Clinical Commentary

Clinical Usefulness of Respiratory Variations in Arterial Pressure

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There is increasing interest in the use of respiratory variations in arterial pulse pressure to predict the $\dot{Q}$ response to a fluid challenge (1–4). This has likely evolved because of the appreciation that excess fluid infusion is harmful, as well as concerns over invasive monitoring (5). Thus, techniques that provide noninvasive assessment of volume status hold great promise. The major impetus for these tests came from the work of Perel and coworkers (6) who followed-up on a preliminary report by Coyle and coworkers (7). They defined the difference between maximum and minimum arterial systolic pressure during a respiratory cycle as systolic pressure variation (SPV) (6). The inspiratory increase in pressure relative to the value at end-expiration was called dUp, and the fall in pressure relative to the end-expiratory value was called dDown (Figures 1 and E1). The larger the dDown and SPV, the larger the predicted increase in $\dot{Q}$ with volume loading.

PHYSIOLOGIC BASIS OF THE PHENOMENA

Many factors contribute to stroke volume and arterial pressure variations during the respiratory cycle, but most have only quantitatively small effects. Respiration effects the circulation by changing pleural pressure (Ppl) and thus the relationship of intrathoracic structures to extrathoracic structures (8), by changing right and left ventriclar loading (9–13), and by changing neurohumeral activity (14). During normal tidal breathing, neurohumeral variations are small and will not be discussed further.

Interaction of Cardiac Function and Return Function

A major determinant of SPV is the interaction of the function that defines the return of blood to the heart (venous return function) and the function that determines the performance of the heart (cardiac function) (15). As described by Guyton, these can be graphically presented together with Pra on the x axis (16)(Figure E2).

Both functions have important limits (Figure E3). When the pressure in the great veins is less than the surrounding pressure, the veins collapse and produce what is termed a vascular waterfall (17). Under waterfall conditions, further decreases in downstream pressure, i.e., right atrial pressure (Pra), no longer affect in-flow and an increase in cardiac function does not increase $\dot{Q}$.

Cardiac function limitation is due to constraints on cardiac filling by the pericardium, cardiac cytoskeleton, or mediastinal structures (18). These create a plateau to the cardiac function curve (19). On the ascending part of the cardiac function curve, increases in return function increase $\dot{Q}$ and represent a volume-responsive phase. However, on the plateau of the function curve, increases in return function do not change $\dot{Q}$ (Figure E4). The plateau thus represents a volume nonresponsive phase, and Pra can even decrease without a fall in $\dot{Q}$.

Effect of Changes in Ppl

By changing the relationship of the pressures in the heart to the rest of the body, changes in Ppl alter the inflow to the right heart and the outflow from the left heart. Outflow from the right heart and inflow to the left heart, however, are not directly affected because both upstream and downstream compartments are equally altered by the change in Ppl. Based on studies by Scharf and coworkers (20) and the demonstration by Deneault and coworkers (21) that opening the chest greatly reduces SPV, I consider the change in Ppl to be the dominant determinant of SPV. This assumption is also supported by the usefulness of respiratory variations in Pra for the prediction of volume responsiveness in patients with spontaneous respiratory efforts (22).

First consider the effects on the right heart (Figure E5). When the heart operates on the ascending part of the function curve, an increase in Ppl raises Pra relative to atmosphere and decreases venous return and right ventricular stroke volume (assuming a constant heart rate). In subsequent beats, left ventricular stroke volume and arterial pressure decrease. This should produce a prominent dDown and SPV and $\dot{Q}$ should be volume responsive. When the heart operates on the plateau of the function curve, there is no fall in venous return with the rise in Ppl and therefore no decrease in right and left ventricular stroke volume (Figure E6). There should only be a small dDown, and volume infusion will not increase $\dot{Q}$. However, a large enough rise in Ppl could shift the cardiac function sufficiently so that the return function intersects the ascending part of the cardiac function curve (Figure E6). This would create a dDown that should decrease with volume loading, but the volume will not necessarily increase $\dot{Q}$, as was observed in one study (23)(Figure E7).

A decrease in Ppl lowers intracardiac pressure relative to atmosphere and increases the gradient for venous return. If the return function is not limited and intersects the ascending part of the cardiac function curve, the decrease in Pra results in increased right heart filling and stroke volume (Figure E8). Left ventricular stroke volume and arterial pressure will subsequently rise during expiration, which is in the opposite direction of what is observed when Ppl increases (Figure E9).

The return function also can change with respiratory effort. Forced expiration raises abdominal pressure and transiently increases the filling pressure of the right heart. Stroke volume will rise if the heart is functioning on the ascending part of the function curve but not if it is functioning on the plateau (Figure E10). This will produce false-positive results in the SPV test.

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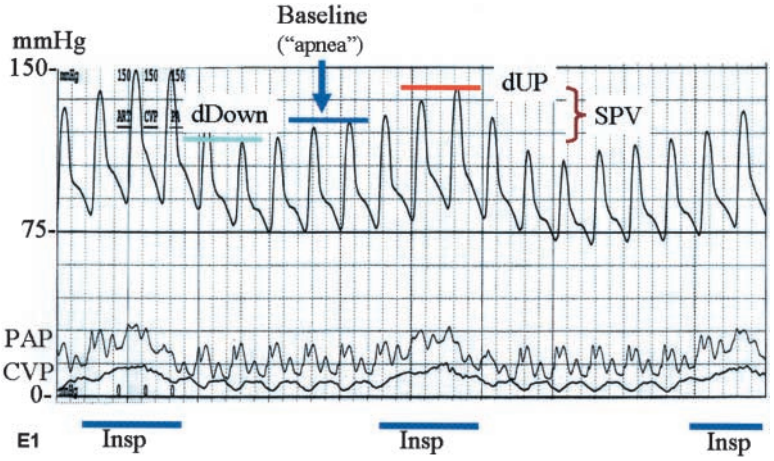

Figure 1. Example of respiratory variation in arterial pressure. The pulmonary artery pressure (PAP) and central venous pressure (CVP) show a rise in pressure during inspiration. The dUp and dDown components of spontaneous variations in arterial pressure are shown. The *bars* at the bottom mark inspiration. The *arrow* at the point marked "apnea" represents the end-expiration value for determining dUp and dDown.

The effects of changes in Ppl on the left heart are much more complicated. First, aortic pressure is determined by its elastance and volume. The volume is dependent on what comes in, i.e., the stroke volume, and what goes out, which in turn is determined by the resistance draining the aorta. Elastance of the aorta is curvilinear so that change in pressure for a change in volume increases with increases in initial aortic volume (24)(Figure E11). Thus, a stroke volume that enters at a high initial aortic volume will produce a larger pulse pressure than one that enters at a lower initial volume. Aortic elastance varies with age and disease and so will the relationship of stroke volume to pulse pressure. For a given $\dot{Q}$, stroke volume also varies with heart rate and therefore so will pulse pressure. Thus, the relationship of stroke volume to pulse pressure varies widely in the population, and this greatly limits quantitative predictions.

An area of some confusion is that of the "direct" effect of Ppl on thoracic structures. If the heart were simply a fluid-filled compliant ball in the chest, with no inflow or outflow, changes in Ppl would be directly reflected in the heart. This simple relationship, though, does not occur, for changes in intra-cardiac pressure change cardiac filling and emptying. The effect of changes in Ppl on aortic pressure is much more complicated. A change in Ppl changes the pressure in the aorta only in so much as it changes the diameter and thus volume of the thoracic portion of the aorta. This effect should be small, considering the magnitude of Ppl changes with tidal breaths, aortic elastance, and the percentage of the aorta in the chest. Thus, in diastole, the direct effect of changes in Ppl on aortic pressure should be small and not the same as that on the heart.

During systole, the aorta is in a continuum with the ejecting left ventricle, which is directly affected by changes in Ppl. The effect of changes in Ppl depends on where the change occurs in the cardiac cycle. For simplicity, I will consider a change in Ppl in diastole. An increase in Ppl raises left ventricular pressure relative to extrathoracic regions but has a minimal effect on aortic diastolic pressure. During systole, the rise from left ventricular end-diastole pressure to end-aortic diastolic pressure is decreased; thus the aortic valve opens earlier and stays open longer. Based on a Sagawa pressure–volume analysis (25), stroke volume will increase and so will aortic pressure (*see* Figure E12), which explains dUp. Furthermore, the end-systolic pressure–volume relationship effectively shifts to the left because of the change in reference pressure relative to atmosphere (Figure E12) and allows increased ejection that is not simply related to a change in afterload. However, because the major vascular reservoir is extrathoracic and increased left ventricular injection has only a small immediate effect on right ventricular output (26), the increase in left ventricular stroke volume cannot be sustained. One could predict that volume loading should result in an increase in dUp because there is more volume in the left ventricle to eject and, indeed, dogs in heart failure had an increase in dUp but the effect is small. Furthermore, changes in Ppl, change systolic and diastolic pressures in the same direction, but the magnitudes are different because aortic elastance varies with volume and arterial runoff increases with increases in aortic pressure. I thus challenge the assumption made by a number of workers (27–29) that "direct" effects alter systolic and diastolic aortic pressures equally.

With spontaneous breaths, the opposite occurs. The aortic valve opens later and closes earlier, so that stroke volume is decreased. Thus, systolic and diastolic aortic pressures decrease.

Changes in Loading

Afterload determines the velocity and degree of muscle shortening when a muscle contracts against a constant load (30). The analysis *in vivo* is complicated because ventricular pressure changes during ejection. On the right side, the increase in transpulmonary pressure with lung inflation increases right ventricular afterload (31). On the left side, the change in Ppl changes left ventricle pressure relative to the rest of the body This alters the timing of left ventricular ejection as well as ventricular loading; an increase in Ppl decreases the afterload (32) and a decrease in Ppl increases the afterload (33, 34). Although the steady-state effect of the typical respiratory changes in afterload is small (35), the beat-to-beat effects can be large because they combine with the timing effect. These likely account for the large transient inspiratory changes in stroke volume readily seen in Doppler studies (36).

EXPERIMENTAL STUDIES IN ANIMALS

Perel and coworkers found that graded hemorrhage progressively increased SPV and dDown in mechanically ventilated dogs, and reinfusion of the volume (6) reversed the increase. The dUp was not affected by changes in volume. This is consistent with dDown being related to a fall in left ventricular stroke volume during expiration. In a subsequent study, they applied external chest compressions synchronized to inspiration in dogs with congestive failure. They found that dDown was reduced, which is consistent with the heart operating on the plateau of the function curve and therefore not being volume responsive; dUp increased with heart failure, possibly because the failing

heart responded more to decreased ventricular loading and possibly due to slower aortic emptying of the transiently increased stroke volume. Chest compression during inspiration primarily increased dUp, which is consistent with the dUp being related to increased left ventricular pressure relative to extrathoracic vessels (37). The increase in dUp with chest compression and lack of effect with hemorrhage, argues against dUp being related to emptying of pulmonary capacitance vessels (38). In another study, these authors showed that SPV is greater when the arterial pressure is reduced by hemorrhage than when it is reduced by pharmacologic vasodilation (39), indicating that it is related to volume status and not vascular resistance. In these studies, changes in SPV with changes in volume were mainly due to changes in dDown, for dUp changed by only a small amount and not always in the same direction. Thus, based on these studies and the theoretic analysis, dDown should be the better parameter for determining volume responsiveness but SPV is much easier to obtain.

From these studies, it is clear that changes in dDown and SPV reflect changes in volume status. However, it needs to be emphasized that these studies were all done in anesthetized and paralyzed animals with highly controlled ventilatory parameters. Furthermore, the linear relationship of changes in SPV and dDown to changes in volume (6) is not easy to explain. On the ascending part of the cardiac function curve the leftward shift of the return function that occurs with hemorrhage should not alter the change in stroke volume with an increase in Ppl and therefore not alter SPV. An explanation is that Pra probably started on the plateau of the function curve, and the heart moved progressively off the plateau (Figure E13).

HUMAN STUDIES

Coriat and coworkers (40) performed the first clinical assessment of SPV for the prediction of volume responsiveness. They also performed transesophageal echocardiography to measure left ventricular diameters and correlated changes with changes in SPV. The dDown and SPV correlated inversely with the end-diastolic area, but there was a lot of variability, so that the predictive value in individual patients was poor. Decreases in SPV and dDown were linearly related to volume given but, interestingly, changes in $\dot{Q}$ were poorly related to the magnitude of initial dDown. As discussed previously, the physiology would not predict a linear quantitative relationship. Furthermore, when the heart operates on the volume unresponsive part of the function curve, a sufficiently large increase in Ppl will decrease venous return and produce SPV, but volume infusion will only correct this extreme part of the respiratory cycle and therefore abolish SPV but have only a small effect on $\dot{Q}$ (Figure E7).

Rooke and coworkers (41) examined the effects of both volume removal and infusion on SPV and gave quantitative guidelines for fluid resuscitation. The variability in the measurement was large, which makes simple recommendations difficult, even if one matches the ventilatory parameters and chest wall compliance. A major limitation of this study is that there was no measurement of $\dot{Q}$, the truly important variable. They also examined spontaneously breathing subjects and not surprisingly, SPV was not at all predictive.

Tavernier and coworkers studied SPV in patients with sepsis (23). They classified patients as responders and nonresponders on the basis of the change in $\dot{Q}$ with volume loading, and then tested the ability of SPV and dDown to appropriately identify them. Nonresponders had lower initial SPV and lower dDown. A dDown of 5 mm Hg or less predicted that $\dot{Q}$ was unlikely to respond to volume loading. Discrimination between responders and nonresponders was much better with dDown than with the pulmonary artery occlusion pressure or left ventricular end-diastolic area. Of importance, when the change in stroke volume was plotted against dDown, the variance of the data was much greater with large dDown, which indicates as expected that dDown predicts the change but not the magnitude.

In summary, animal and human studies indicate that SPV, and even more so, dDown are sensitive parameters for qualitative but not quantitative prediction of the response to volume infusion. However there are some important caveats. This only applies to patients who do not have *any* spontaneous inspiratory *or* expiratory efforts. In the one study that included spontaneously breathing patients (41), SPV was "problematic," and dDown could not be used. Furthermore, ventilation parameters were standardized and V_Ts in the study on patients with sepsis were much larger than those used today (42, 43). Lower V_Ts will reduce the inspiratory decrease in venous return and the magnitude of the fall in stroke volume (44). Thus, specific values of dDown or SPV are not generalizable.

ARTERIAL PULSE PRESSURE

Michard and coworkers (27, 28) tried to make SPV more specific by examining respiratory changes in pulse pressure. They calculated the difference between maximum and minimum pulse pressure during the ventilatory cycle and normalized the difference to the average of the maximum and minimum pulse pressure (dPP). They reasoned that pulse pressure is more related to stroke volume than systolic pressure and should not be affected by direct transmission of Ppl pressure to the aorta, but I have already discussed my problem with this reasoning. Thus, this test too, would likely be better if only the decrease in pulse pressure from end-expiration were used (the equivalent of dDown). On the other hand, the predictive value was still strong, and dPP is much easier to measure than just the dDown component. They first showed that dPP correlated well with PEEP-induced changes in cardiac index, and the increase in dPP with an increase in PEEP correlated with the decrease in cardiac index (27). They found that dPP could be used in patients with sepsis to predict volume responsiveness of cardiac index with high specificity and sensitivity and that it was better than SPV (28). Volume expansion, decreased dPP, and the decrease in dPP correlated with the increase in $\dot{Q}$, so that a decrease in dPP could be used to indicate a successful increase in $\dot{Q}$ after volume infusion. Although the predictive value of dPP for classifying patients as responders and nonresponders was high, a change in cardiac index of 20% was observed with dPP ranging from 10 to 30%.

As in SPV studies, subjects were either paralyzed or sufficiently sedated so that they had no voluntary ventilatory effort. Thus, these results, too, cannot be generalized to patients with *any* spontaneous ventilatory efforts, including inspiratory triggered breaths or active expiratory efforts. With a spontaneous inspiratory effort, there is a rise in right heart filling and a fall in left ventricular output. The combined increase in right-sided output and increased left ventricular residual volume, can lead to larger dPP, but with the peak during expiration (*see* Figure 1 in Reference 41)(Figure E9). If the breath is triggered with an initial decrease in Ppl, followed by a ventilator-induced rise in Ppl, the results are very hard to predict because they depend on the size of the inspiratory effort, the response of the ventilator, the chest wall compliance, the volume status, as well as other factors.

A very significant problem with all these tests is recruitment of abdominal muscles and forced expiration, which is a very common phenomena in patients in the intensive care unit. This can occur in association with spontaneous inspiratory efforts, as

well as with nontriggered breaths. The consequence is a large rise in arterial pressure during expiration, with or without a change in stroke volume. This means that SPV and dPP will not be useful in a large part, if not the majority of patients in the intensive care unit.

Some other technical factors must be considered before trying to predict fluid responsiveness with respiratory changes in arterial pressure. The change in Ppl is dependent on the volume of the breath and the compliance of the lungs and chest wall. Indeed, Perel and coworkers bound dog's chests to increase the otherwise low signal (6). Conversely, patients with tense abdomens have decreased thoracic wall compliance and will have much greater changes in Ppl for a given V_T (Figures E14–E17). Therefore, caution should be exercised before using these tests in patients undergoing laprascopic surgery for they have high abdominal pressure. Furthermore, in most studies (23, 27, 40, 41), patients were ventilated with V_Ts of 8 to 12 ml/kg, which is higher than the standard used today for patients with lung injury (42). This means that quantitative recommendations from these studies do not apply to most patients today.

We recently had a case that brings up a potential false-positive SPV test. The patient had a Pra higher than 20 mm Hg but yet had a SPV of almost 30 mm Hg and therefore would have been expected by this test to respond to volume but did not. A possible explanation for the SPV in this case is that the right ventricle was overdistended and the increase in Ppl during inspiration decreased venous return and decompressed the right ventricle, thus allowing improved left ventricular ejection as shown by Atherton and coworkers in patients with uncompensated heart failure (45).

STROKE VOLUME VARIATION

Because SPV and dPP are used as surrogates for stroke volume variations, it is not surprising that results with techniques that measure stroke volume variation are similar to those with SPV and dPP (36, 46–48). In these studies there is also large variance in the $\dot{Q}$ for a given stroke volume variation, and these measures have not been shown to be superior to SPV. Furthermore, continuous stroke volume is calculated from the pulse pressure contour and requires regular calibration of the signal by a thermodilution $\dot{Q}$ (49). Thus, it makes more sense to just follow the adequacy of the $\dot{Q}$ rather than a surrogate. True beat-to-beat variations can be obtained with transesophageal echocardiography (36, 50), but this has much more limited use.

CLINICAL ROLE

SPV, dPP, and stroke volume variation predict volume responsiveness under specific conditions, but just because a patient *can* respond to fluids, does not mean that the patient *needs* fluid. It is likely that most of the readers of this paper would have an increase in $\dot{Q}$ if given a fluid bolus, but this does not mean that they *need* fluid. The actual need for fluid should be based on another set of clinical criteria and as noted by others (2, 4, 49), this has not been studied. Studies of these tests typically purport to monitor for "optimizing fluid therapy" (46) but give no measure of clinical efficacy.

CONCLUSIONS

The trends over time in the respiratory variations in arterial pressure and stroke volume can provide a qualitative guide to fluid responsiveness in patients with no inspiratory or expiratory efforts. However, quantitative recommendations are not generalizable, because the magnitude is affected by the individual patient's heart rate, aortic properties, V_T, chest wall characteristics, and lung compliance. These tests are of no value in patients who have *any* ventilatory effort, including forced expiration. This excludes a large percentage of patients in the intensive care unit. Finally, regarding the impact on clinical decision making, it needs to be emphasized that a *potential* increase in $\dot{Q}$ in response to fluids does not mean that the patient *needs* the increase in $\dot{Q}$.

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