Respiratory variability after opioids: see it happen

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SHORT-TERM RESPIRATORY VARIABILITY can contain information on the control systems that continuously adapt the pulmonary ventilation to the needs of the body. This information comes spontaneously: all we have to do is to record changes in ventilation from breath to breath and to interpret the found patterns of variability. Is it really that simple? In this issue of the Journal of Applied Physiology, Mitsis et al. (6) make use of respiratory variability to gain insight into the influence of a short-acting opioid, remifentanil, on the action of the respiratory control system in healthy subjects. They describe how the variability changes under the influence of the drug and show how these changes can be understood using a simple chemoreflex model.

The subjects received increasing doses of remifentanil in 15-min intervals, interrupted by 5-min periods of equilibration. The mean ventilation decreased (VT/TTOT, the ratio of tidal volume to breath duration) due to a longer expiration time (TE), while the mean end-tidal PCO2 (PETCO2) increased, all in a dose-dependent manner. The overall variability of PETCO2 and VT/TTOT remained largely unchanged.

For clarity, the explaining chemoreflex model is shown in Fig. 1. The feedback loop consists of the influence of PETCO2 on VT/TTOT through the chemoreflexes (the “controller”) and the influence of VT/TTOT on PETCO2 through pulmonary gas exchange (the “plant”). To separate these influences, breath-to-breath values were fitted to two models. The controller model has PETCO2 as input and VT/TTOT as output (after removal of sighs, which are likely not due to chemoreflex activity). The residual noise in this model consists of “spontaneous” changes in VT/TTOT (noise 2). The plant model describes pulmonary gas exchange and has VT/TTOT as input and PETCO2 as output (including the sighs that are now considered as part of the input). Here the residual noise consists of “spontaneous” changes in PETCO2 (noise 1).

Mitsis et al. (6) found that the effect of the controller was suppressed by remifentanil, which one would expect. This agrees with the well-known decreased chemosensitivity after opioids (7), where it should be noted that the peripheral chemoreflex was partly suppressed since end-tidal PO2 (PETCO2) was artificially kept at ~30 kPa. The drug had a stronger, and positive, effect on the plant part of the loop. As the authors point out, this is probably related to the higher mean PETCO2, since the expiratory CO2 fraction is the main determinant of ventilatory efficiency. This may in turn be related to the decreased ventilation, mainly because of an increased mean TE (almost twice as high at the highest dose). This implies that the chemoreflex operates at a higher mean PETCO2 and lower VT/TTOT. One may speculate that this is related to the right-shift of the CO2 response curve that has been found after opioids, in relation with a higher apneic threshold (9).

The question rises to which extent the two components of the feedback loop are indeed separated by this approach. Assuming that sighs are not influenced by chemoreflex feedback, it is plausible that changes in PETCO2 at the end of a sigh and during the next few breaths are almost exclusively due to the “plant.” It can be expected, however, that these changes are modulated by the peripheral chemoreflex after a number of breaths. This agrees with the observations of Khoo and Marmarelis (5), who estimated the chemoreflex response from respiratory oscillations after spontaneous sighs in anesthetized dogs. In the present study, the relation between PETCO2 and VT/TTOT showed oscillatory behavior after changes in PETCO2, at baseline (with a cycle time of ~14 breaths). These oscillations may be ascribed to the band-pass filter characteristics of the closed feedback loop (4, 11). It also seems plausible that the first changes in VT/TTOT after a change in PETCO2 are mainly due to the “controller” (after correction for the lung-to-chemoreceptor delay).

Although the estimated relations were derived from a closed-loop situation, an interpretation of respiratory instability in terms of the “loop gain” is still possible. The authors used linear and nonlinear coefficients to estimate the components of the feedback loop. In the frequency domain, the linear coefficients yield the “controller gain” (the frequency-dependent amplification from PETCO2 to VT/TTOT) and the “plant gain” (the frequency-dependent amplification from VT/TTOT to PETCO2). In the closed-loop situation, the product of the controller gain times the plant gain equals the “double loop gain” (11). This is the loop gain for a system with two simulta-

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Invited Editorial

Fig. 1. The used simple chemoreflex feedback model. End-tidal PCO2 (PETCO2) stimulates ventilation VT/TTOT (the ratio of tidal volume to breath duration) through the “controller,” which in turn causes a response in PETCO2 through the “plant.” The variability of PETCO2 and VT/TTOT is driven by 2 independent sources of noise. In the study of Mitsis et al. (6), remifentanil suppressed the controller and increased the effect of the plant (in a more pronounced way). Remifentanil also caused a dose-dependent reduction of noise 2 (“wakefulness drive” without feedback from the chemoreceptors).
neous and independent inputs (*noise 1* and *noise 2*). Like the well-known “single loop gain” (the loop gain for a single input), the double loop gain determines the tendency of the system to oscillate. Analogous to the Nyquist criterion for the single loop gain, dampened respiratory oscillations occur if the double loop gain is less than unity (see Online article notes II to Ref. 2).

Mitsis et al. (6) found that nonlinear versions of the model better explained the relation between $\text{PETCO}_2$ and $\text{VT/TTOT}$ (and vice versa) than linear versions of the model—“better” in the sense that the residual noise was significantly smaller. But the residual noise also has a physiological meaning here. Remifentanil decreased the noise in $\text{VT/TTOT}$ in a dose-dependent manner, possibly due to a decreased “wakefulness drive” without feedback from the chemoreceptors (10). The cause of the apparent nonlinearity is not clear. A possible explanation is that the chemoreflex gain changes in time. This may have occurred, since the equilibration times of 5 min are relatively short for a drug with a half-time of 3–4 min [see references in the article (6)]. Even then, the system may be approximately linear over shorter time scales and be treated as such by using time-frequency analysis with a higher time resolution.

Showing that part of the variability can be explained by the model is one thing. But, in line with the philosophy of Karl Popper (8), one would also like to falsify all conflicting hypotheses. One conflicting hypothesis is of course that changes in $\text{PETCO}_2$ and $\text{VT/TTOT}$ are not correlated at all, which is refuted by the used significance tests. This does not exclude the possibility that the two variables are coupled through other mechanisms. For instance, suppose that changes in $\text{VT/TTOT}$ are induced by the “wakefulness drive” without feedback from the chemoreceptors. Because of short-term potentiation (the “flywheel effect”) (1), a large breath would then increase the subsequent breaths. Since a large breath instantaneously decreases $\text{PETCO}_2$, this could also explain a relation between $\text{PETCO}_2$ of a given breath and $\text{VT/TTOT}$ of subsequent breaths. The sign of the obtained coefficients would then be mainly negative, however, which was apparently not the case here.

The model would be further supported if it can be shown that the supposed relations do not hold if one of the interactions is blocked, for instance, if the peripheral chemoreflex is further suppressed by 100% $\text{O}_2$ or if the experiment is repeated in animals in whom the reflexes are surgically interrupted. Ideally, more information on the control system could be obtained if variables are measured that are more closely related to input and output of the chemoreflexes, such as continuous arterial $\text{PCO}_2$ or phrenic nerve activity.

The study of Mitsis et al. (6) is probably the first to show that respiratory variability provides information on the influence of an opioid drug on the respiratory control system. Still, the analysis of respiratory variability may also be disappointing. Sometimes there is simply too much noise (measurement noise or “physiological” noise). Sleep is probably an exception, because of reduced wakefulness drive without feedback from the chemoreceptors (*noise 2* in Fig. 1) (10). Otherwise, additional inputs may help to induce chemoreflex responses, such as intermittent changes in inspiratory $\text{PCO}_2$ or artificial deep breaths (3). But if the chemoreflexes react to spontaneous changes, and if we have the appropriate analysis techniques, then we only have to watch and see it happen.

REFERENCES