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Original Contribution

Impact of altitude-adjusted hypoxia on the Pulmonary Embolism Rule-out Criteria

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ABSTRACT

Background: The Pulmonary Embolism Rule-out Criteria (PERC) defines hypoxia as an oxygen saturation (O2 sat) < 95%. Utilizing this threshold for hypoxia at a significant elevation above sea level may lead to an inflated number of PERC-positive patients and unnecessary testing. The aim of this study was to determine the effect of an altitude-adjusted O2 sat on PERC's sensitivity and the potential impact on testing rates.

Methods: At the University of Utah Emergency Department (ED) (elevation: 4980 ft/1518 m), we prospectively enrolled a convenience sample of patients presenting with chest pain and/or shortness of breath. We calculated PERC utilizing triage vital signs and baseline clinical variables and noted the diagnosis of acute PE during the ED visit. We adjusted the PERC O2 sat threshold to <90% to account for altitude to determine the potential impact on outcomes and decision tool performance.

Results: Of 3024 study patients, 1.9% received the diagnosis of an acute PE in the ED, resulting in a sensitivity of 96.6% for the traditional PERC (95% CI: 88.1%–99.6%). Utilizing a definition of hypoxia of <90%, the sensitivity of the altitude-adjusted PERC rule was 94.8% (95% CI: 85.6%–98.9%). Assuming that imaging would not have been pursued for PERC-negative patients, the altitude-adjusted PERC rule would have reduced the overall rate of advanced imaging by 2.7% (95% CI: 1.8%–4.1%).

Conclusion: Adjusting the PERC O2 sat threshold for altitude may result in decreased rates of advanced imaging for PE without a substantial change in the sensitivity of the PERC rule.

1. Introduction

Since its derivation and validation, use of the Pulmonary Embolism Rule-out Criteria (PERC) decision tool has become the standard in the emergency department evaluation of pulmonary embolus (PE). When applied correctly, PERC negative-patients are assumed to have a low enough pre-test probability of PE that no PE testing is necessary. One component of PERC is hypoxia, defined as an oxygen saturation (O2 sat) of <95%. When applying PERC, a patient with an O2 sat <95% requires testing for PE, even if they do not meet any of the additional components of PERC. This O2 sat threshold applies to patients in all settings, regardless of elevation above sea level [1-3].

Under approximately 35,000 ft (10,668 m), the partial pressure of oxygen decreases with atmospheric pressure in a roughly linear relationship as elevation increases. During ascent, the lung's alveoli are exposed to a lower partial pressure of oxygen, and a predictable decrease in oxygen exchange and O2 sat inevitably follows [4]. Even individuals with healthy lungs will demonstrate an O2 sat less than normal at elevations above 4921 ft (1500 m) [5,6]. Utilizing 95% as the threshold for hypoxia in settings at significant elevation above sea level may lead to a higher number of PERC-positive patients and unnecessary testing. We evaluated the impact of an adjusted O2 sat on the sensitivity of PERC in an ED at a significant elevation above sea level and the potential effect on advanced imaging for PE.

2. Methods

2.1. Study design and setting

We performed a prospective, observational study of patients presenting with chest pain and/or shortness of breath to the University ED between June 2010 and December 2015. The study site is an urban, academic ED with approximately 50,000 patient visits per year. The ED is the primary training site for an emergency medicine residency program and is staffed with medical students, resident physicians, advanced practice clinicians, fellows, and attending physicians who are board certified in emergency medicine. Located at an elevation of 4980 ft (1518 m), the University of Utah ED is one of the highest EDs within an academic center in the United States [7]. By comparison, the Denver Health Medical Center ED sits at an elevation of 5280 ft

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(1609 m) [8]. The University of Utah Institutional Review Board approved this study.

2.2. Selection of participants

Research associates staffed the ED 16 h per day, 7 days per week, and identified ED patients with a chief complaint of chest pain and/or shortness of breath. They administered a baseline survey early in the ED stay and confirmed with the patient the presence of chest pain or shortness of breath by asking the questions "Have you experienced chest pain in the past 24 h?" and "Have you experienced shortness of breath in the past 24 h?" Patients who did not answer "yes" to either of these questions were excluded from the study. Research associates collected additional clinical and historical data at the time of the baseline survey. They asked questions specifically related to the components of PERC: "Have you ever had a blood clot in your lungs or legs?," "Have you had surgery in the past 4 weeks?," "Have you been immobilized (bed rest due to trauma or illness) for >3 days in the past 4 weeks?," "Have you coughed up blood since the onset of your symptoms?," "Do you take hormones (birth control pills/hormone replacement)?" and "Do you have calf pain or swelling in one leg?".

Research associates noted patients who were potentially eligible for study participation, those who were screened, and reasons that patients were not screened or were not eligible for participation. Patients may have been potentially eligible but were not screened due to lack of availability owing to physician or nursing presence in the room or being away at testing. While research associates returned to the room later to attempt screening, patients who were repeatedly occupied with clinical staff or procedures did not undergo study screening. Once patients were screened, they were deemed ineligible for study participation if they failed to meet enrollment criteria or were unable to provide consent owing to an inability to speak English, altered mental status, or other limitations as determined by the research associate. In the case of multiple ED visits, we considered only the initial ED visit and consent as eligible for study inclusion.

Research associates noted triage vital signs, including room air O2 sat and heart rate. They also recorded patient age, gender, and additional demographic information. Research associates later reviewed the medical record for testing performed at the time of the ED stay, including computed tomography pulmonary angiography (CTPA) and ventilation-perfusion (VQ) scan, and recorded the results of this testing. The principal investigator [TM] reviewed all cases of PE diagnosed in the ED to confirm the presence of acute PE on ED imaging.

Research associates enrolled patients as a convenience sample based on the presence of the research associate in the ED and patient availability and willingness to participate. All data acquisition was performed independent of the treating clinician's evaluation. Clinicians were blinded both to the purpose of the study and to the patients' responses to questions. In most cases, clinicians were likely unaware that the patient had even been enrolled in the study. The ED did not have an altitude-adjusted protocol for PERC during the study period, and all testing decisions were at the discretion of the treating physician.

2.3. Methods and measurements

We classified patients as PERC-positive or PERC-negative based on triage vital signs and on their response to the questions administered at the time of ED presentation. Those who had an O2 sat of 95% or greater and age < 50 were classified as "PERC-negative." Those who met any of these criteria or who answered "yes" to any of the relevant questions were classified as "PERC-positive."

We applied the PERC decision tool utilizing triage vital signs and baseline clinical variables and noted the diagnosis of acute PE during the ED visit. We calculated the sensitivity and specificity of the traditional PERC using the outcome of acute PE diagnosed during the ED stay. We then adjusted the PERC O2 sat threshold to <90% to account for altitude and applied this altitude-adjusted PERC rule to calculate the sensitivity and the potential impact on the overall rate of CTPA/VQ scan. We employed an O2 sat threshold of 90% given the precedent of a previous PERC validation study from Denver which utilized this threshold [8]. Published tables for room air oxygen values additionally demonstrate the expected change in O2 sat between sea level and 1500 ft elevation (4921) and serve as additional justification of an adjusted PERC O2 sat threshold of 90% [9].

We calculated a Wells' score for all patients who were PERC negative to assure that we had not inappropriately applied PERC. PERC was designed to be applied when "clinicians believed that that patients were at low enough risk to justify exclusion of pulmonary embolism on the basis of a negative D-dimer," or, by definition, patients who are low-risk by Wells' Criteria [1]. We utilized a dichotomous Wells' score (<4.5 = low risk) and excluded patients from the PERC-negative group if they had a Wells' score of 4.5 or greater. While uncommon, it is possible for a patient to be both PERC-negative and to have a Wells' score of 4.5 or greater given that Wells' Criteria include two objective factors which are not part of PERC: immobilization of at least three days in the previous four weeks (1.5 points) and malignancy with treatment within six months (one point). Additionally, Wells' criteria assign three points if the clinician assumes that PE is the most likely diagnosis or is equally likely to other possible diagnoses (clinician gestalt). We first calculated Wells' score using objective data obtained at baseline. For patients who were PERC negative but who had a Wells' score of 1.5 or greater based on objective factors, we reviewed the medical record and assigned an additional 3 points in cases in which the clinician performed CTPA or VQ scan based on clinician gestalt [10]. We noted the documentation of physician gestalt leading to the performance of CTPA or VQ scan without d-dimer testing and classified these patients as having a Wells' score of 4.5 or greater. Using this methodology, we reclassified as "PERC-positive" five patients who would have been PERC-negative solely based on the objective components of PERC, one of whom had a Wells' score of 5.5 while the remainder had a Wells' score of 4.5.

With little precedent for a study evaluating an altitude-adjusted PERC rule, we sought to enroll a large number of patients within a reasonable time frame and targeted a total study enrollment of 3000 patients over 5 years. We continued enrollment six months beyond the five-year mark to reach our goal of 3000 study patients.

2.4. Outcomes

The primary outcome of interest was the sensitivity of the altitude-adjusted PERC rule for acute PE diagnosed in the ED. We noted all cases of acute PE diagnosed by CTPA or VQ scan. We first calculated the sensitivity of the traditional PERC rule for cases of PE in our population. We then applied the altitude-adjusted PERC rule by reclassifying as "PERC negative" all patients who had a documented room air oxygen saturation of ≥90% and who otherwise were PERC-negative by the traditional PERC rule.

2.5. Analysis

We analyzed data utilizing descriptive statistics, with data presented with percentages for categorical variables and means for continuous variables. We calculated sensitivity and specificity for the traditional and altitude-adjusted PERC rules and included 95% confidence intervals (95% CI) (Stata v. 12.0, StataCorp, College Station, TX).

3. Results

Over the 5.5-year study period, 3024 ED patients with chest pain and/or shortness of breath agreed to participate in the study [Fig. 1]. Average patient age was 51.7 years (95% CI: 51.1%–52.3%), 54.8% (1657/3024, 95% CI: 53%–56.5%) of patients were female, and 78.6%

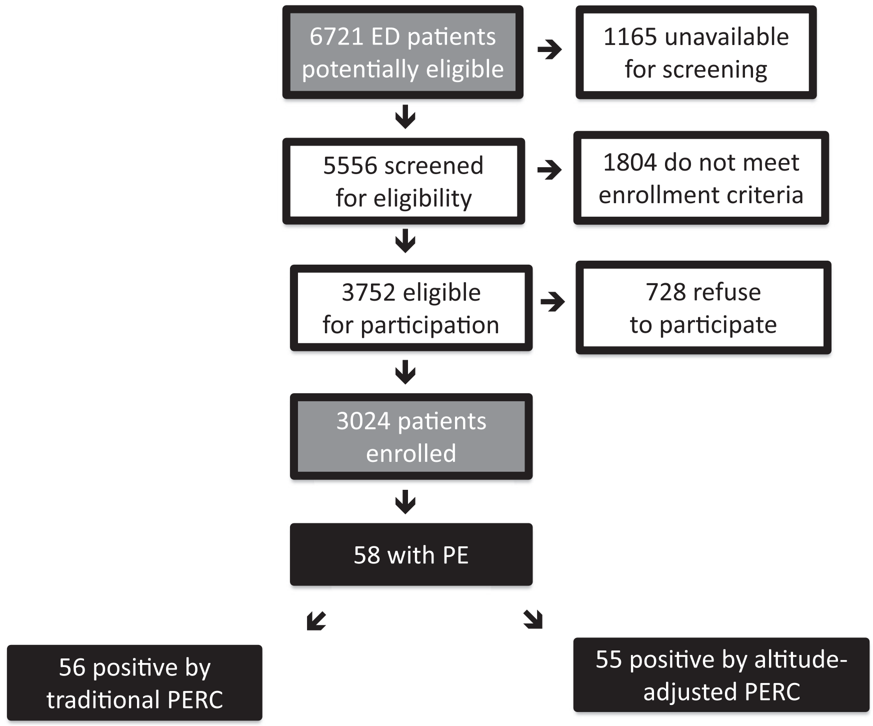

Fig. 1. Flow chart for screening, enrollment, and outcomes of study patients.

(2377/3024, 95% CI: 77.1%–80%) of patients self-identified their race/ethnicity as White non-Hispanic. Of the study population, 56.4% (1707/3024, 95% CI: 54.7%–58.2%) presented with chest pain and shortness of breath, 23.2% (701/3024, 95% CI: 21.7%–24.7%) presented with shortness of breath without chest pain, and 20.4% (616/3024, 95% CI: 19%–21.8%) with chest pain without shortness of breath.

Of the 3024 study patients, 33.1% (1000/3024, 95% CI: 31.4%–34.5%) had testing for PE: 48.2% (482/1000, 95% CI: 45.1%–51.3%) of these patients had a d-dimer and 51.8% (518/1000, 95% CI: 48.7%–54.9%) had a CTPA or VQ scan without a d-dimer. Among those with a d-dimer, 46.1% (222/482, 95% CI: 41.7%–50.5%) went on to have a CTPA or VQ scan due to a positive d-dimer.

Of all study patients, 1.9% (58/3024, 95% CI: 1.5%–2.5%) received the diagnosis of an acute PE in the ED. Utilizing the traditional PERC rule with an O2 sat cutoff of 95%, we classified 82.5% of patients (2494/3024, 95% CI: 81.1%–83.8%) as PERC positive. Of the 58 patients who had an acute PE, 56 were PERC positive, resulting in a sensitivity of 96.6% (95% CI: 88.1%–99.6%) and specificity of 17.8% (95% CI: 16.5%–19.2%) for the traditional PERC rule.

We applied the altitude-adjusted PERC rule to our population by reviewing all patients who were classified as PERC-positive solely due to a triage SpO2 of <95%. We reclassified these patients as PERC-negative if their triage SpO2 was ≥90%. This altitude-adjusted PERC resulted in 4.3% of PERC-positive patients (107/2494, 95% CI: 3.6%–5.2%) being reclassified as PERC negative. This also led to one patient with an acute PE being reclassified as PERC negative, so that 55 of the 58 patients with an acute PE were positive by the altitude-adjusted PERC. The sensitivity of the altitude-adjusted PERC was 94.8% (95% CI: 85.6%–98.9%) with a specificity of 21.4% (95% CI: 19.9%–22.9%) [Fig. 2].

Of those patients reclassified as PERC negative by the altitude-adjusted PERC, 18.7% (20/107, 95% CI: 12.4%–27.1%) had advanced imaging for PE (CTPA or VQ scan). Assuming that none of these patients would have undergone advanced imaging when classified as PERC negative, this would have reduced the number of CTPA/VQ scans in the study by 2.7% (20/740, 95% CI: 1.8%–4.1%).

Given the reduced sensitivity of the altitude-adjusted PERC in our population, it is worth reviewing the specifics of the one patient who was reclassified as PERC negative. The patient's room air O2 sat was 93%, which led to a PERC-positive classification by traditional PERC but PERC-negative by altitude adjusted PERC. This individual had recently completed an 8-hour car ride and reported sudden-onset chest pain and shortness of breath. The patient also had an electrocardiogram demonstrating a new incomplete right bundle branch block. While these additional factors are not components of PERC, and the patient was classified as low-risk by Wells' Criteria, some may argue that clinical gestalt alone would necessitate PE testing in this patient and that application of PERC would be inappropriate.

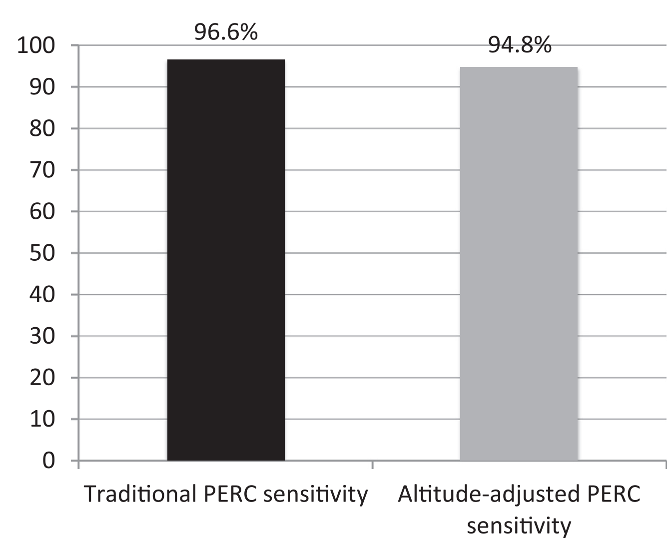

Fig. 2. Sensitivity of the traditional PERC vs. altitude-adjusted PERC for PE in the study population.

4. Limitations

This study contains several limitations. We performed the study at a single site, which affects the generalizability to other institutions. The study hypothesis necessitated the performance of the research in an ED at elevation, which also limited the potential for a study across multiple institutions. The nature of a study at elevation, of course, also limits the relevance of the study to other EDs which are at similar elevation. Given the paucity of academic EDs at significant elevation, future studies may wish to include multiple community EDs in mountainous regions at similar elevations.

An additional limitation relates to the enrollment criteria. We enrolled patients in the study based on their chief complaint and not the treating clinician's suspicion for PE. We included patients who reported either chest pain or shortness of breath. Certainly the treating clinician would not suspect PE in all patients with these complaints, which accounts for the low rate of PE in the study. Previous studies of PERC have utilized a clinician's suspicion for PE, with the decision to test for PE as a surrogate for this suspicion [1,2]. Given that these studies aimed to reduce these testing rates, and given the subsequent impact of these studies on the decision to test for PE, utilizing the clinician's suspicion to test for PE as a requirement for study inclusion presents certain logistical challenges. Thus, our study may be open to criticism for including all patients with symptoms potentially related to PE, rather than limiting it just to those in whom a clinician suspected PE. However, we felt this broad inclusion criteria would allow us to most effectively capture all patients in whom PE testing may be performed while allowing for a denominator to compare these testing rates.

We categorized patients as PERC-positive and PERC-negative based on triage vital signs and on standardized questions administered by research associates and not by clinicians. Clinicians may have asked the clinical questions of PERC differently from the standard questions we employed, and may have additionally relied on physical exam findings when assessing a patient for signs such as unilateral leg swelling. Additionally, while we relied triage O2 sat, similar to the methodology employed in previous studies of PERC, vital sign changes over the course of the ED stay may prompt clinicians to reclassify a patient as PERC-positive whom they initially categorized as PERC negative. We suspect these discrepancies were the exception, but these factors may have led to differences in categorization between our research findings and actual clinical practice.

We reclassified five patients as PERC-positive from PERC-negative based on a Wells' score of 4.5 or greater. To do so, we relied on a review of the medical record to document clinician gestalt and to assign the Wells' score points for this, given that we did not prospectively collect gestalt data from the treating clinician. This presents a significant limitation in its reliance on the medical record. However, none of these reclassified patients had a pulmonary embolism, and the small number of patients who were reclassified would seem to have little impact on the sensitivity and specificity of the altitude-adjusted PERC.

Finally, while we collected data prospectively on patients presenting to the ED, we relied on review of the medical record for certain components of the study, including outcomes related to PE testing in the ED. The retrospective nature of certain components of the study may present a potential limitation. Future studies which employ rigorous prospective methodology will provide additional data to validate our findings.

5. Discussion

In this study, we found that adjusting the O2 sat to <90%, rather than <95%, led to a comparable sensitivity between this altitude-adjusted PERC rule and the traditional PERC rule. Application of an altitude-adjusted rule may have reduced the rate of advanced imaging in our study population. While not a component of this study, the application of an altitude-adjusted PERC, with its reduced testing rates, would also presumably reduce ED length of stay and cost. Use of such a rule may be advantageous for EDs at comparable elevations.

One previous study adjusted for elevation when using the PERC decision tool. A 2008 study in Denver validated the PERC rule and, in this study, the authors defined hypoxia as an O2 sat < 90%. They explained their use of an O2 sat <90% by stating, "Although the original PERC rule used an oxygen saturation of 95%, in our study, an oxygen saturation of 90% was used to adjust for the altitude (5,280 ft above sea level) in which patients were enrolled" [8].

This adjusted O2 sat has its basis in previous research demonstrating this expected reduction in O2 sat between sea level and an elevation of approximately 4900 ft (1500 m) [9,11]. The authors of the Denver paper did not design the study to compare the altitude-adjusted PERC rule to the traditional PERC but, instead, simply used the 90% threshold rather than 95%. They reported 100% sensitivity for PERC in their population, but the study was limited by the small number of PEs (16) and low enrollment (138 patients) [8]. Given that the University of Utah and Denver Health Medical Center are at similar elevations, we considered this study as providing precedent for the use of an altitude-adjusted O2 sat and utilized this threshold in our attempt to validate the altitude-adjusted PERC rule.

As noted in the study results, there was one patient who was PERC positive by the traditional PERC but PERC negative by the altitude-adjusted PERC. We applied Wells' Criteria prior to the application of PERC, given that PERC was designed only to apply to patients who are low-risk enough that a clinician would feel comfortable sending a d-dimer to rule out pulmonary embolism [1,2]. By definition, these patients are those who are low-risk by the dichotomous Wells' Criteria [10,12-15]. While this patient was classified as low-risk by Wells' Criteria, and thus would seem appropriate for application of PERC, it could be argued that the multiple factors in the patient's presentation would lead a clinician to test for PE regardless of PERC classification. Given our study methodology, however, we employed a strict application of Well's Criteria and PERC. Had we performed a much larger study across multiple institutions, the impact of unique cases such as this would have likely been attenuated. Regardless, given the confidence interval ranges on the two rules' sensitivities, we note that the rules did not differ significantly in their ability to detect PE.

The primary benefit of applying the altitude-adjusted PERC relates primarily to a reduction in CTPA and VQ scans in patients with suspected PE. Both imaging studies lead to significant radiation exposure in patients, while CTPA carries the additional risks of contrast allergy and contrast-induced nephropathy [16,17]. Additional considerations relate to the cost associated with the procedure, prolonged ED length of stay, and the potential for false-positive results and inappropriate anticoagulation. Given that some patients who are PERC negative continue to undergo PE testing in real-world practice, it may be inappropriate to assume that all patients reclassified as negative by altitude-adjusted PERC would not have had CTPA or VQ testing [18]. However, this reclassification would have at least created the potential for the elimination of 20 CTPAs and VQ scans in our study population.

6. Conclusion

In a non-selected group of patients with a chief complaint of chest pain and/or shortness of breath, adjusting the PERC for altitude resulted in similar sensitivity and increased specificity when compared to the traditional PERC rule. An altitude-adjusted PERC rule may lead to decreased testing among ED patients suspected of PE. EDs at a similar elevation may wish to implement a strategy which accounts for altitude when applying the PERC O2 sat threshold.

Meetings

Presented at the Annual Meeting of the Society for Academic Emergency Medicine, Orlando, FL, May 17–19, 2017.

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Conflicts of interest

Troy Madsen, MD, currently receives funding from Roche Diagnostics for an emergency department study of high-sensitivity troponin T. None of the other authors has any conflicts of interest to report.

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