

# Hypercapnic Acidosis

## How Far?

SINCE the publication of two randomized studies<sup>1,2</sup> highlighting the interest in reduction of tidal volume for patients with acute lung injury (ALI) and acute respiratory distress syndrome, the place of hypercapnic acidosis (HCA) in the complex puzzle of ALI has become a matter of debate. HCA was first considered as a sign of the degree of respiratory disease with lung volume amputation, and the concept of “tolerated hypercapnia” (as an undesirable consequence) has progressively changed to that of “therapeutic hypercapnia.” In this issue of the Journal, Ni Chonghaile *et al.*<sup>3</sup> provide complementary evidence of the protective effect of this therapeutic hypercapnia.

On the pro side, the presence or induction of HCA seems to reduce ALI in several conditions. This protective role has been repeatedly demonstrated in a variety of experimental models (endotoxin instillation, lung stretch, systemic or pulmonary ischemia reperfusion)<sup>4-7</sup> with mechanisms involving immunomodulating effects, lung barrier protection, and complex effects on reactive oxygen species intermediates. HCA has also demonstrated clinical potential in improving tissue oxygenation by increasing cardiac output and inducing vasodilation.<sup>8</sup> Conversely, acute hypercapnia has been thought to worsen lung damage caused by bacterial infection<sup>9</sup> and to contribute to lipopolysaccharide-induced lung injury.<sup>10</sup> Furthermore, acute HCA has been reported to impair muscle function. In this regard, in a recent study published in the Journal, Jaber *et al.*<sup>11</sup> demonstrated that exposure to HCA decreased diaphragmatic contractility. Moreover, these adverse effects seem proportional to the level of hypercapnia and the duration of exposure.<sup>9,11</sup>

Consequently, it seems that HCA has the potential to exert either deleterious or protective effects during pulmonary inflammatory responses. This conclusion highlights the necessity of experimental models that are closer to clinical situations to reflect the more complex inflammatory process of pulmonary sepsis encountered in our patients.

In their experimental study, Ni Chonghaile *et al.*<sup>3</sup> aimed to evaluate the influence of induced HCA on lung

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injury related to bacterial pneumonia. Their methodology allowed distinction between the specific effect of induced HCA and the association with the etiologic (antibiotic) treatment. The evaluation of the effects of HCA without antibiotic treatment indicates that HCA could reduce the mechanical lung alteration linked with the infectious process without adverse effects on bacterial growth. This “mechanical” effect has also been reported by Doerr *et al.*<sup>12</sup> in an *ex vivo* rat lung model associated with preservation of vascular barrier function. Once antibiotic therapy was included, further attenuation in the extent of histologic lung injury was observed. Based on the authors’ conclusions, it seems that HCA was able not only to promote the action of antibiotic therapy, but also and perhaps more importantly to protect the lung against the development of an infectious process. Another interesting issue tackled in this study was the time of HCA induction in the time course of the infectious process. The current study shows a benefit when HCA is administered after injury is established, confirming previous results from the same team on endotoxin-mediated lung injury.<sup>7</sup> This potential late effect is of paramount importance because in clinical practice, we are able to intervene only after the onset of lung disease. Also of interest is the infection model used, which is closer to clinical situations than are previously studied experimental models.

Therefore, if we consider HCA as a promising therapeutic agent in clinical practice, should the cumulative experimental data and the preliminary clinical observations<sup>13</sup> lead us to use it intentionally in patients with ALI? Before this next step, we must answer several questions. If HCA is an interesting option, should we administer it by deliberate hypoventilation or by addition of inspired carbon dioxide, as did Laffey *et al.*<sup>7</sup>? Based on the results reported by Sinclair *et al.*,<sup>14</sup> it seems that a further reduction in tidal volume or in respiratory rate only to obtain HCA (once a protective ventilatory strategy is established) is not mandatory and that inspired carbon dioxide might be a better way. These results could be explained both by the heterogeneity of carbon dioxide delivery with a greater level in poorly ventilated areas secondary to a low-tidal-volume, low-respiratory-rate strategy and by the potential to promote injury induced by recruitment-derecruitment. Conversely, the inspired carbon dioxide delivery might result in a more homogeneous distribution of carbon dioxide throughout the lung. Whether the protective effect of HCA results from the hypercapnia or from the acidosis itself remains equally questioned. It seems that the protective effects result partly from inhibition of xanthine oxidase<sup>15</sup> and

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are abrogated by acidosis buffering.<sup>4</sup> That is, would metabolic acidosis result in same or different observations? Finally, the question of exposure duration necessitates further investigation. Limited exposure results in a positive balance, but a more prolonged period may result in the opposite effect.<sup>9</sup> In one of the first models exposed to sustained HCA (2 days), O'Croinin *et al.*<sup>9</sup> reported a worsening in bacterial infection-induced lung injury, notably by increasing the bacterial load.

Undoubtedly, the study of Ni Chonghaile *et al.*<sup>3</sup> provides complementary information toward our understanding of the effects of HCA. Taken together, the evidence seems to indicate that the induction of moderate hypercapnia during a limited time is able to reduce ALI without causing significant adverse effects. Therefore, the balance between positive and negative HCA-related effects leads to the positive effects outweighing the negative effects in these conditions. Further experimental evaluations of the effect of time exposure and remaining and/or rebound effect after cessation of hypercapnia are mandatory before further trials investigating the therapeutic use of HCA can be conducted.

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