Occasional reviews

Pulse transit time: an appraisal of potential clinical applications

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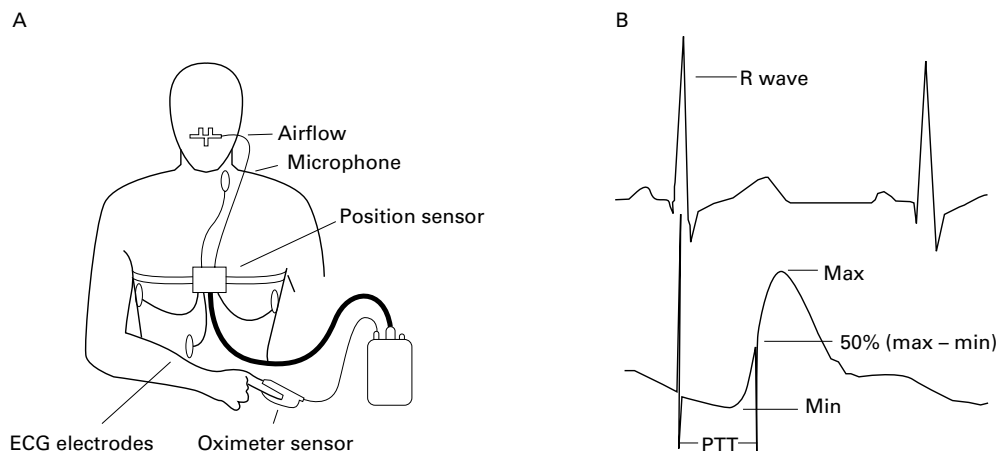J Argod
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Current techniques for investigating patients with suspected sleep disordered breathing are inadequate. Not only are many of the tests expensive, but they are also cumbersome and many centres require these investigations to be performed in the sleep laboratory. At the heart of the problem is the difficulty in identifying and quantifying the spectrum of respiratory events responsible for the sleep fragmentation and disabling excessive daytime sleepiness that is characteristic of obstructive sleep apnoea and its related conditions. Obstructive apnoeic episodes are not usually difficult to detect, even when only a basic measure of respiratory effort such as thoracic and abdominal movement is used. On the other hand, correctly identifying obstructive hypopnoeas and episodes of upper airway resistance needs a sensitive measure of airflow and inspiratory effort. The measurement of swings in pleural pressure by oesophageal manometry is the current gold standard technique for detecting changes in inspiratory effort. However, the placement of an oesophageal catheter is often uncomfortable and unacceptable, it may modify the upper airway dynamics,[1] and some believe that it contributes to the sleep disturbance during the sleep study, though this is disputed.[2] Furthermore, this technique is available in only a proportion of sleep laboratories and, if performed, adds significantly to the cost of the sleep study. These issues pose a clinical dilemma because it is important to detect and define hypopnoeas and upper airway resistance episodes as they are as relevant as apnoeas in producing sleep fragmentation.

The assessment of sleep structure also creates problems. Not only is high quality electroencephalographic (EEG) monitoring difficult to achieve outside the laboratory, but the scoring is laborious in terms of technician time and is hence expensive. In addition, there remains uncertainty regarding the definition of an arousal.[3] It is likely that "micro-arousals" which fall short of the standard EEG criteria for arousal[4] may contribute significantly to the patient's hypersomnolence.[5] It is well recognised that not all obstructive respiratory events end with a recognisable arousal. Indeed, in normal individuals "non-visible" sleep fragmentation caused by repetitive auditory stimulation has been shown to cause significant daytime sleepiness in normal subjects.[6] It has also been shown that some stimuli, which are not

sufficient to produce cortical arousals detectable on the EEG, may nevertheless result in an acute rise in blood pressure.[7] The clinical significance of these "subcortical" autonomic arousals is not clear and is the focus of much research activity. If both "micro-arousals" and "subcortical" arousals turn out to be important in terms of excessive daytime sleepiness and cardiovascular risk, then methods which detect the associated sympathetic and cardiovascular activation may be more relevant than cortical arousals detected with EEG.

It is clear that new techniques for detecting signs of arousals and changes in respiratory effort are needed. Ideally they should be less invasive, more practical, and cheaper than (but as reliable as) current tests used for investigating patients with suspected sleep disordered breathing. Pulse transit time (PTT) is a physiological measure which shows promise in these respects, not only in the sleep laboratory but also in domiciliary sleep studies. In this review we will briefly describe how it is measured and where its possible clinical applications might be. Also discussed are the limitations of PTT and areas requiring validation and further development.

What is pulse transit time?

Pulse transit time refers to the time it takes a pulse wave to travel between two arterial sites. The speed at which this arterial pressure wave travels is directly proportional to blood pressure. An acute rise in blood pressure causes vascular tone to increase and hence the arterial wall becomes stiffer causing the PTT to shorten. Conversely, when blood pressure falls, vascular tone decreases and PTT increases. We do not know of any published comparison between PTT and blood pressure measured using an indwelling arterial line. However, the Oxford team has reported a comparison between PTT values and non-invasive measurement of blood pressure using "Finapres"[8] which shows that PTT is inversely proportional to blood pressure. Absolute values of PTT cannot be extrapolated as absolute values of blood pressure at a given point in time, but PTT is capable of predicting changes in blood pressure over a short period of time. Lea *et al* have shown that swings in pleural pressure during obstructed inspiration can be estimated from the changes in systolic blood pressure as measured non-invasively by the "Finapres".[9]

PTT is not particularly well correlated with absolute blood pressure values at a given point in time, but it is capable of predicting changes in blood pressure over a short period of time. Indeed, since the 1970s it has been used in a number of different scenarios as a non-invasive surrogate marker of changes in blood pressure. In investigations of patients with suspected sleep disordered breathing, PTT has recently been proposed as a means of quantifying respiratory effort by detecting changes in the blood pressure oscillations associated with pleural pressure swings (pulsus paradoxus).[8] Likewise, the blood pressure surges associated with micro-arousals can also be detected by PTT,[10] thus offering the possibility of estimating sleep fragmentation without the need for EEG recordings.

Originally PTT was measured by recording the time interval between the passage of the arterial pulse wave at two consecutive sites. More recently, for ease of measurement, the electrocardiographic R or Q wave has been used as the starting point as it corresponds approximately to the opening of the aortic valve (fig 1). Advances in technology have allowed accurate estimation of the arrival of the pulse wave at a peripheral site such as the finger using photoplethysmography. Other sites where an arterial wave form can be detected such as the ear lobe can also be used, though they are less convenient. Conventionally the point on the photoplethysmograph pulse wave form which is either 25% or 50% (depending on which equipment is used) of the height of the maximum value is taken to indicate the arrival of the pulse wave. Using ECG leads and finger photoplethysmography reproducible PTT measurements can be made very simply. A new PTT value is available with every heart beat and it is typically oversampled at 5 Hz to ensure no values are missed. The equipment needed to measure this physiological signal is commercially available, relatively cheap, and portable.

Using the electrocardiographic R wave as a starting point is convenient as it is easily identifiable, but it introduces an inaccuracy as there is a short delay between the occurrence of the R wave and the opening of the aortic valve (isometric contraction time). The "measured" PTT therefore includes this time interval in addition to the time taken for the pulse wave to travel from the aortic valve to the periphery ("true" PTT). Isometric contraction time is itself influenced by the variables that affect PTT such as blood pressure and ventricular stroke volume.[11] It has been shown that much of the lengthening in "measured" PTT during increased inspiratory effort is due to a prolongation of isometric contraction time rather than "true" PTT.[12] These changes in isometric contraction time are in fact advantageous when attempting to measure changes in respiration as they amplify the PTT signal and hence increases in inspiratory effort are more easily detectable.

Potential clinical uses for pulse transit time

MEASUREMENT OF RESPIRATORY EFFORT

Identifying changes in inspiratory effort is one of the key aims of a sleep study. Detection of dysynchrony between the rib cage and abdominal components of respiration is the most widely used tool for detecting upper airway obstruction and increased respiratory effort during sleep. However, this technique is difficult to standardise as there is considerable variation with body position, sleep stage, and degree of obesity, and the criteria used for scoring vary from centre to centre. Several other non-invasive methods for detecting obstructive events have been proposed. Condos et al have shown that plateauing of the inspiratory wave form derived from a pneumotachograph while under continuous positive airway pressure (CPAP) therapy correlates with increases in upper airway resistance.[13] Hosselet et al have suggested that a nasal cannula pressure transducer can be used to distinguish central from obstructive respiratory events.[14] In this study the flow/time contour becomes flattened during an obstructive event, whereas it becomes rounded during central events when the upper airway resistance is low. This technique, which remains unvalidated in large clinical trials, is compromised if there is significant mouth breathing[15] and, in addition, the inspiratory flow pattern can be difficult to interpret as there is considerable inter-subject variability as a consequence of differences in shape and compliance of the upper airway.[16] Forced oscillometry is another non-invasive
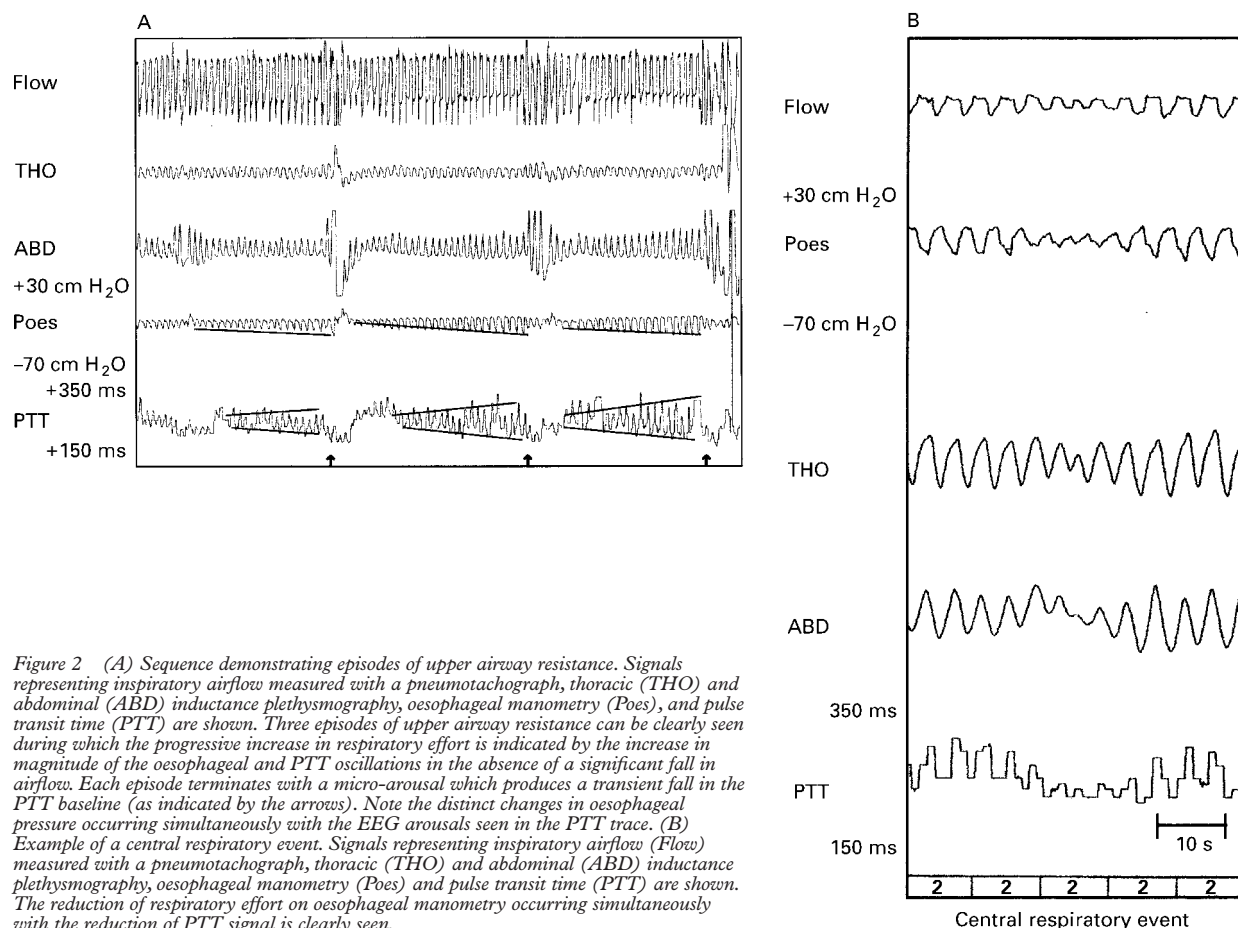
Figure 2 (A) Sequence demonstrating episodes of upper airway resistance. Signals representing inspiratory airflow measured with a pneumotachograph, thoracic (THO) and abdominal (ABD) inductance plethysmography, oesophageal manometry (Poes), and pulse transit time (PTT) are shown. Three episodes of upper airway resistance can be clearly seen during which the progressive increase in respiratory effort is indicated by the increase in magnitude of the oesophageal and PTT oscillations in the absence of a significant fall in airflow. Each episode terminates with a micro-arousal which produces a transient fall in the PTT baseline (as indicated by the arrows). Note the distinct changes in oesophageal pressure occurring simultaneously with the EEG arousals seen in the PTT trace. (B) Example of a central respiratory event. Signals representing inspiratory airflow (Flow) measured with a pneumotachograph, thoracic (THO) and abdominal (ABD) inductance plethysmography, oesophageal manometry (Poes) and pulse transit time (PTT) are shown. The reduction of respiratory effort on oesophageal manometry occurring simultaneously with the reduction of PTT signal is clearly seen.

method capable of detecting changes in upper airway resistance during sleep. By applying a small pressure oscillation through a face mask, superimposed onto the patient's own spontaneous breathing, changes in upper airway impedance can be detected during sleep. A study in patients with severe sleep apnoea suggested that forced oscillometry may be a clinically useful tool for detecting obstructive respiratory events.[17]

Oesophageal pressure monitoring remains the reference technique for detecting changes in inspiratory effort and is particularly useful if the upper airway resistance syndrome is suspected.[18] However, for the reasons already discussed it cannot always be applied and, in any case, it is not available in all centres. PTT, on the other hand, is non-invasive, well tolerated, and easy to measure. PTT fluctuations have been shown to be correlated with inspiratory effort against a threshold valve in awake normal volunteers.[19] As is the case with blood pressure, individual PTT values correlate poorly with absolute intrathoracic pressure values. However, in a study of patients with obstructive sleep apnoea a good correlation between the amplitude of PTT oscillations (ΔPTT) and the magnitude of negative pleural pressure swings, as measured by oesophageal manometry, was found during upper airway obstructive events.[8 10] On the basis of this the authors concluded that PTT allows a quantitative estimate of inspiratory effort to be made.

Data from our centre show that PTT has good sensitivity (91%), specificity (95%) and negative predictive value (95%) at differentiating obstructive from central apnoeas and hypopnoeas when compared with oesophageal pressure monitoring, the gold standard.[20] Absolute Poes values, at a given point in time, cannot be directly calculated from changes in PTT but an increase in ΔPTT values can be used to detect obstructive hypopnoeas or upper airway resistance episodes (fig 2A). Conversely, with central hypopnoeas/apnoeas a decrease in ΔPTT is observed (fig 2B). When this visual pattern is used to distinguish obstructive from central events, good interobserver agreement (95%) can be achieved.[20] This is clinically important as the treatment of obstructive and central respiratory events are quite different and making the distinction can be difficult unless a good measure of respiratory effort is available. Likewise, identifying episodes of upper airway resistance is considered by most centres to be important but this too is difficult and, in the absence of detectable hypoxaemia or reduction in airflow, has traditionally relied on oesophageal manometry to detect the increased fluctuations in pleural pressure associated with increased upper airway resistance. It is possible that PTT may provide an effective alternative to oesophageal manometry for detecting these events (fig 2A), but as yet there are very few data available to show this. PTT is not capable of recognising different patterns of obstructive

events such as apnoeas, hypopnoeas, and upper airway resistance episodes. This needs an additional signal such as nasal pressure which can measure airflow semi-quantitatively and identify hypopneas.[14] Using the inspiratory waveform—that is, flattened during an obstructive event or rounded during a central event— nasal pressure can also provide useful information regarding the nature of the respiratory event. The properties of PTT and nasal pressure complement each other and the combination of these two signals may provide a powerful technique for classifying respiratory events. This remains to be shown in clinical studies.

An alternative way of using PTT to provide an index of respiratory effort is to calculate the mean ΔPTT over the whole night. Rather than analysing individual respiratory events, this technique permits a global assessment of respiratory effort to be made. This is less useful for diagnostic purposes but has been used for comparing the effects of specific treatment modalities such as mandibular advancement devices.[21] Clearly this is a rather crude method and, as there is significant variation in upper airway resistance during sleep even between normal individuals,[22] this technique is likely to be limited to within individual comparison.

DETECTION OF MICROAROUSALS

PTT has the advantage over oesophageal pressure monitoring that it is also capable of detecting micro-arousals.[10] Irrespective of whether the respiratory event is a full blown apnoea, a hypopnoea, or an episode of upper airway resistance, the associated arousal is accompanied by changes in heart rate and by a transient burst of sympathetic activity which in turn produces a characteristic surge in blood pressure. Using beat to beat blood pressure monitoring it has been possible to score these cardiovascular changes to estimate sleep fragmentation.[7 23] These "autonomic arousals" are also easily recognisable with PTT which exhibits a transient but significant dip in the baseline value (fig 2). In this way PTT has been shown to be a sensitive marker of arousal in normal volunteers using auditory stimuli.[10] In a study of patients undergoing investigation for suspected sleep apnoea, PTT defined arousals correlated well with oximetric desaturation ($r = 0.71$) and EEG micro-arousals ($r = 0.65$).[24] Although not fully validated for this purpose in clinical practice, some centres already employ PTT for the detection of micro-arousals. Clearly, if a simple technique such as PTT has the ability to detect micro-arousals without the need for EEG or other complicated physiological monitoring, then it offers great potential as part of a simplified investigation package, particularly in the field of domiciliary studies.

Heart rate rises during the apnoea and rises further at apnoea termination, with resumption of ventilation. These heart rate changes, which reflect alterations in sympathetic function, may be useful for identifying autonomic arousals. The burst in sympathetic activity associated with the termination of a respiratory event also produces a surge in heart rate. Detecting such heart rate changes may be usful for detection of autonomic arousals. Automated Fast-Fourier transformation techniques measuring R–R variability are less useful as they require a period of stable heart rhythm which is rarely present during periods of apnoeic interrupted breathing. However, a visual analysis of heart rate variations could be used in conjunction with PTT to further improve the recognition of autonomic arousals.

There remains considerable debate as to what in fact constitutes a clinically significant microarousal. Definitions using EEG criteria vary[4 5] and they correlate poorly with either objective or subjective measures of daytime sleepiness. There are marked regional variations in the distribution of alpha activity associated with arousal. It is therefore possible that standard EEG monitoring may miss some cortical microarousals, and equally it is possible that not all "cortical arousals" detected are clinically relevant in terms of causing excessive daytime sleepiness. It has been suggested that frontocentral alpha activity may be related to sleep maintenance rather than sleep disturbance[25] which, if the case, would have important implications for the definition of EEG arousal. It is likely that some arousals cannot even be detected with optimal EEG monitoring. These "subcortical" or "autonomic" arousals still produce the classical surge in sympathetic activity which manifests in a transient rise in blood pressure and these cardiovascular changes, which form the final common pathway of arousal, can be detected by PTT. Although PTT arousals were not shown to be better correlated with subjective daytime sleepiness in the study by Pitson *et al*,[10] a more recent study by Bennett *et al*[26] of subjects representing the full spectrum of sleep disordered breathing has suggested that PTT autonomic arousals were at least as good as American Sleep Disorders Association (ASDA) defined EEG arousals at predicting the quality of life (SF36) and objective daytime sleepiness (OSLER test[27]) responses to nasal CPAP therapy. It is possible that this surrogate marker of arousal that measures the autonomic consequences of arousal may turn out to be more sensitive and clinically relevant than EEG scored arousals.

Problems with PTT

We have described a number of potentially useful ways in which PTT may be exploited in sleep investigation. However, this measure is not without certain flaws which may limit its usefulness in clinical practice. Some of these are potentially surmountable, whereas others are not.

MEASUREMENT TECHNIQUE

Although PTT can be used to estimate respiratory effort this measure should really be regarded as only semi-quantitative. As a PTT recording is only available with each cardiac cycle, measurements may fall on either side of the peak or trough of the blood pressure oscillation associated with respiratory effort and this results in a tendency to undersample (fig 3A). The ΔPTT may therefore not truly represent the maximum and minimum values of inspiratory effort. By the very nature of PTT
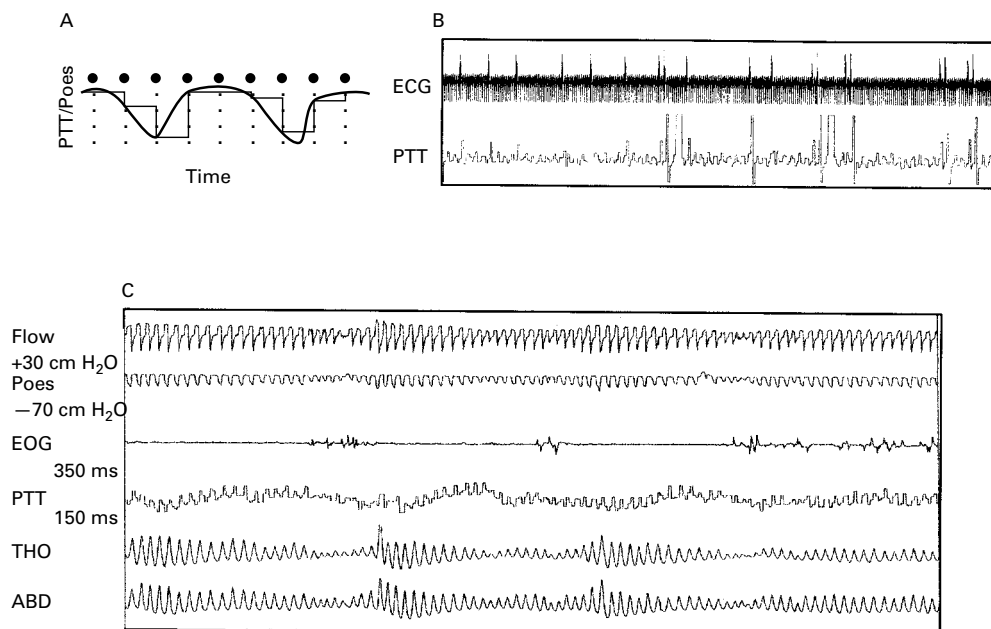
Figure 3 (A) Undersampling error of PTT signal. Each black dot represents a cardiac cycle. The thick and thin black lines represent oesophageal pressure and PTT, respectively. The trace shows two respiratory cycles of obstructive sleep apnoea. The nadir of the first cycle happens to coincide with the arterial pulse wave and therefore the PTT amplitude is an accurate representation of the Poes swing. The second respiratory cycle does not coincide with a pulse wave and consequently the PTT swing underestimates the Poes swing (adapted from Pitson et al[8]). (B) PTT artefact arising as a consequence of ventricular extrasystoles. This trace was recorded during a period of stable respiration. There are frequent ventricular extrasystoles resulting in artefact in the PTT recording which is particularly marked when two extrasystoles occur close together. (C) Difficulties of interpretation arising during REM sleep. REM sleep is associated with marked physiological variations in respiratory effort and airflow so identification of the classical pattern of PTT or Poes changes associated with obstructive respiratory events is more difficult. REM sleep is also associated with marked blood pressure changes and, as can be clearly seen, this causes the baseline PTT value to fluctuate, compounding further the interpretational difficulties. Shown here are inspiratory airflow measured with a pneumotachograph, oesophageal manometry (Poes), electro-oculography (EOG), pulse transit time (PTT), and thoracic (THO) and abdominal (ABD) inductance plethysmography.

recording it is technically not possible to overcome this problem, but this does not prevent accurate classification of individual respiratory events nor does it detract from the clinical usefulness of PTT.

The most troublesome problem with PTT measurement is that of artefact. This is almost always due to interference with the photoplethysmographic signal at the finger, but can also occur when chest wall movement disturbs the ECG leads. There may be a shift in the baseline which could be confused with the occurrence of a micro-arousal, or the artefact may be interpreted as a change in inspiratory effort. Such artefacts can usually be screened out if the signal is scored manually but, if automatic scoring is employed, then spurious interpretation can occur.

Scoring the PTT signal during REM sleep is difficult because this sleep state is associated with large variations in respiratory drive that are especially pronounced during phasic REM sleep (fig 3C). This physiological phenomenon makes recognition of classical PTT patterns associated with respiratory events difficult. The problem is not unique to PTT as it also affects oesophageal pressure recordings or, indeed, any method which uses changes in respiratory effort to recognise obstructive respiratory events. This is particularly unfortunate as REM sleep is a period associated with increased upper airway resistance and a higher frequency of both central and obstructive respiratory events. REM sleep is also associated with a labile haemodynamic state. There is an increase in sympathetic activity causing fluctuations in pulse rate and blood pressure, and consequently the PTT baseline is more variable. This variable baseline, which can be clearly seen in fig 3C, further compounds the difficulties encountered when reading a PTT trace.

Improvements in the technique of recording the ECG and photoplethysmographic signals may reduce the incidence of artefact, but overcoming the problems encountered in interpreting the variability of the respiratory effort signal during REM sleep will be difficult. Perhaps a system which interprets the respiratory effort and arousal aspects of PTT separately, and expresses the findings independently, may increase the clinical usefulness of this physiological measure and may also lend itself to the development of software algorithms which permit accurate automated interpretation.

PATIENT VARIABILITY
There is significant variation in PTT between individuals as a result of differences in blood pressure and vascular compliance. This does not unduly affect interpretation as it is the pattern of ΔPTT change by which respiratory events are scored. The estimation of the impact of variations in cardiac contraction on ΔPTT is unclear. Left ventricular dysfunction, cardiac conduction defects, cardiac pace makers, and vasoactive medication can all affect isometric contraction time and, as this time interval forms a major part of the measured PTT, the way in

which it behaves in response to arousal and to changes in respiratory effort is clearly important. There are very few data which describe the behaviour of PTT in these pathological states. From our own anecdotal experience it is known that cardiac arrhythmias such as atrial fibrillation render the PTT signal almost uninterpretable. This is potentially a major drawback as many patients with sleep disturbed breathing have co-existing cardiac disease (fig 3B).

In summary, the capability of PTT to identify and semi-quantitatively measure respiratory effort has been established.[10] PTT is able able to separate obstructive and central respiratory events adequately during polysomnography with a negative predictive value of 95%.[20] The value corresponding to the mean ΔPTT over the whole night provides a global index of respiratory effort sensitive enough to assess therapeutic efficiency when within individual comparisons are done.[21] Finally, PTT autonomic arousals seem at least as good as EEG arousals at predicting quality of life or subjective and objective daytime sleepiness.[21] Thus, experimental studies on small subsets of patients exist demonstrating the potential interest of PTT in clinical practice. However, such a parameter has not yet been extensively used except in two teams in Europe. The clinical usefulness of PTT needs to be confirmed by large scale investigations. Finally, further studies should be addressed to the potential limitations in subgroups of patients with arrhythmias and/or cardiac insufficiency. Clear statements regarding the validity of PTT in such situations will help to decide whether to add the technique to the technical armamentarium needed for sleep studies.

Conclusions

There is currently a need to simplify tests used in the investigation of patients with suspected sleep disturbed breathing without necessarily compromising the accuracy of their findings. PTT offers a number of advantages over more conventional physiological sleep tests in that it is easy to measure, well tolerated by patients, relatively cheap and, perhaps most importantly, is fully portable thus lending itself to domiciliary studies. Although experimental studies have proposed a clinical role for PTT, and indeed it is already used in some centres, it remains to be fully validated in clinical practice. A possible role might be as an alternative to oesophageal manometry for measuring respiratory effort as part of polysomnography. Its greatest potential, however, is likely to be as part of simplified sleep monitoring outside the sleep laboratory—be it on a general hospital ward or in the patient's own home. The ability to detect both changes in inspiratory effort and the presence of micro-arousals opens up all sorts of possibilities for the development of simplified diagnostic tests which would be welcome in the present climate where there is conflict between the drive to reduce health care costs and the need to deal with the rising number of patients being referred for investigation. Such a simplified diagnostic package would use PTT in conjunction with other easy to measure tests such as pulse oximetry, snoring detection, body position, and nasal cannulae inspiratory flow limitation detectors. Technical improvements for dealing with artefact and the development of software algorithms to permit automated interpretation may further improve the diversity of this simple physiological measure.

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