneumothoraces. Cardiac ultrasound examination was feasible in 90.8% of the cases. *Post hoc* sensitivity analyses to determine the diagnostic accuracy for ultrasound, when only the first placement and infeasible ultrasound examinations were included, showed similar sensitivity and specificity for both circumstances.

Our study produced an excellent positive likelihood ratio and good negative likelihood ratio, in spite of the low incidence and moderate sensitivity. There were seven false-negative cases, of which the majority (n = 5) represented malposition in the brachiocephalic vein. These veins are situated under the sternum, meaning that they cannot be visualized during vascular examination. Interestingly, malposition in these veins apparently causes a laminar flow of microbubbles to appear in the right atrium within 2 s. One could argue that if the central venous catheter is situated in the brachiocephalic vein, a laminar flow of microbubbles appears within 2 s and no difficulties advancing the guidewire were encountered—meaning that there is most likely no distal obstruction in the superior vena cava and delivery of medication is not impaired—the brachiocephalic vein might be a safe position. Moreover, it has been suggested that administration of vasopressors through midline or peripheral catheters is safe as well.[31] Therefore, we might conclude that, if catheter tip position in the brachiocephalic vein is considered to be safe, the portrayed sensitivity is a low estimation.

The threshold of 2 s (within which agitated saline needs to be visualized in the right atrium) is a rather arbitrary value. If we look at this cutoff value with regard to the "Hagen–Poisseuille equation," we can derive that the flow velocity of the agitated saline through the central venous catheter is dependent on pressure difference—pressure generated by the syringe (operator dependent) minus central venous pressure—catheter length, catheter diameter, and fluid viscosity. In other words, shorter catheters with larger diameters can significantly increase flow velocity and cause a faster delivery of agitated saline to the right atrium. Moreover, the delivery of agitated saline is also dependent on central venous flow velocity; in case of high cardiac output, one can hypothesize that the agitated saline is more quickly delivered to the right atrium and the 2-s cutoff value could, in case of a malpositioned central venous catheter, produce a false-negative test. In light of these assumptions, accepting a duration less than 2 s can produce a higher sensitivity. In fact, another study, using a cutoff value of 500 ms, showed a sensitivity and specificity of 100% and 99%, respectively.[32] Nevertheless, visualization of agitated saline in the right atrium within 2 s ascertains intravenous central venous catheter position and an unimpaired fast delivery of medication into the right atrium.

Concerning pneumothorax diagnosis, the advantages of ultrasound in comparison to chest x-ray film have already been shown by numerous studies in different populations.[22,27,33–35] Our study shows that ultrasound identified all but one questionable case of pneumothorax detected by chest x-ray film. Nevertheless, ultrasound and chest x-ray film detected all clinically relevant pneumothoraces. Of note, these pneumothoraces were most likely not caused by central venous catheterization, but were already present beforehand. It is worth mentioning that lung ultrasound was not routinely performed before central venous catheterization; therefore, it is uncertain whether the pneumothoraces were caused by it. We advise performing lung ultrasound before cannulation as it increases the specificity of absence of lung sliding after the procedure to detect pneumothorax.

The incidence of catheter malposition in our study population was lower than described in previously published literature; 3.3% *versus* up to 6.8%.[16,36] Clinically relevant incidence was even lower (0.7%). A complication rate this low strongly raises the question of whether central venous catheter location needs to be verified in all cases or only in selected ones, *e.g.*, in case of postprocedural cardiac arrhythmias, inability to aspirate blood, difficulties advancing the guidewire, or multiple cannulation attempts. Such a strategy could lead to a significant cost reduction and can be justified based on our results: 1 clinically relevant complication out of 758 placements was missed. A possible explanation for the low incidence is that intraatrial position of the catheter tip was not considered to be malpositioned. This decision was based on three reasons. First, the risk of developing a serious complication secondary to catheter tip position in the right atrium is virtually zero.[37] Second, chest x-ray films

are not sufficiently accurate to identify intraatrial catheter tip position.[21,38,39] Third, catheter flow rate is better when the tip is placed in the upper right atrium; therefore, some guidelines even recommend intraatrial catheter tip position.[40] The low incidence may also be explained by the fact that a large number of the study participants received a central venous catheter preoperatively (table 1): it seems likely that postprocedural complications occur more often in an emergency setting (*i.e.*, at the emergency department or intensive care unit) than in an elective setting (*i.e.*, preoperatively at the operating theater).

Our study bears some limitations. The incidence of primary catheter malposition was lower than expected. Consequently, despite the large number of included patients, the sensitivity is easily influenced by one additional or fewer false-negative case. Another limitation of postprocedural ultrasound in comparison to chest x-ray film is that the microbubble test provides confirmation that the catheter tip resides in the superior vena cava or upper right atrium, but is not able to locate exact tip position. Therefore, certain cardiac anomalies may predispose to false-negative tests if they are asymptomatic. For example, a recent case report described a malpositioned central line, placed *via* the left internal jugular vein into a persistent left superior vena cava. Initially, this was missed by the microbubble test and only detected after chest x-ray film and a formal transthoracic echocardiogram.[41] A limitation of ultrasound to detect postprocedural pneumothorax is that mandating the presence of a lung point could cause complete pneumothoraces to be missed. However, complete pneumothoraces would lead to evident symptoms, whereas partial pneumothoraces are often occult and more likely to occur directly after central venous catheterization. Therefore, to detect iatrogenic pneumothorax, we believe ultrasound is ideally suited.[42] An inherent limitation of ultrasound is that it is operator but also patient-dependent. For example, this study showed that body mass index significantly differs between feasible and infeasible cardiac ultrasound examinations. In total, cardiac ultrasound examinations were infeasible in 9.2% of all included cases and, consequently, two cases of catheter malposition were not detected. Practitioners wanting to employ cardiac ultrasound should bear this in mind and make an individual assessment based on their skill and patient characteristics. In comparison, chest x-ray film is feasible in most cases and should, in case of infeasible ultrasound examination, be considered an alternative.

Strengths of our study are its large size, including over seven times more patients than previous studies on the same topic, multicenter design, and heterogeneous population.[10–13,16] This renders a higher validity and reliability. Another strength of our study is that multiple operators (N = 36) with different amounts of experience performed ultrasound examinations. Therefore, it may be concluded that the ultrasound protocol is easy to learn and perform.

Taken together, this study validates the use of ultrasound to detect central venous catheter malposition and pneumothorax and provides, in contrast to previously published literature, a higher validity and reliability. Due to the low incidence of malposition and pneumothorax, further research should be conducted to investigate the costs and health gains of routinely performing diagnostics to confirm proper catheter placement. Moreover, future research should aim to investigate factors contributing to catheter malposition or pneumothorax. Identifying those factors could lead to a situation in which only cases with a high probability of complications are followed up by ultrasound or, when in doubt, chest x-ray film.

Conclusions

The main findings of this large prospective observational multicenter study on the diagnostic accuracy of ultrasound to detect central venous catheter malposition are a moderate sensitivity and high specificity. There is a moderate agreement between chest x-ray film and ultrasound to detect pneumothorax. This study shows that the complication rate of central venous catheterization is low and that ultrasound is a highly feasible and accurate diagnostic modality to detect central venous catheter malposition and iatrogenic pneumothorax.

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Competing Interests

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Appendix 1.

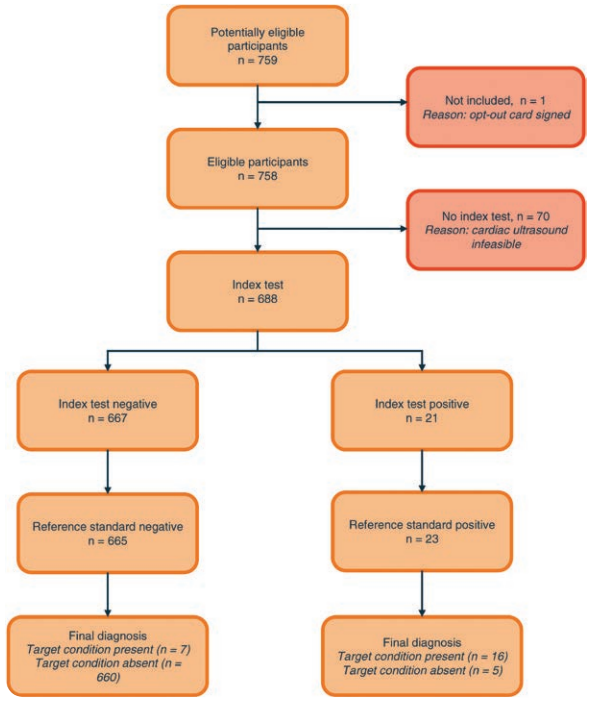

Fig. A1.1. Diagram depicting flow of participants through the study.

Table A1.1. Standards for Reporting Diagnostic Accuracy Studies (STARD) Guidelines; Flow Diagram and Checklist

Section and Topic	No.	Item	Reported on Page No.
Title or abstract			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or area under the curve)	1
Abstract			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
Introduction			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	1, 2
	4	Study objectives and hypotheses	2
Methods			
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	2
Participants	6	Eligibility criteria	2
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	2
	8	Where and when potentially eligible participants were identified (setting, location, and dates)	2
	9	Whether participants formed a consecutive, random, or convenience series	2
Test methods	10a	Index test, in sufficient detail to allow replication	2, 3, Appendix 2
	10b	Reference standard, in sufficient detail to allow replication	3
	11	Rationale for choosing the reference standard (if alternatives exist)	3
	12a	Definition of and rationale for test positivity cutoffs or result categories of the index test, distinguishing prespecified from exploratory	2, 3, Appendix 2
	12b	Definition of and rationale for test positivity cutoffs or result categories of the reference standard, distinguishing prespecified from exploratory	3
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	2
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	3
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	3, 4
	15	How indeterminate index test or reference standard results were handled	3, 4
	16	How missing data on the index test and reference standard were handled	4
	17	Any analyses of variability in diagnostic accuracy, distinguishing prespecified from exploratory	4
	18	Intended sample size and how it was determined	4
Results			
Participants	19	Flow of participants, using a diagram	Appendix 1
	20	Baseline demographic and clinical characteristics of participants	Table 1
	21a	Distribution of severity of disease in those with the target condition	Table 2, Table 3
	21b	Distribution of alternative diagnoses in those without the target condition	Not applicable
	22	Time interval and any clinical interventions between index test and reference standard	2
Test results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 2, Table 3
	24	Estimates of diagnostic accuracy and their precision (such as 95% CIs)	Table 3
	25	Any adverse events from performing the index test or the reference standard	Not applicable
Discussion			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalizability	8
	27	Implications for practice, including the intended use and clinical role of the index test	7, 8
Other information			
	28	Registration number and name of registry	2
	29	Where the full study protocol can be accessed	Appendix 2
	30	Sources of funding and other support; role of funders	8

Appendix 2. Detailed Description of Ultrasound Protocol

Ultrasound operators were trained according to a Dutch Intensive Care Ultrasound course. The course consists of lessons in ultrasound theory and performing cardiac, lung, and venous sonography. It is nationally recognized by the Dutch Society of Intensive Care Medicine.

The ultrasound protocol consisted of three parts:

1. Bilateral ultrasound evaluation of the internal jugular vein and subclavian vein

The first part was carried out using a high-frequency transducer. Initially, the linear probe was placed at the insertion site to ascertain intravenous position of the central venous catheter. Afterwards, the probe was placed transversally at the anterior triangle of the neck, and the internal jugular vein was examined upwards to the mandible and downwards to the junction with the subclavian vein. The subclavian vein was scanned longitudinally and transversally from the manubrium until the transition of the subclavian vein to the axillary vein. During this process, an aberrant course of the central venous catheter was evaluated. It was considered to be malpositioned if the tip did not progress into the superior vena cava and was detected in any other vein than that of the insertion site.

2. Ultrasound evaluation of the right atrium and ventricle

The second part was carried out using a low-frequency phased-array transducer. The cardiac probe was utilized to visualize, *via* the subcostal acoustic window, the right atrium and ventricle. If the heart was not visible, an apical four-chamber view was obtained. In case the heart still could not be visualized in this view, ultrasound examination was deemed infeasible. If visualization succeeded, the right cardiac cavities were scanned to detect the catheter tip. Visualization of the catheter tip was facilitated by contrast-enhanced ultrasound; first, a 10-ml syringe with 1 ml air and another 10-ml syringe with 9 ml saline solution were connected through a stopcock and mixed rigorously to create microbubbles. Second, the stopcock was connected to the distal port of the central venous catheter, and 5 ml of the solution was injected. If the tip was located in the superior vena cava, a laminar flow of microbubbles appeared in the right atrium within 2 s after injection. If the flow of microbubbles appeared after 2 s or was not seen at all, the central venous catheter was considered to be malpositioned.[10,14] Whenever turbulent flow microbubbles immediately appeared in the right atrium, the tip was located there. The central venous catheter was considered to be in an aberrant position if it was detected in the ventricle or deep in the right atrium close to the tricuspid valve. Intraatrial position of the catheter tip was in essence not considered to be a malposition due to the fact that chest x-ray film does not accurately identify it.[21] Therefore, only deep intraatrial positioning that was unlikely to be missed on chest x-ray film was considered to be misplaced.

3. Lung ultrasound evaluation for pneumothorax

The third part was carried out using a high-frequency transducer (linear probe). The evaluation for pneumothorax was performed according to the BLUE protocol. The upper and lower BLUE points were, ipsilateral to central venous catheterization, evaluated. The standardized BLUE points can be identified as follows: one places two hands (thumbs excluded) just below the clavicle; the fifth digit of the upper hand touches the lower border of the clavicle and the lower hand is just below the upper one, fingertips touching the midline. The upper BLUE point is at the middle of the upper hand (root of third and fourth digit), whereas the lower BLUE point is at the middle of the lower palm.[22] Both BLUE points were evaluated for lung sliding and B-lines, and, if both were absent, the lung point was searched for. Identification of the lung point proved pneumothorax, whereas presence of lung sliding ruled it out. If the lung point could not be identified, presence of the lung pulse was evaluated. Presence of lung pulse ruled out pneumothorax, whereas absence ruled it in.[23] During the ultrasound examination, harmonics were turned off (Phillips CX50) or the operator switched to lung ultrasound setting (SonoSite Edge II).

Appendix 3. Example of Malpositioned Central Venous Catheter in Right Subclavian Vein

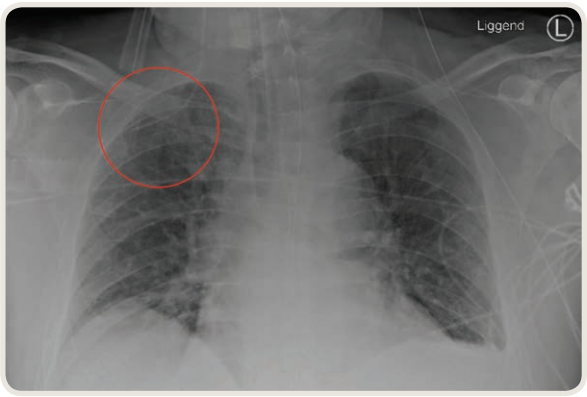

Fig. A3.1. A chest x-ray film of a patient with a central venous catheter malpositioned in the right subclavian vein. The *red circle* denotes the malposition.

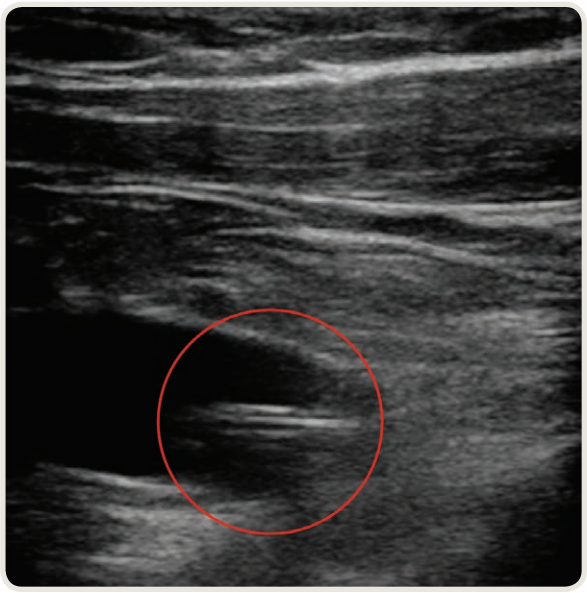

Fig. A3.2. Corresponding ultrasound image of the right subclavian vein in the patient offigure A3.1. The central venous catheter is denoted by the *red circle*.

Appendix 4. Comparison of Ultrasound Feasibility with Individual Patient Characteristics

Table A4.1. Mean of Patient Characteristics Compared to Feasibility of Ultrasound Examination

	Ultrasound Examination Feasible Mean ± SD	Ultrasound Examination Infeasible Mean ± SD	Mean Difference	*t* Value	*P* Value
Age, yr	65.9 ± 12.5	66.70 ± 11.6	0.8	0.501	0.616
Body mass index, kg/m^2	26.9 ± 4.8	28.6 ± 4.7	1.7	2.750	0.006*

An independent *t* test did not show a significant association between age and ultrasound feasibility, but did show a significant association between ultrasound feasibility and body mass index. $P < 0.05$ was considered statistically significant.

*$P < 0.05$.

Table A4.2. Categorical Patient Characteristics Compared to Feasibility of Ultrasound Examination

	Ultrasound Examination Feasible, N (%)	Ultrasound Examination Infeasible, N (%)	Total, N (%)	*P* Value
Sex				
Male	473 (68.8)	46 (65.7)	519 (68.5)	0.603
Female	215 (31.2)	24 (34.3)	239 (31.5)	
Reason for ICU or PACU admission				
Elective surgery	408 (59.3)	41 (58.6)	449 (59.2)	
Emergency surgery	16 (2.3)	3 (4.3)	19 (2.5)	N/A†
Medical	244 (35.5)	26 (37.1)	270 (35.6)	
Trauma	20 (2.9)	0 (0)	20 (2.6)	
Setting of central venous catheterization				
Emergency department	13 (1.9)	3 (4.3)	16 (2.1)	N/A†
Intensive care department	234 (34.0)	16 (22.9)	250 (33.0)	
Preoperative	441 (64.1)	51 (72.9)	492 (64.9)	
Insertion site				
Right internal jugular vein	606 (88.1)	60 (85.7)	666 (87.9)	N/A†
Left internal jugular vein	55 (8.0)	5 (7.1)	60 (7.9)	
Right subclavian vein	14 (87.5)	2 (2.9)	16 (2.1)	
Left subclavian vein	13 (1.9)	3 (4.3)	16 (2.1)	
Insertion technique*				
Landmark-guided	248 (57.7)	21 (53.8)	269 (57.4)	0.643
Ultrasound-guided	182 (42.3)	18 (46.2)	200 (42.6)	

Chi-square test did not show a significant association between categorical patient characteristics and feasibility of ultrasound examination. $P < 0.05$ was considered statistically significant.

*In 469 out of 758 central venous catheter insertions, data were available regarding ultrasound guidance during insertion. In 289 cases, it was unclear whether the landmark technique or ultrasound guidance was used during insertion. †Not applicable due to low sample sizes in infeasible group.

ICU, intensive care unit; N/A, not applicable; PACU, postanesthesia care unit.

Appendix 5. *Post Hoc* Sensitivity Analyses

Table A5.1. Sensitivity Analysis to Determine Diagnostic Accuracy for Malposition When Only the First Central Venous Catheter Placements Were Included

Malposition First Placement

	Chest X-ray Film +	Chest X-ray Film –	Chest X-ray Film Total
Ultrasound +	16	5	21
Ultrasound –	6	632	638
Ultrasound total	22	637	659
Sensitivity	0.73 (95% CI, 0.52–0.88)		
Specificity	0.99 (95% CI, 0.98–1.0)		

Contingency table showing results of diagnostic accuracy when only the first central venous catheter placement was considered. Consecutive central venous catheter placements in the same patient were excluded from the analysis. A malposition is defined as positive outcome (+), whereas correct central venous catheter position is considered to be a negative outcome (–).

Table A5.2. Sensitivity Analysis to Determine Diagnostic Accuracy for Malposition When All Cases Intended to Be Tested Were Included

Malposition Pooled Data

	Chest X-ray Film +	Chest X-ray Film –	Chest X-ray Film Total
Ultrasound +	16.8	9.2	26
Ultrasound –	8.2	723.8	732
Ultrasound total	25	733	758
Sensitivity	0.67 (95% CI, 0.51–0.86)		
Specificity	0.99 (95% CI, 0.98–1.0)		

Contingency table of pooled results and sensitivity analysis to determine sensitivity and specificity of bedside ultrasound in the total population; infeasible ultrasound examinations were taken into account as well. A fully conditional specification method (SPSS 22) was used for multiple imputation. Missing data were assumed to be missing at random, and a total of 10 imputations were performed. Rubin's rules were used for pooling of data. Variables used in the imputation phase were sex, age, weight, height, reason for intensive care or postanesthesia care unit admission, setting of central venous catheter insertion, insertion site, and results of ultrasound examination. A malposition is defined as positive outcome (+), whereas correct central venous catheter position is considered to be a negative outcome (–).