MINERVA ANESTESIOL 2009;75293-9

REVIEW ARTICLE

Targeting transpulmonary pressure to prevent ventilator induced lung injury

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ABSTRACT

Acute respiratory distress syndrome (ARDS) and ventilator induced lung injury (VILI) continue to challenge clinicians who care for the critically ill. Current research in ARDS has focused on ventilator strategies to improve the outcome for these patients. In this review, we emphasize the limitations of managing ventilators based on airway pressures alone. Specifically, basic pulmonary mechanics — including chest wall compliance and transpulmonary pressure — are reviewed. This review suggests that perturbations in chest wall compliance and transpulmonary pressure may explain the lack of efficacy observed in recent clinical trials of ventilator management. We present a method for estimating pleural and transpulmonary pressures from esophageal manometry. Quantifying these variables and individualizing ventilator management based on individual patient physiology may be useful to intensive care clinicians who treat patients with ARDS.

Key words: Lung injury - Respiratory distress syndrome, adult - Ventilator-induced lung injury.

It is well-recognized that positive pressure mechanical ventilation can exacerbate acute lung injury (ALI). This injury, termed ventilator-induced lung injury (VILI), results from several mechanisms including the cyclic over-distension and collapse of alveoli with tidal breathing on the ventilator. Overdistension injury, or "volutrauma", is the result of excessive stress at end-inflation, presumably due to high transpulmonary pressure.[1, 2] "Atelectrauma", on the other hand, is induced by the repetitive opening and closing of alveolar units at end-exhalation,[3] presumably due to levels of positive end-expiratory pressure (PEEP) that are inadequate to prevent derecruitment. Finally, mechanical injury leads to release of biological mediators which may lead to further lung injury as well as distal organ damage. This has been referred to as "biotrauma".[1-3]

Lung protective ventilation

Extensive research has been undertaken to understand and ultimately minimize these ventilator-associated mechanisms of lung injury. Most notably, the National Institutes of Health acute respiratory distress syndrome (ARDS) network demonstrated a 22% reduction in mortality when patients were ventilated with tidal volumes (V_T), 6 mL/kg of ideal body weight *vs.* 12 mL/kg, and plateau pressures (P_{plat}) were maintained at less than 30 cmH_2O.[4] This trial clearly defined a "lung protective" strategy for minimizing the effects of "volutrauma".

A subsequent trial by the ARDS network investigators (ALVEOLI) attempted to address the mechanism of "atelectrauma" by evaluating the effects of higher *vs.* lower levels of PEEP.[5] Significant preclinical data suggests that minimiz-

ing derecruitment of alveoli at end-exhalation with higher levels of PEEP would mitigate this injury. In this study, patients diagnosed with ARDS/ALI and already receiving the low tidal volume strategy were randomized to either high or low PEEP set by two different sliding scales, based solely on the patient's oxygenation. The resulting average level of PEEP in the two groups was ~14 cmH_2O *vs.* ~8 cmH_2O in the high and low PEEP groups, respectively. The authors were unable to demonstrate improvement in the primary endpoint, intensive care unit (ICU) mortality, with a high strategy.[5]

Grasso *et al.* have postulated that the ALVEOLI trial did not capture beneficial effects of higher of PEEP because the study protocol failed to individualize PEEP to each patient's respiratory system.[6] Through measurements of gas exchange and respiratory mechanics in a small series of patients, they demonstrated applying higher PEEP using the ALVEOLI protocol resulted in a widely variable response. Specifically, only 9 out of 19 patients had a favorable response to higher PEEP as measured by alveolar recruitment (*via* pressure-volume curves plotted during low-flow tidal inflation), increased arterial oxygen partial pressure/fraction of inspired oxygen ratio and a reduction in static lung elastance.[6] Conversely, the remaining 10 patients, termed "non-recruiters", failed to show improvement in any of these measurements — some even demonstrating increased lung elastance when exposed to higher PEEP. The authors concluded that random application of elevated PEEP not only failed to induce recruitment in many patients, but could lead to over distension and thus risk negating the beneficial effects of the low-tidal volume strategy.[6]

Within the last year, two additional multicentered randomized control trials have been published comparing high *vs.* low PEEP in patients with ARDS. In the LOV trial, Meade *et al.* randomized 983 patients to either "conventional" levels of PEEP (mean 9.8 cmH_2O) or an "open lung" approach, whereby PEEP was increased but still based on a predetermined F_iO_2 scale (mean 14.6 cmH_2O).[7] The methods in this study were similar to ALVEOLI with the exception that recruitment maneuvers were permitted in the study group.[7] Plateau pressures were maintained at <30 cmH_2O and <40 cmH_2O in the control and study groups, respectively. There was no statistical difference in the primary end-point, all-cause hospital mortality.[7]

In the EXPRESS trial Mercat *et al.* randomized 767 patients with ARDS to either a moderate PEEP strategy of 5-9 cmH_2O or a high PEEP strategy, whereby PEEP was increased to reach a plateau pressure of 28 to 30 cmH_2O.[8] This protocol was unique in that it allowed for the titration of PEEP in the study group to a quantifiable variable of respiratory mechanics, rather than simply oxygenation. The protocol resulted in day one PEEP differences of 15.8 *vs.* 6.4 cmH_2O for the study and control groups, respectively.[8] The primary endpoint was mortality at 28 days and secondary end points were hospital mortality at 60 days, ventilator-free days, and organ failure-free days. The results showed no significant difference in either 28 day or hospital mortality.[8] However, the study group had a higher median number of ventilator-free days, 7 *vs.* 3 (P=0.04) and organ failure-free days, 6 *vs.* 2 (P=0.04).[8] Although the EXPRESS trial utilized physiologic variables of respiratory system mechanics and demonstrated improvement in some important secondary endpoints, the use of plateau pressures to titrate PEEP may still fail to account for other important variables of the respiratory system, for example, chest wall elastance.

Two earlier trials compared the effects of PEEP set at 2 cmH_2O above the lower inflection point on the pressure-volume curve of the respiratory system (P_{flex}) to lower levels of PEEP. These PEEP strategies, in the trials by Amato *et al.*[9] and Villar *et al.*,[10] are difficult to interpret as the control group in both studies received tidal volumes that would now be considered potentially injurious. Furthermore, the measurement of static and quasi-static pressure-volume loops and the determination of P_{flex} to set PEEP, has proven to be challenging.[11] Another limitation of P_{flex} is that substantial lung recruitment and derecruitment occurs as airway pressure and lung volume rise and fall in a range that is well above the lower inflection point of the pressure-volume curve.[12] This technique also fails to distinguish the effects of the chest wall on airway pressure and the shape of the pressure volume relationship.[13, 14]

Pleural and transpulmonary pressure

The lack of consensus on a method to determine the optimal PEEP has led some to conclude that setting and managing the "optimal PEEP" is the "holy grail" for clinicians who manage patients with ALI.[15] While the titration of PEEP based on measurement of airway pressures may be adequate for the management of most mechanically ventilated patients, we know that this is an oversimplified surrogate for pressures actually seen by the two components of the respiratory system, the lung and the chest wall. It is now widely accepted that chest wall mechanics can be severely abnormal in critically ill patients.[13, 14, 16, 17] And as we continue our search for better lung protective strategies, it is obvious that the contribution of the chest wall elastance should not be ignored. Chest wall (E_{cw}) and lung elastance (E_L) combine to form the total respiratory system elastance (E_{tot}) by the equation: $E_{tot}=E_{cw}+E_{L.}$[16]

Delineation of these two variables requires an understanding of the entire respiratory system and, in particular, the variable that separates the lung from the chest wall, *i.e.* pleural pressure (P_{pl}). The distending pressure of the lung is termed transpulmonary pressure (P_L), and during static airway conditions is simply the difference between alveolar pressure (P_{alv}) and pleural pressure (P_{pl}), *i.e.* ($P_L=P_{alv}–P_{pl}$). Alveolar pressure can be approximated from the pressure at the airway opening (P_{ao}) during static maneuvers (*i.e.*, end-expiratory and end-inspiratory breath hold maneuvers). Chest wall elastance can then be separated by the pleural pressure, if known, by the equation: $P_{pl}=P_{ao} \times E_{cw}/E_{tot}$.[16] The major difficulty lies in achieving accurate and reproducible measurements of the P_{pl}. Some authors have noted the correlation between abdominal pressures and chest wall elastance.[14, 16, 17] However, this ignores other components of chest wall elastance, including the thoracic rib cage, diaphragm elastance and pleural effusions. It is possible to directly insert pressure transducers into the chest and obtain direct measurements in experimental models.[18] However this is clearly not feasible in clinical practice. One proposed alternative is to obtain pleural pressure measurements by measuring the pressure in the esophagus.[14, 19]

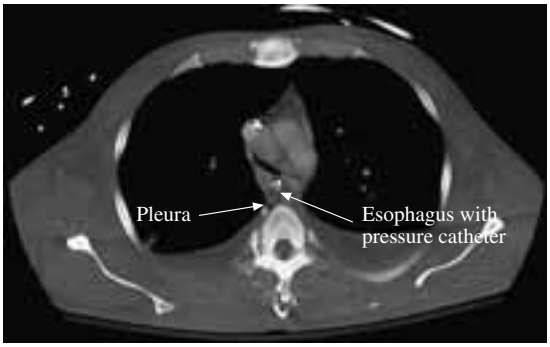

Figure 1.—Computed tomogram of the chest, showing the proximity of the esophagus and an inserted balloon-catheter to the pleural space as well as the relative height of the esophagus in the chest.

Estimating pleural pressure in ARDS

In healthy subjects and upright spontaneously breathing patients, the close proximity of the esophagus and pleural space (Figure 1) has allowed P_{pl} to be estimated from measurements of esophageal pressure (P_{es}) with a pressure transducing balloon catheter.[20] However, this has rarely been done in patients with acute lung injury, possibly because of a widespread belief that artifacts induced by the heart and mediastinal contents make P_{es} an unreliable estimate of P_{pl} in these patients.[21] Washko *et al.* characterized the magnitude and variability of postural effects on esophageal pressure in healthy subjects.[19] They found that transpulmonary pressure during relaxation ($P_{L\ rel}$) averaged 3.7±2.0 cmH_2O upright and -3.3±3.2 cmH_2O supine. Approximately 58% of the decrease in $P_{L\ rel}$ between the upright and supine postures was due to a corresponding decrease in relaxation volume. The remaining 2.9 cmH_2O difference is consistent with reported values of a presumed postural artifact. The authors concluded that postural differences in estimated transpulmonary pressure at a given lung volume are small when compared with the substantial range of P_L in patients with acute lung injury and recommended that adding a 3 cmH_2O correction to the estimated P_L measured by P_{es} for the effects of lying supine.[19]

In a series of patients with ARDS, Gattinoni *et al.* utilized P_{es} measurements at varied levels of PEEP to define two different subtypes of ARDS/ALI, having either pulmonary or extra-

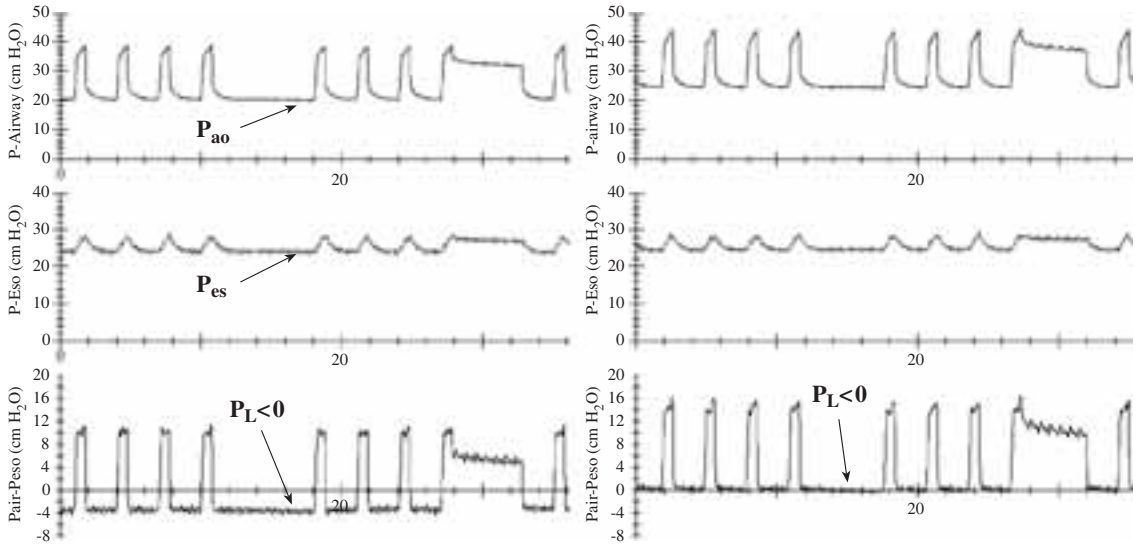

Figure 2.—Two serial measurements with static occlusion maneuvers in a patient with ALI demonstrating esophageal pressures (P_{es}); airway opening pressure (P_{ao}); and transpulmonary pressure ($P_L=P_{ao}–P_{es}$). This figure also demonstrates the effect of increasing PEEP with the resulting elevation of P_L above zero at end-expiration, thus, we theorize, reducing atelectasis and atelectrauma.

pulmonary ARDS, with very different respiratory mechanics.[22] The authors found that lung elastance was markedly higher in patients with pulmonary ARDS, whereas chest wall elastance was abnormally increased in the patients with extrapulmonary ARDS. The intra-abdominal pressure was higher in the extrapulmonary ARDS patients than in pulmonary ARDS patients, and significantly correlated with chest wall elastance.[22]

Pelosi *et al.* have reported a series of animal experiments where they compared the pressures obtained in the esophagus to those recorded by pressure transducers placed directly in the chest wall. The authors found good correlation between P_{es} and the P_L measured in the mid portion of the chest wall in supine lung-injured dogs.[18]

In an observational study of patients with ALI/ARDS,[14] Talmor *et al.* found P_{es} averaged 17.5±5.7 cmH_2O at end-expiration and 21.2±7.7 cmH_2O at end-inflation and were not significantly correlated with body mass index or chest wall elastance. Estimated P_L was 1.5±6.3 cmH_2O at end-expiration, 21.4±9.3 cmH_2O at end-inflation, and 18.4±10.2 cmH_2O during a static end-inspiratory maneuver. Interestingly, the P_L calculated using P_{es} was a negative number in many patients, suggesting that significant numbers of ventilated patients continue to have cyclic collapse of lung units at end-expiration.[14]

Based on these observations, it was postulated that P_{es}, corrected for a positional artifact as described by Washko *et al.*, reflects an effective estimate of P_{pl} in critically ill patients as it does in healthy individuals and can be used to estimate the P_L during static maneuvers as a guide to setting PEEP and preventing "atelectrauma" at end-exhalation.[14, 19] Despite the limitation noted by Pelosi that the absolute values did not always correlate with the direct pleural pressure measurements for all regions of the lung,[18] consistent trends in P_L estimated from P_{es} have now been observed by Pelosi, Gattinoni, and Talmor.[14, 18, 22]

Esophageal pressure measurements in clinical practice

With the balloon in the midesophagus per our reported technique,[14, 23] we perform static airway-occlusion maneuvers at end-inspiration and end-expiration to obtain static measurements of P_L with the correction applied per Washko *et al.* as follows: $P_L=P_{ao}–P_{es}+5$ cmH_2O. These measurements are graphically presented in Figures 2-4. Patients in whom the P_{es} exceeds the P_{ao} at end-expiration (*i.e.*, estimated P_L is negative at end-

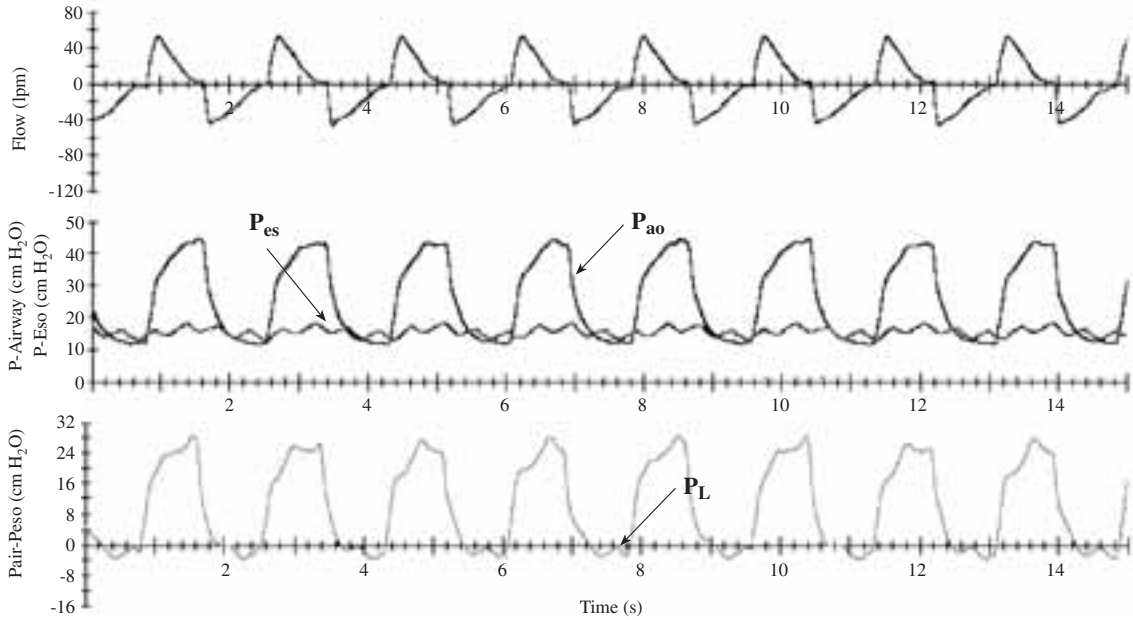

Figure 3.—In a patient with ALI, this tracing exemplifies noncompliant lungs and a normally compliant chest wall, with the P_{es} tracing superimposed on P_{ao}. The P_{es} tracing is in good position as noted by the visible cardiac oscillations, however, there is little change in the P_{es} tracing despite large change in P_{ao} with each tidal breath (~12 cmH_2O end expiration to ~40 cmH_20 end-inspiration). Also of note, this patient's end-expiratory transpulmonary pressure is nearly zero as noted by the arrow connected to the label P_L, indicating that this patient would likely not benefit from further PEEP elevation based on our observations.

expiration) are considered to be at risk for derecruitment of viable lung segments with each tidal breath. Talmor *et al.* have postulated the unexpected findings of a negative P_L in mechanically ventilated patients meeting criteria for ALI is due to one of several of mechanisms.[14] Possibly, proximal airway closure during exhalation could cause alveolar gas trapping and, thus, true alveolar pressure and P_{es} to be higher than P_{ao}, and thus the estmated P_L to be negative.[14] Additionally, regional variations in pleural pressure may cause P_{es} (and P_{pl} at mid-lung height) to be higher than P_{pl} near the non-dependant lung, allowing part of the lung to be ventilated while estimated P_L in the mid-lung is negative.[14] That is, the negative estimate of P_L does not insinuate a vacuum inside the chest cavity; rather it simply represents the known limitations of calculating the "relative" P_L. Thus, esophageal pressures are an estimate of global pleural pressures (as noted by Pelosi *et al.*[18]) just as airway pressures are an estimate of global alveolar pressure, both with known limitations. And despite these limitations, a "negative" P_L relative to these estimated variables appears to result from underinflation at end-expiration and generally indicates PEEP responsiveness without evidence of hyperinflation by respiratory mechanics variables or cytokine response.[14, 23, 24] For example, in a patient with ARDS secondary to severe pancreatitis and elevated bladder pressures, it is very common to see the tracing in Figure 4, demonstrating normally compliant lungs with very elevated P_{es} measurements, thus leading to the remarkably negative P_L tracing at end-expiration (Figure 4).

Translating these findings into clinical practice, Talmor *et al.* theorized that esophageal pressures could be used as a guide for the titration of PEEP in patients with ARDS. Incorporating this theory into a protocol, we recently published a single center study of 61 patients randomized to either PEEP titrated to the ARDSnet sliding scale or to $P_{L,}$ estimated from esophageal pressure, to keep P_L>0 cmH_2O during static end-expiratory maneuvers. The primary endpoint was patient oxygenation. Unlike other studies, the study protocol did not require PEEP to be increased in the study group and, in fact, it was decreased in some patients. Overall, however, the PEEP levels were

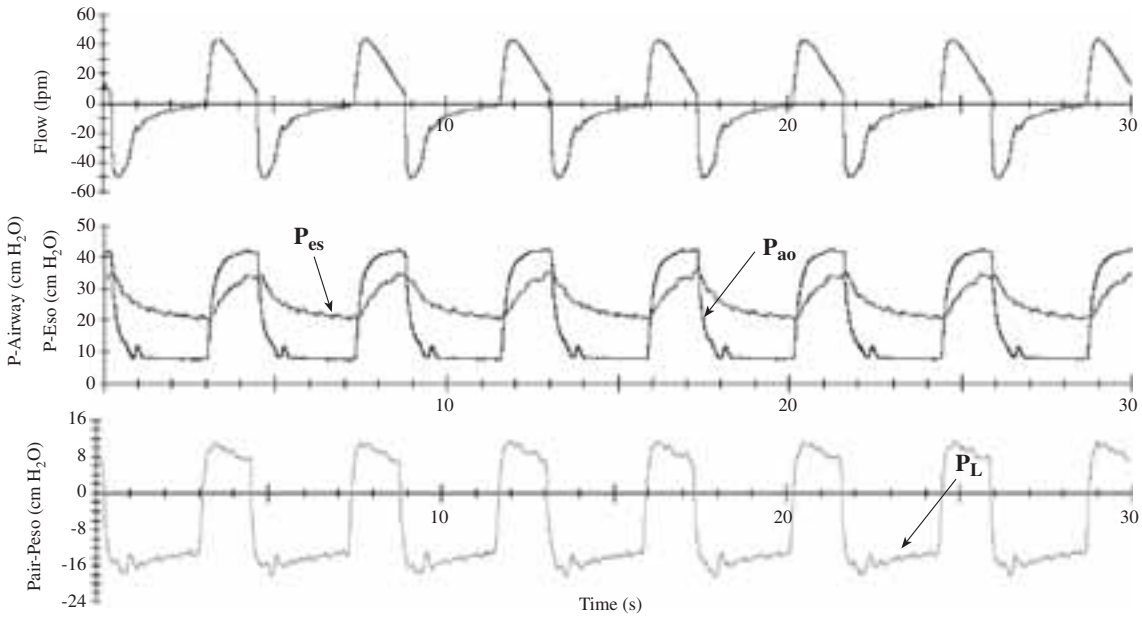

Figure 4.—In contrast to Figure 3, this patient exemplifies a patient with extrapulmonary ARDS, with a non-compliant chest wall but compliant lungs. Notice the very elevated P_{es} measurements (>20 cmH_20), in contrast to Figure 3, however, there is marked change and elevation of P_{es} with each tidal breath and increase of P_{ao}. Also notice the very negative P_L at end-expiration, indicating this patient would respond favorably to elevation of PEEP based on our and Gattinoni's observations.

clearly higher in the study group with PEEP at 72 hours averaging 17±6 *vs.* 10±4 cmH_2O in the study and control groups, respectively. After meeting early stopping criteria, the PaO_2/FiO_2 ratio at 72 hours was significantly different at 88 mmHg higher in the study group than the control (95% confidence interval, 78.1 to 98.3; P=0.002). This effect was persistent over the entire follow-up time (at 24, 48, and 72 hours; P=0.001 by repeated-measures analysis of variance). Respiratory-system compliance was also significantly better at 24, 48, and 72 hours in the esophageal pressure–guided group. Talmor *et al.* concluded that this method can be useful, effective and safe.

Conclusions

Higher levels of PEEP have been shown to be lung-protective in numerous animal models of ARDS but have demonstrated inconsistent benefits in clinical investigations.[5, 9] Undetected variations in P_{pl} may have contributed to negative outcomes in these trials. Failure to account for P_{pl} may lead to under- or over-application of PEEP in some patients as well as misinterpretation of high plateau airway pressures as evidence of lung over-distension.[25, 26] Measuring P_{es} to estimate transpulmonary pressure may allow customization of ventilator settings to accommodate individual variations in lung and chest wall mechanical characteristics. This individual approach may reduce the risk further lung injury in ARDS.[21, 25, 27] Use of esophageal pressure measurements as an estimate of pleural pressure, have been demonstrated safe and efficacious in a small clinical trial.[23] Larger, randomized, multi-centered trials are required to further validate the use of PEEP titrated to transpulmonary pressure as estimated by esophageal pressure.

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Received on April 21, 2009. - Accepted for publication on April 27, 2009.

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