

reinfarction, there was a statistically significant benefit demonstrated for enoxaparin vs unfractionated heparin in the full-dose tenecteplase group (4.4% vs 15.9%, log-rank  $P=.003$ ) that was attenuated in the combination therapy group (5.5% vs 6.5%,  $P=.67$ ).<sup>3</sup> We believe that the superior efficacy of enoxaparin vs unfractionated heparin, as well as the unequal and nonrandom use of these agents in these 3 trials, confound the results of the meta-analysis.

Individual trial data may be more illuminating. Compared with conventional treatment of STEMI with full-dose fibrinolytic drugs and unfractionated heparin, the use of half-dose fibrinolytic drugs, adjunct abciximab, and unfractionated heparin confers efficacy benefit, while the use of full-dose fibrinolytic drugs and enoxaparin confers both efficacy and safety benefits.<sup>2</sup> However, when adjunctive abciximab is used in combination with enoxaparin, the benefits are not additive.<sup>3</sup> We believe that the choice of using adjunctive abciximab or enoxaparin in individual patients with different levels of risk remains undetermined but will ultimately be superseded by cost considerations.

Daniel Shao-Weng Tan, BSc, MBBS  
David Kheng-Leng Sim, MBBS, MRCP  
Department of Cardiology  
National Heart Centre  
Singapore

Edwin Shih-Yen Chan, BSc, BVMS, PhD  
Clinical Trials and Epidemiology Research Unit  
Singapore

Ru-San Tan, MBBS, MRCP  
Tan\_Ru\_San@nhc.com.sg  
Department of Cardiology  
National Heart Centre  
Singapore

**Financial Disclosures:** None reported.

1. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA*. 2005;293:1759-1765.
2. Assessment of the Safety and Efficacy of a New Fibrinolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605-613.
3. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation*. 2002;105:1642-1649.
4. Topol EJ. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. *Lancet*. 2001;357:1905-1914.

**In Reply:** We agree with Dr Tan and colleagues that the use of low-molecular-weight heparin has the potential to be a confounding factor in our meta-analysis, particularly in the results of trials with thrombolysis, whereas unfractionated heparin was used in all primary angioplasty trials. However, we believe that actual confounding is unlikely. The support for this hypothesis comes from a post hoc observation of a small trial (ENTIRE-TIMI 23),<sup>1</sup> whereas the largest trial included in the meta-analysis (GUSTO V)<sup>2</sup> showed that in patients treated with unfractionated heparin, combination therapy does not give any additional benefit in terms of mor-

tality. Furthermore, no data on the comparison between thrombolysis plus abciximab in patients receiving unfractionated heparin vs low-molecular-weight heparin have been reported in the ASSENT-3 trial.<sup>3</sup> Finally, in our study we analyzed death and reinfarction as separate end points, whereas the data cited from the ENTIRE-TIMI 23 trial<sup>1</sup> are based on a combined end point of death, reinfarction, or both.

Giuseppe De Luca, MD, PhD  
Harry Suryapranata, MD, PhD  
h.suryapranata@diagram-zwolle.nl  
Department of Cardiology  
Isala Klinieken  
Hospital De Weezenlanden  
Zwolle, the Netherlands

**Financial Disclosures:** None reported.

1. Antman EM, Louwerenburg HW, Baars HF, et al. Enoxaparin as adjunctive antithrombin therapy for ST-elevation myocardial infarction: results of the ENTIRE-Thrombolysis in Myocardial Infarction (TIMI) 23 Trial. *Circulation*. 2002;105:1642-1649.
2. Lincoff AM, Califf RM, Van de Werf F, et al; Global Use of Strategies To Open Coronary Arteries (GUSTO) Investigators. Mortality at 1 year with combination platelet glycoprotein IIb/IIIa inhibition and reduced-dose fibrinolytic therapy vs conventional fibrinolytic therapy for acute myocardial infarction: GUSTO V randomized trial. *JAMA*. 2002;288:2130-2135.
3. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605-613.

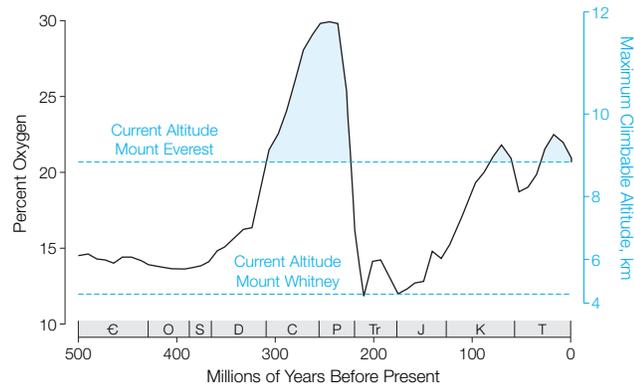
## RESEARCH LETTER

### Climbing a Triassic Mount Everest: Into Thinner Air

**To the Editor:** At a height of 8850 m, Mount Everest has long been a magnet to Himalayan mountaineers, and its summit has been reached 2251 times through 2004.<sup>1</sup> Because 130 of those ascents were made without supplemental oxygen,<sup>1</sup> contemporary humans are undoubtedly capable of climbing higher than 8850 m without supplemental oxygen, if a higher summit were available. The upper limit for mountaineers has probably varied over time because atmospheric oxygen concentrations (currently 20.9%) have changed drastically over the past 570 million years.<sup>2</sup> We simulated how these oxygen shifts would have affected the maximum altitude reachable by hypothetical "paleo-mountaineers."

**Methods.** To estimate past maximum potential altitudes, we first determined the maximum altitude reachable in today's atmosphere. West<sup>3</sup> calculated that Mount Everest's summit should be close to the limit of human climbing without supplementary oxygen. Consistent with this, we used 9.0 km as a conservative limit. This is feasible because it approximates the "physiological" altitude reached by Sherpa Ang Rita when he summited Mount Everest without using supplemental oxygen on December 22, 1987. The estimated summit partial pressure of inspired oxygen (PIO<sub>2</sub>) on that winter day was physiologically equivalent to 9.0 km during the customary spring climbing season when PIO<sub>2</sub> is

**Figure.** Change in Percent Oxygen and in the Maximum Climbable Altitude Reachable by "Paleo-Mountaineers" Over Geological Time



Geological periods: C, Cambrian; O, Ordovician; S, Silurian; D, Devonian; C, Carboniferous; P, Permian; Tr, Triassic; J, Jurassic; K, Cretaceous; T, Tertiary. Blue shading indicates times with sufficient oxygen for ascents of a peak the height of Mount Everest to be summited without using supplemental oxygen. The intervals on the right vertical axis (maximum climbable altitude) are not equal because the relationship between percent oxygen and maximum climbable altitude is nonlinear.

higher.<sup>4</sup> Although Bailey<sup>5</sup> recently proposed a much higher limit (9972.7 m), his estimate was incorrectly based on a linear (rather than curvilinear) regression model and is unrealistic given slow climbing rates at extreme altitude.

We used a model atmosphere equation for barometric pressure vs altitude<sup>4</sup> to compute present-day  $PI_{O_2}$  at 9.0 km, and then used this amount as the minimum level tolerable by both present-day and hypothetical paleo-mountaineers. We next expanded an equation<sup>4</sup> for  $PI_{O_2}$  as a function of percent oxygen and of the summed partial pressures of oxygen and of nitrogen (including minor gasses, all assumed constant over time<sup>2</sup>). We then corrected the  $PI_{O_2}$  for percent oxygen, and solved for altitude.<sup>6</sup> This estimated the maximum altitude reachable under a given percent oxygen. We assumed that maximum altitude is determined only by  $PI_{O_2}$  and ignored minor effects of concurrent climate change<sup>6</sup> and of uncertainty in percent oxygen.<sup>2</sup>

**Results.** During the mid-Permian era, oxygen was relatively abundant<sup>2</sup> and  $PI_{O_2}$  is thought to have reached approximately 30 percent (FIGURE). By the early Triassic era, however,  $PI_{O_2}$  fell to approximately 12%.<sup>2</sup> Shifts in oxygen concentration would have dramatically altered the maximum climbable altitude over time (Figure). During the Permian high oxygen concentration, hypothetical paleo-mountaineers would have been aerobically capable of reaching nearly 12 km, about one third above the current summit of Mount Everest. During the Triassic low oxygen concentration, climbers would have been stopped at 4.5 km, below the summit of Mount Whitney (4.4 km). A prehistoric Ang Rita would have been incapable of reaching a Triassic base camp on Mount Everest (5.3 km).

**Comment.** On a geological scale, neither Mount Everest nor humans existed until recently. Nevertheless, our findings add a novel, deep-time perspective on high-altitude

physiology and medicine. Our analysis suggests that peaks as high as Mount Everest would have been physiologically reachable by humans during less than one third of the past 570 million years. Thus, it is only through a fortunate accident of geology and biology that humans evolved and have always lived during a time in which oxygen levels have been sufficiently high to allow (a few of) us to reach the highest summit on Earth.

Raymond B. Huey, PhD  
hueyrb@u.washington.edu  
Peter D. Ward, PhD  
Department of Biology  
University of Washington  
Seattle

**Financial Disclosures:** None reported.

**Author Contributions:** Dr Huey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.  
**Funding/Support:** This research was supported by the National Science Foundation (Dr Huey) and the NASA Astrobiology Institute (University of Washington Node, Dr Ward, principal investigator).

**Role of the Sponsors:** The funding agencies had no role in the design and conduct of this study, in the collection, analysis, and interpretation of the data, or in the preparation, review, and approval of the manuscript.

1. Salisbury R. *The Himalayan Database: The Expedition Archives of Elizabeth Hawley*. Golden, Colo: The American Alpine Club; 2004.
2. Berner RA. Examination of hypotheses for the Permo-Triassic boundary extinction by carbon cycle modeling. *Proc Natl Acad Sci U S A*. 2002;99:4172-4177.
3. West JB. Climbing Mt. Everest without oxygen: an analysis of maximal exercise during extreme hypoxia. *Respir Physiol*. 1983;52:265-279.
4. Ward MP, Milledge JS, West JB. *High Altitude Medicine and Physiology*. London, England: Arnold; 2000.
5. Bailey DM. The last "oxygenless" ascent of Mt Everest. *Br J Sports Med*. 2001;35:294-296.
6. Huey RB, Ward PD. Hypoxia, global warming, and terrestrial Late Permian extinctions. *Science*. 2005;308:398-401.

## CORRECTION

**Incorrect Labels in FIGURE:** In the 3-page timeline foldout entitled "Albert Lasker Medical Research Awards, 60 Years of Basic Discoveries and Clinical Advances" published in the September 21, 2005, issue of JAMA (2005;294:1426 A-F), the labels indicating RNA bases and amino acids were incorrect. The labels for the RNA bases should have read U instead of T, and labels for amino acids should have read (from 5' to 3') Ala, Val, Phe.

The detail is reproduced below at full size and can be cut out and affixed to the original poster.

