$$CVP = \alpha + f\left(pos_{cardiac}\right) + f\left(pos_{ventilation}\right) + f(time) + \epsilon$$

This is a strictly additive model and therefore assumes no interaction between the effect of ventilation and heart beat on CVP; i.e. this model assumes that every heartbeat produces the same CVP pattern. This pattern is simply raised and lowered with ventilation (see Fig. 4).

This model describes most of the variation in CVP, but the depth of the *x'* descent (corresponding to the ventricular contraction) is systematically off at specific places in the respiratory cycle. Clearly, the pattern in CVP produced by a heart beat depends on its position in the respiratory cycle. To address this, we introduce a smooth interaction term to the model.

$$\begin{aligned} CVP = \alpha &+ f\left(pos_{cardiac}\right) + f\left(pos_{ventilation}\right) \\ &+ f\left(pos_{cardiac}, pos_{ventilation}\right) + f(time) + \epsilon. \end{aligned}$$

$f\left(pos_{cardiac}, pos_{ventilation}\right)$ is a smooth function that represents the interaction between the cardiac and respiratory cycles. It is based on a non-cyclic spline in the x-direction (cardiac cycle) and a cyclic spline in the y-direction (respiratory cycle). It can be visualised as a surface (or more specifically, a cylinder, since it is cyclic in the Y direction), where the x-axis represents the cardiac cycle, the y-axis represents the respiratory cycle, and the z-axis represents the effect of the interaction on CVP (see Fig. 5).

To aid comprehension of the model—CVP as the interaction of two repeating cycles—we attach an animation of the model's prediction, simultaneously on a time scale and projected onto a plane with cardiac cycle position and respiratory cycle position as independent variables (see Online Resource 2). The plane is equivalent to the contour plot in Fig. 6b, before 250 ml fluid.

2.3.1 Autocorrelation

Like other regression models, a GAM assumes that observations are independent, conditional on the model (i.e. that the residuals are independent). First, if there is some pattern remaining in the residuals, it is important to consider that the model may have underfitted the data (as in the example without an interaction term; shown in Fig. 4). But, even with an "optimal" fit, models of high resolution waveforms will likely have a high degree of autocorrelation in the residuals, as noise itself is often autocorrelated in these waveforms. To correct for this, we have included in the CVP models a first-order autoregressive model [AR(1)] for the residuals (see Online Resource 1 for details). Failure to deal with autocorrelation will give too narrow confidence intervals and can cause overfitting [20, 21].

2.3.2 How the CVP waveform changes after a fluid bolus

To illustrate the type of responses that can be estimated, we fitted a GAM to two one-minute sections of a CVP recording: the first section before administration of a 250 ml fluid bolus and the other after. Separate splines were fitted to each section:

$$\begin{aligned} CVP = \alpha + \beta_s &+ f_s\left(pos_{cardiac}\right) + f_s\left(pos_{ventilation}\right) \\ &+ f_s\left(pos_{cardiac}, pos_{ventilation}\right) + f_s(time) + \epsilon, \end{aligned}$$

where β_s is an additional constant, that is zero for the pre-fluid section, and f_s is a spline for each section of data (before or after 250 ml fluid). This model also extends the previous model (Fig. 5) by using an *adaptive* smoothing spline to estimate $f_s\left(pos_{ventilation}\right)$. An adaptive smoothing spline allows the spline's smoothing parameter to vary across the range of the independent variable. This allows the spline to adapt to the sharp transition between inspiration and expiration, and to fit a subtle disturbance at the beginning of the expiration[2] while remaining smooth in areas where there is no change in the effect of the independent variable on the response. The model is visualised in Fig. 6. We see that after fluid, this subject's CVP varies more over a cardiac cycle, but less over a respiratory cycle, compared to before fluid. This is clearest in Fig. 6d. In Fig. 6c, we show the predicted CVP at end expiration and at end inspiration before and after fluid. This lets us compare how the interaction between the cardiac cycle and the respiratory cycle changes with fluid administration. The pressure during atrial contraction (*a* wave in Fig. 6c) increases with fluid, but the effect of ventilation on this pressure is lower after fluid. Another interesting difference is the shape of the *v* wave, representing the pressure in the right atrium before the tricuspid valve opening. Before fluid, the *v* wave has a flat peak, but after fluid, it increases gradually and reaches a higher pressure. This difference disappears at end-inspiration.

[2] The small disturbance at the beginning of the inspiration corresponds to the closing of the ventilator solenoid valve at end-inspiration. The sudden drop in pressure makes the ventilator tubing move and disturb the adjacent CVP line. It is most visible in Fig. 6d, but can also be recognized in the residuals in Fig. 5f.