Prone Positioning for a Morbidly Obese Patient with Acute Respiratory Distress Syndrome: An Opportunity to Explore Intrinsic Positive End-expiratory Pressure–Lower Inflexion Point Interdependence

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Since the description in the 1970s of external positive end-expiratory pressure for acute respiratory distress syndrome (ARDS),1 the optimum level of external positive end-expiratory pressure remains unresolved.2 In the 1990s, the lower inflection point, an inspiratory phenomenon on the low-flow pressure–volume curve, was defined as the point above which external positive end-expiratory pressure should be set to ensure full opening of the lung, e.g., open lung approach.3 The significance of the lower inflection point is, however, in part explained by expiratory flow limitation in ARDS patients4 unmasked by the presence of intrinsic positive end-expiratory pressure (PEEPi). Interestingly, the lower inflection point has been observed in morbidly obese patients without ARDS.5 Prone positioning has been applied to ARDS patients, especially those with severe hypoxemia. We report a morbidly obese ARDS patient exhibiting PEEPi–lower inflection point interdependence after a period of prone positioning.

Case Report

A 56-yr-old man with a body mass index of 42 kg/m2 was admitted to our intensive care unit with the diagnosis of febrile acute respiratory failure. He had a medical history of arterial hypertension and diabetes mellitus and was a nonsmoker. At initial examination, the patient was conscious, was hemodynamically stable, had bilateral crackles predominating on the left side, and had an arterial oxygen saturation of 92% while on 15 l/min oxygen. The initial workup revealed positive urinary antigen for legionella pneumophila, leading to the administration of intravenous erythromycin and rifampicin. After the first 24 h, the patient was successfully weaned from the ventilator. On day 19, the patient was discharged from the intensive care unit to the ward, then to a rehabilitation facility on day 41, and finally to home on day 60.

Discussion

Acute respiratory distress syndrome management in morbidly obese patients is challenging, with few previous reports.9 Expiratory flow limitation has been one of the key findings in these patients. One of the explanations has been small airway closure10 with atelectasis. Furthermore, it is well known that functional residual capacity decreases when a supine position is assumed,11 especially in morbidly obese patients5 because of unopposed intraabdominal pressure. While supine, our patient displayed an expiratory flow limitation with a large PEEPi. Because of the distribution of consolidation on lung computed tomography scan, we reasoned that prone positioning would be helpful. Prone positioning has been shown to improve respiratory system mechanics in ARDS12 and morbidly obese patients.13 As shown in our patient, the response was impressive, with almost disappearance of PEEPi with the concomitant diminution of lower inflection point. At the same time, we observed an improvement in alveolar ventilation, an already reported marker of good prognosis in ARDS patients.14 From a physiologic point of view, spontaneously breathing nonobese individuals11 had greater functional residual capacity in a prone position compared with a...
supine one, and this was also reported in morbidly obese patients during general anesthesia.\textsuperscript{13} In our patient, prone positioning improved alveolar ventilation comparable with what has been previously reported in nonobese ARDS patients,\textsuperscript{12} e.g., homogenization of tidal ventilation. This improvement was prompted by unloading of the abdominal contents and relief of pressure on the diaphragm, thereby opening small airways and finally the dependent parts of the lungs.

By applying an “open lung approach,” this patient would have been ventilated with external positive end-expiratory pressure of at least 16 cm H\textsubscript{2}O, leading to a reduction in tidal volume and consequent respiratory acidosis, and possible hemodynamic instability, especially in this patient with ARDS related acute cor pulmonale.

This clinical case report questions the physiologic basis of the open lung approach compared with the prone positioning strategy when applied to morbidly obese patients, and at the same time highlights interdependence between PEEPi and the lower inflection point, especially in morbidly obese ARDS patients. Obesity is a major health problem,\textsuperscript{15} and it would be of great public health interest to launch a clinical trial testing the impact of prone positioning on ARDS patients.

\begin{table}
\centering
\caption{Respiratory Settings, Mechanics, and Arterial Blood Gases}
\begin{tabular}{lcc}
\hline
 & Supine Position & After 12 h Prone Positioning \\
\hline
Tidal volume, ml/kg IBW & 8 & 8 \\
Respiratory rate, breaths/min & 15 & 15 \\
PEEP\textsubscript{e}, cm H\textsubscript{2}O & 8 & 8 \\
Plateau pressure, cm H\textsubscript{2}O & 29 & 22 \\
PEEP\textsubscript{i}, cm H\textsubscript{2}O & 12 & 2 \\
Crs, ml/cm H\textsubscript{2}O & 40 & 54 \\
FIO\textsubscript{2} & 0.7 & 0.6 \\
pH & 7.38 & 7.43 \\
PaO\textsubscript{2}, mmHg & 65 & 82 \\
PaCO\textsubscript{2}, mmHg & 57 & 50 \\
HCO\textsubscript{3}\textsuperscript{-}, mM & 34 & 33 \\
Base excess, mM & 7.4 & 7.4 \\
SaO\textsubscript{2}, % & 93 & 97 \\
PaO\textsubscript{2}/FIO\textsubscript{2} ratio & 93 & 137 \\
\hline
\end{tabular}
\end{table}

Crs = compliance of the respiratory system; FIO\textsubscript{2} = fraction of inspired oxygen; HCO\textsubscript{3}\textsuperscript{-} = bicarbonate; IBW = ideal body weight; PaCO\textsubscript{2} = arterial partial pressure of carbon dioxide; PaO\textsubscript{2} = arterial partial pressure of oxygen; PEEPe = external positive end-expiratory pressure; PEEPi = intrinsic positive end-expiratory pressure; SaO\textsubscript{2} = arterial oxygen saturation.

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of prone positioning in severely hypoxemic, morbidly obese ARDS patients. A previous randomized trial of prone positioning conducted in normal-size patients was negative, but a post hoc analysis showed a significantly lower 10-day mortality rate in the prone group compared with the supine group in those with the lowest arterial oxygen pressure to fraction of inspired oxygen ratio. From these results, we speculate that a randomized trial of prone positioning in severely hypoxemic morbidly obese ARDS patients might be positive.

References


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Naloxone-insensitive Epidural Placebo Analgesia in a Chronic Pain Patient

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RECENT brain imaging studies have furthered our understanding of the neurobiologic mechanisms underlying placebo analgesia.1,2 The majority of these studies have used experimental pain stimuli in a laboratory setting3–6 and used a controversial criterion of 10–20% difference in pain rating to classify subjects as placebo responders.7 In addition, they only performed a single placebo challenge, which leaves us ignorant about the persistence of the placebo effect over time. We here describe behavioral, pharmacologic, and brain imaging results of a long-term placebo response in a chronic pain patient.

Case Report

A 55-year-old chronic pain patient presented at the pain clinic with severe pain in the lower lumbar region radiating to the left lower leg. In 1999, she developed back pain problems which became progressively worse. A lumbar myelography and magnetic resonance imaging examination revealed a disc protrusion, compressing the fifth lumbar root. Two laminectomies provided only temporary pain relief. In 2003, an arthrodesis was performed between L3 and L5, resulting in aggravation of the pain. Various drug and interventional therapies had little therapeutic effect. The patient was referred to us for a trial therapy with spinal opioids. As part of the routine screening procedure of candidates for an intrathecal drug delivery system, approved by the local ethics committee, patients are tested first for their response to epidurally administered morphine and saline. The patient was randomly assigned to be first submitted to placebo testing. In short, an epidural catheter is implanted and connected to a patient-controlled analgesia (PCA) pump filled with saline. Patients are sent home and are...
asked to fill in a pain diary three times daily. Each second day, they are visited by a nurse to check the PCA system and to collect the pain ratings. A major difficulty when assessing placebo responses in individual patients is to separate placebo responses from factors such as natural history of the disease and regression to the mean. To circumvent these possible confounds, we randomly selected two ‘placebo holidays’ over the course of the placebo-evaluation period, during which the PCA pump was switched off knowingly to the patient and remained inactive for the whole day. To test for the involvement of the opioid system in the placebo response, naloxone (0.14 mg/kg) and saline (0.9% NaCl) were injected intravenously (0.1 ml/s; total infusion time < 2 min) by means of a programmable infusion pump in a double-blind manner. The naloxone test was conducted on a day of normal use of the PCA pump (fig. 1A). Pain was measured before and 2, 5, 10, 15, 20, 30, and 60 min after the start of the infusion.

After given written informed consent, she participated in a positron emission tomography (PET) study approved by the ethics committee (week 5). The PCA pump was switched off 16 h before scanning. Changes in regional cerebral blood flow (rCBF) data were measured using a CTI 951 16/32 PET scanner (Knoxville, TN). Fifteen scans were acquired in three-dimensional mode after injections (5 ml) of 300 MBq of $^{15}$O over a period of 20 s. The first four scans were taken with the PCA pump switched off. We next assessed the placebo effect using a stepwise titration method: The patient was told that the PCA pump would be turned on and that infusion rate would be gradually increased in 33% steps after each second scan. When maximal placebo responses had been reached (scan 12), the patient was informed that an opioid ‘antagonist’ was going to be injected, and three further scans were obtained. In reality, a saline solution was injected. After each scan, the patient rated pain intensity and pain unpleasantness on a 10-point rating scale (0 = no pain and 10 = worst pain imaginable). PET data were preprocessed and analyzed using Statistical Parametric Mapping (SPM2) as described elsewhere. Results were thresholded for significance at $P < 0.001$ (small volume corrected for multiple comparisons at $P < 0.01$). Coordinates (x, y, z) of peak voxels are given in standardized stereotaxic space.

The patient showed a prominent placebo response throughout the 50-day observation period (fig. 1B). Mean pain ratings decreased from 6.7 ± 0.6 (week preceding placebo) to 0.6 ± 0.7 ($P < 0.0001$). During placebo holidays, pain intensity ratings rapidly returned to prestudy values (fig. 1C). Naloxone did not abolish the placebo response ($P > 0.05$, paired t test). The patient was pain free at the moment of the naloxone test and remained pain free for 60 min after injection. During PET scanning, pain ratings gradually decreased after epidural placebo, and the patient was pain free during scans 9–12. Suggestion that an opioid antagonist was given (scans 13–15) made the pain increase to worst pain imaginable ($P < 0.05$). PET images with significant changes in brain activation and metabolism are depicted in figure 2. PCA-related rCBF decreases were identified bilaterally in medial thalamus (x = −2, y = 18, z = 12 mm; Z value = 4.81), rostral anterior cingulate cortex (rACC; x = −14, y = 40, z = 18 mm; Z value = 4.01), and left nucleus accumbens (x = −10, y = 10, z = −8 mm; Z value = 3.81) (fig. 2A). Figure 2B illustrates the relation between PCA-related changes in thalamic rCBF and reported pain ratings. A similar rCBF time course was observed for rACC and accumbens. We observed no significant rCBF increases. Finally, placebo-induced changes in functional connectivity (i.e., cross-correlation in rCBF, as described in Laureys et al.13) were observed between the previously identified rACC and the right superior frontal gyrus (area 10; x = 24, y = 68, z = −4; Z value = 3.45).

Discussion

We present a case of long-term placebo analgesic response in a clinical pain case. Our patient showed a long-lasting average pain reduction of more than 90%, which stands in sharp contrast with the moderate placebo effects observed in most experimental pain studies. During placebo holidays, pain returned to prestudy levels within a couple of hours. When placebo treatment was resumed the next morning, pain ratings rapidly decreased again within the same time span. This finding is difficult to reconcile with the idea that regression to the mean or natural course of the disease are at the basis of the observed changes in pain perception.
We tested our patient with an epidural catheter for 50 days, which is much longer than in our routine clinical practice. We are aware that this unusually long period of long-term outpatient epidural administration, partly imposed by the study demands, carries the risk of meningitis.

The purported role of the endogenous opioid system in the mediation of the placebo response remains an issue of debate. Behavioral studies have shown that the placebo response can be blocked by the opioid antagonist naltrexone.19,20 PET studies further showed a significant overlap in the brain areas activated by an opioid and placebo.4 However, some forms of placebo analgesia—mainly in clinical pain conditions or in experimental pain conditions using longer-lasting pain stimuli, which more closely resemble clinical forms of pain—are not or are only partially antagonized by naltrexone.13,14 The placebo response in our patient was not antagonized by naltrexone. In a second placebo responder, we got similar results. Additional information regarding this patient is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

In conclusion, our data further underscore the powerful contribution of placebo in clinical pain practice. Placebo analgesia was not blocked by naltrexone, suggesting the involvement of nonopioidergic mechanisms, and correlated with a deactivation in parts of the pain matrix, possibly under top-down control from the prefrontal cortex.

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References