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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 patients[4] 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/m^2 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 intensive care severity score–new simplified acute physiology score (SAPS II)[6] was 52 points.

On day 2, the patient became even more dyspneic, with encephalopathy leading to tracheal intubation, deep sedation, and paralysis. A ventilatory protective pressure limited ($<$ 30 cm H_2O) strategy was implemented with a Servo^i ventilator (Maquet Critical Care AB, Solna, Sweden) with the following values on 100% oxygen: pH, 7.24; arterial partial pressure of oxygen, 83 mmHg; arterial partial pressure of carbon dioxide, 59 mmHg; bicarbonate, 23 mM; base excess, −5 mM; arterial oxygen saturation, 96%. A chest radiograph revealed bilateral alveolointerstitial infiltrates. This clinical picture was compatible with ARDS as defined by American–European consensus conference[7] and a Lung Injury Severity Score of 2.75.[8]

Because of hemodynamic instability, transesophageal echocardiography was performed, showing acute cor pulmonale. Thereafter, hemodynamic stabilization was rapidly achieved with norepinephrine infusion.

On day 7, ARDS persisted, and a lung computed tomography scan (fig. 1) revealed bilateral posterior alveolar consolidation. At that time, standard ventilator software was used to perform the following respiratory mechanics measurements: an expiratory occlusion technique showing a PEEPi of 12 cm H_2O and a low-flow (9 l/min) inspiratory pressure–volume curve exhibiting a lower inflection point of 14 cm H_2O (fig. 2). The patient was then positioned prone with upper chest and pelvic support to ensure free movement of the abdomen. After 12 h of prone positioning, the PEEPi was 2 cm H_2O, and the low flow inspiratory pressure-volume curve was repeated, showing a lower inflection point of 3 cm H_2O (fig. 3). Respiratory settings, mechanics, and arterial blood gas tension measurements before and after the first 12 h of prone positioning are reported in table 1. Considering this improvement, the patient was turned from supine to prone and was kept prone 12 h per day, for 3 consecutive days.

On day 19, the patient was successfully weaned from the ventilator. On day 24, 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 closure[10] with atelectasis. Furthermore, it is well known that functional residual capacity decreases when a supine position is assumed,[11] especially in morbidly obese patients[5] 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 ARDS[12] 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 individuals[11] had greater functional residual capacity in a prone position compared with a

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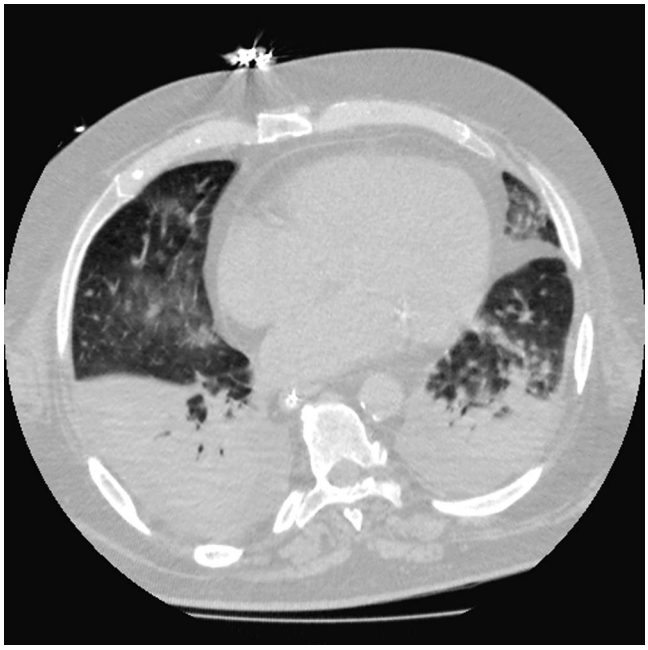

Fig. 1. Lung computed tomography scan.

supine one, and this was also reported in morbidly obese patients during general anesthesia.[13] In our patient, prone positioning improved alveolar ventilation comparable with what has been previously reported in nonobese ARDS patients,[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

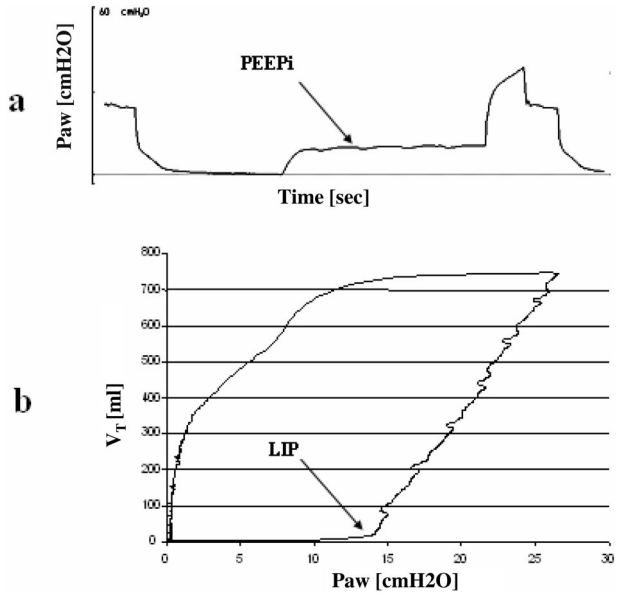

Fig. 2. Supine position. (*A*) P_{aw} = airway pressure curve; PEEPi = intrinsic positive end-expiratory pressure of 12 cm H_2O. (*B*) Low-flow inspiratory pressure–volume curve. P_{aw} = airway pressure; LIP = lower inflection point of 14 cm H_2O; V_T = tidal volume.

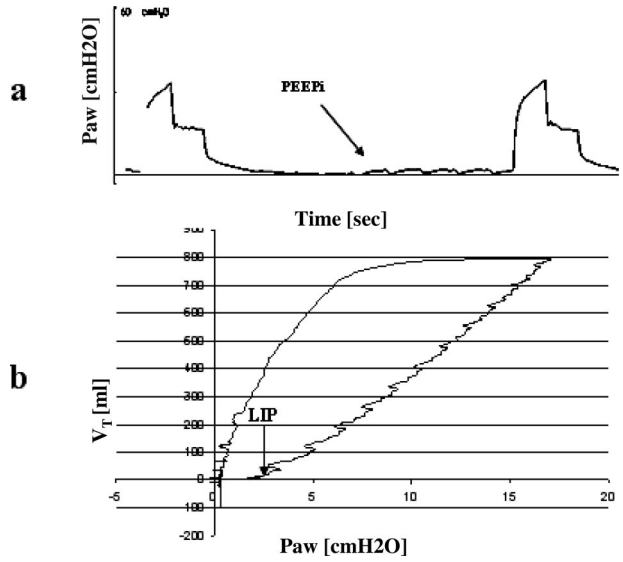

Fig. 3. After 12 h of prone positioning. (*A*) P_{aw} = airway pressure; PEEPi = intrinsic positive end-expiratory pressure of 2 cm H_2O. (*B*) Low-flow inspiratory pressure–volume curve. P_{aw} = airway pressure; LIP = lower inflection point of 3 cm H_2O; V_T = tidal volume.

have been ventilated with external positive end-expiratory pressure of at least 16 cm H_2O, 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,[15] and it would be of great public health interest to launch a clinical trial testing the impact

Table 1. Respiratory Settings, Mechanics, and Arterial Blood Gases

	Supine Position	After 12 h Prone Positioning
Tidal volume, ml/kg IBW	8	8
Respiratory rate, breaths/min	15	15
PEEPe, cm H_2O	8	8
Plateau pressure, cm H_2O	29	22
PEEPi, cm H_2O	12	2
Crs, ml/cm H_2O	40	54
F_{IO_2}	0.7	0.6
pH	7.38	7.43
Pa_{O_2}, mmHg	65	82
Pa_{CO_2}, mmHg	57	50
HCO_3^-, mM	34	33
Base excess, mM	7.4	7
Sa_{O_2}, %	93	97
Pa_{O_2}/F_{IO_2} ratio	93	137

Crs = compliance of the respiratory system; F_{IO_2} = fraction of inspired oxygen; HCO_3^- = bicarbonate; IBW = ideal body weight; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2} = arterial partial pressure of oxygen; PEEPe = external positive end-expiratory pressure; PEEPi = intrinsic positive end-expiratory pressure; Sa_{O_2} = arterial oxygen saturation.

of prone positioning in severely hypoxemic, morbidly obese ARDS patients. A previous randomized trial of prone positioning conducted in normal-size patients was negative,[16] 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.

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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 setting[3–6] 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.

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or at the top of the HTML version of the article.

Case Report

A 53-yr-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 discus 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

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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.[8] 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.[9] 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 $H_2{}^{15}O$ over a period of 20 s.[10] 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.[10] 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 prestudy levels. 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.*[11]) 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).

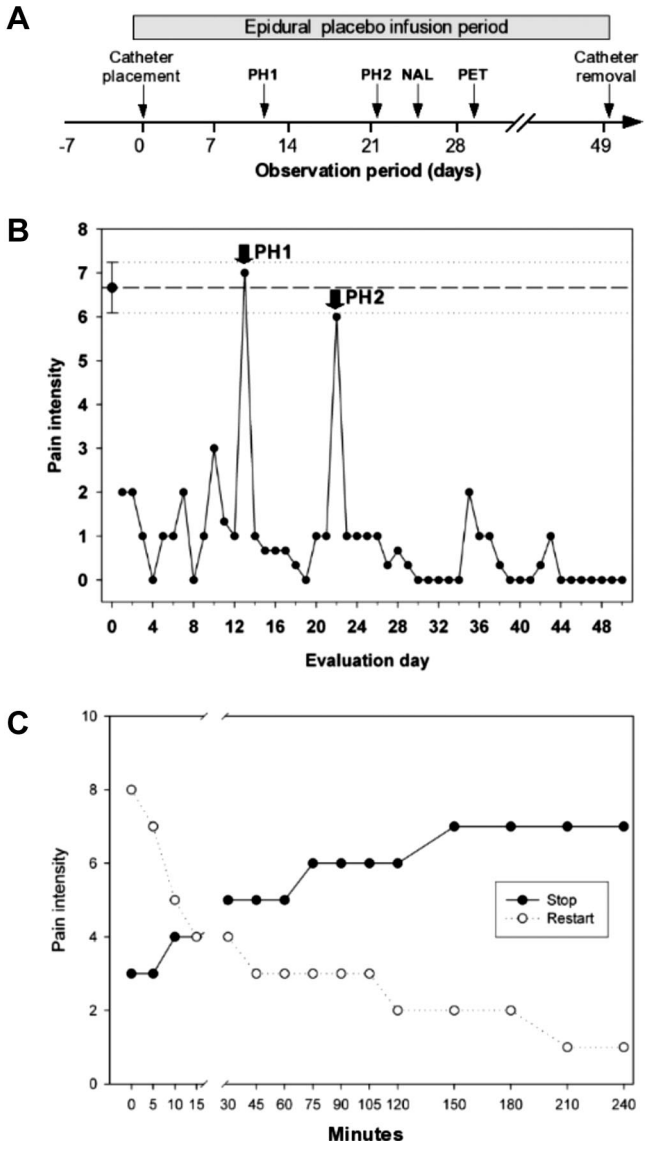

Fig. 1. Study design and time course of the placebo analgesic response and effect of naloxone on placebo analgesia. (*A*) Time course of the study. Patient's pain was recorded daily starting from 1 week before catheter implantation until 50 days after implantation. The timing of the placebo holidays (PH1, PH2), the naloxone (NAL) test, and the positron emission tomography (PET) investigation are indicated. (*B*) Average pain ratings (± 1 SD) before the start of the placebo trial are illustrated by the *interrupted* (and *dotted*) *lines*. Placebo significantly diminished pain ratings during the 50-day home evaluation period. During placebo holidays, pain ratings increased to preplacebo levels. (*C*) Time course of the pain ratings during the first 4 h when switching off and restarting the patient-controlled analgesia pump during PH1.

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.[3–6] 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.[8]

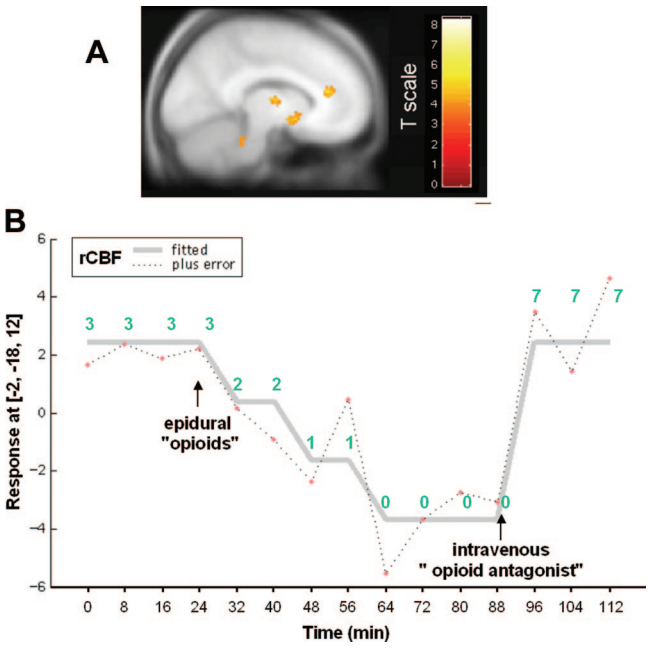

Fig. 2. Placebo-induced changes in regional cerebral blood flow (rCBF). (*A*) Placebo-related decreases in rCBF in medial thalamus, rostral anterior cingulate cortex, and nucleus accumbens. (*B*) Thalamic blood flow changes (*red dots*; centered adjusted rCBF) and changes in pain ratings (*green values*; scores on 10) over the course of the study. Thalamic activity decreased gradually between scans 5 and 9, *i.e.*, the period of stepwise titration of the placebo response (the *arrow* indicates injection of epidural "opioids"). The patient was pain free during scans 9–12. Before the last three scans, a nocebo suggestion was given (the *arrow* indicates injection of intravenous "opioid antagonist"), which resulted in a prompt increase in pain ratings and a concomitant increase in thalamic activity.

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 naloxone.[9,12] 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 naloxone.[13,14] The placebo response in our patient was not antagonized by naloxone. 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. The dose and infusion rates were the same as those used in studies that reported successful blockade of the placebo analgesic response in experimental pain.[9] Our data therefore provide additional evidence that some forms of placebo analgesia are not opioid mediated. One of the possible explanations for the lack of effect of naloxone is that opioids play no role in placebo effects that are not opioid conditioned.[9]

Placebo analgesia was associated with significantly reduced activity in the medial thalamus, rACC, and nucleus accumbens. So far, only two brain imaging studies have shown placebo-induced rCBF reductions in the pain matrix,[5,15] which may be explained by the low amplitude of the placebo analgesic responses in these studies. To be able to dissociate placebo effects from possible time-related changes in rCBF, we added a nocebo suggestion, which resulted in a sharp increase in pain ratings and a concomitant rCBF increase in the identified areas (fig. 2B). Placebo-related negative correlations between activity in right superior frontal gyrus area 10 and rACC suggest a top-down modulation from the prefrontal cortex on activity in part of the pain matrix.[16] We did not observe increased activity in periaqueductal gray, perigenual anterior cingulate cortex, or orbitofrontal cortex as shown in previous studies.[3–6] This might reflect a type II error due to the limited statistical power (n = 1). At lower level for significance the orbitofrontal cortex (coordinates x = 12, y = 30, z = −24 mm; voxel-level $P = 0.008$, cluster-level $P < 0.05$) did show PCA-related rCBF increases. The periaqueductal gray is often a difficult area to assess because of its small size and partial volume effect. Also, activity in these brain areas might be more transient and in direct relation to the initial instigation of the placebo treatment, making them undetectable for longer-lasting placebo responses.

In conclusion, our data further underscore the powerful contribution of placebo in clinical pain practice. Placebo analgesia was not blocked by naloxone, 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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