Abstract

Described by Jean Chevaillier in 1967, autogenic drainage is an airway clearance technique that is widely used throughout Europe. The technique is characterised by breathing control, where the individual adjusts the rate, depth and location of respiration in order to clear the chest of secretions independently. This paper describes the technique, based on the work of Chevaillier, offering a physiological explanation for how the technique works. This paper will also review the evidence supporting the use of autogenic drainage.

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Keywords: Chest physiotherapy; Airway clearance techniques; Autogenic drainage

Introduction

Autogenic drainage (AD) is an airway clearance technique that is widely used throughout Europe [1]. It is characterised by breathing control, where the individual adjusts the rate, depth and location of respiration within the thoracic cavity [2] in order to clear the chest of secretions independently. The technique was first conceived in Belgium by Jean Chevaillier in 1967, after he observed young asthmatic patients sleeping, laughing and playing. During this time, he noted an enhanced clearance of secretions compared with clearance following conventional forms of physiotherapy including postural drainage, clapping and vibration [2], and he attributed this to expiratory air flow [3]. Inspired by physiological papers published at this time [4,5], Chevaillier went on to describe a technique where the patient is trained to breathe in such a way that the velocity of expiratory flow is maximised and secretions are cleared.

Proximal movement of mucus is usually achieved by the expiratory air flow of tidal breathing [6], the action of the mucociliary escalator and an effective cough [7]. Some pulmonary pathology renders the respiratory system less able to generate expiratory forces through decreased elastic recoil, e.g. emphysema, renders the mucociliary system dysfunctional, e.g. in heavy smokers, and causes loss of bronchial calibre through bronchial wall instability or increased resistance, e.g. asthma and chronic bronchitis [6]. In addition, pathologies that combine some of these features are also characterised by an increase in secretion production, e.g. cystic fibrosis and chronic obstructive pulmonary disease. In cases of secretion retention, it may be necessary to perform an airway clearance technique. AD is a breathing technique, based on a series of physiological principles, that patients can adapt individually to suit their pathological status and lung function [3].

AD has been described by many authors with some variation, but this paper aims to provide a definitive description based on the work of Chevaillier. The technique was originally based on a series of physiological principles, and these have not been clearly and fully described by any source. Therefore, this paper also aims to offer a physiological explanation about how the technique works and will examine the evidence base for AD.

The AD technique

While performing the AD technique, the patient inspires a deeper than normal breath, described by Chevaillier [6] as the functional tidal volume (1.5–2 times the size of the normal tidal volume), and exhales in a gentle but active way. The aim of breathing in this way is to achieve the highest possible expiratory air flow simultaneously in different generations of

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the bronchi, keeping bronchial resistance low, and avoiding bronchospasm and dynamic airway collapse [8]. Under these circumstances, the speed of air flow may mobilise secretions by shearing them from the bronchial walls and transporting them from the peripheral airways to the mouth [1,9]. The specific style of breathing described is performed at different lung volumes, usually starting within the expiratory reserve volume (ERV) and progressing into the inspiratory reserve volume (IRV). Each component of the technique is described in detail below.

Preparation

Prior to starting the technique, the upper airways (nose and throat) should be cleared by huffing or blowing the nose. Inhalers or nebulisers should be taken as prescribed to moisten and dilate the airways, facilitating bronchial clearance. The patient should perform the AD technique throughout this inhalation therapy. Chevaillier [8] stated that experienced patients may evacuate up to 50% of their bronchial secretions during this period.

Position

Chevaillier [8] recommended that a ‘breath-stimulating’ position should be used, such as sitting upright or lying. The term ‘breath-stimulating’ is somewhat ambiguous, although it probably indicates that the patient must be able to breathe comfortably and without restriction.

Inspiration

Inspiration should be performed slowly through the nose [2,8,10], and the breath should be held for 2–4 seconds [3]. In order to perform a correct breath hold at the end of the desired inspiration, the breathing movement should be stopped in its three dimensions with the glottis remaining open. The inspiration should be performed diaphragmatically, and should be up to twice the size of a normal tidal breath, as described previously, depending upon patient ability, pathology and lung function.

A slow inspiration through the nose is needed to provide adequate warming and moistening of the air [2]. This prevents unnecessary coughing and subsequent airway collapse of the segment distal to the equal pressure point [11], or bronchospasm, both of which may prevent secretions from moving proximally. Slow inspiration also avoids ventilatory asynchronism [9], allowing for more even filling of the lung as obstructive areas are slower to fill. The alveolar pressure, or driving force [4], will subsequently be more uniform throughout, with only minor paradoxical air flow [10].

The breath hold also allows more time for obstructed areas of the lung to fill equally. Whilst the breath is held with the inspiratory effort suspended for several seconds and the glottis open, atmospheric air continues to move into areas of the lung that are not yet fully expanded. This is because gas flows from areas of higher pressure to areas of lower pressure, as in normal respiration [12].

Expiration

The expiration itself should be an active sigh. Breathing out may be through the nose or the mouth. Chevaillier [8] stated that expiration through the nose is preferable, provided that flow is not slowed in this way. However, breathing out through the mouth, keeping the glottis open, may enhance the auditory feedback needed to locate secretions. The glottis should remain open during expiration, and David [2] suggested breathing out as if steaming up a mirror or spectacles; if performed correctly, this manoeuvre will be completely silent as any noise such as sighing indicates that the glottis is partially closed. According to Chevaillier [8], the amount of air exhaled with each breath should rarely exceed the amount inhaled, but Kraemer et al. [13] described the expiration period as being slightly longer than the inspiration period. However, this is specifically in order to achieve the low lung volume stage (see next section). All the sources examined agreed that the urge to cough should be suppressed during expiration, avoiding distal movement of secretions.

Patient effort during such expiratory manoeuvres needs to be controlled carefully to avoid dynamic compression and airway collapse, resulting in limited flow velocity [10]. Similarly, Chevaillier [8] described the need for the subject to balance the expiratory forces, so that the highest possible speed of flow is achieved without causing airway narrowing. If expiration is performed properly, secretions will be heard or felt vibrating as the velocity increases; if not, a wheeze may be audible as the airways collapse. High-frequency vibrations will indicate the presence of secretions in the peripheral airways, and low-frequency vibrations will indicate the presence of secretions in more central airways [8].

Variations in the description of the expiratory component of AD include avoiding expiration through the nose [10,13] and pursed lip breathing [2,13] in order to maintain a low resistance. However, these strategies, which increase positive expiratory pressure, were recommended by Chevaillier in those with easily collapsible airways. He also stated that pursed lip breathing may be helpful for beginners who have difficulty balancing the expiratory forces (breathing out through the nose may have a similar effect). In severe pathology, it is recommended that breathing out should be done as a sigh, and in very severe cases, little more than a normal exhalation is used [8].

Finding the correct balance of forces has been described as the ‘art’ of AD [1]. Once a balance is found, secretions will be transported proximally by turbulent flow. Turbulence occurs when the speed of the air has reached a critical velocity. It is more effective than laminar flow at ‘purging’ the contents of a tube, as laminar flow is stationary at the bronchial wall.
Gas–liquid interaction is known to be necessary for secretion clearance; this interaction occurs once flow has become turbulent. High flow rates will also generate a negative pressure at the inner wall of a tube, and this will decrease the adhesion of the mucus and enhance the effects of the shearing forces.

Lung volumes

As described previously, one of the aims of AD is to move secretions from the periphery to the mouth. This is done by adjusting the lung volume at which the patient is performing the AD-style breathing. Schoni [10] described three phases of AD as ‘unstick’, ‘collect’ and ‘evacuate’. During the first phase, the patient breathes the functional tidal volume starting below the level of functional residual capacity, in the range of their closing volume. This is known as low lung volume breathing. The patient will be instructed to breathe out as far as possible and then to breathe the functional tidal volume in and out as taught previously. By studying flow-volume loops [14], it can be seen that higher inspiratory flow rates were achieved at a low lung volume when the subject breathed in an AD style compared with forced expiration. This is because the airways of the subject were compressed by the extrabronchial pressure during the forced manoeuvre, and remained patent during the AD manoeuvre. Airway collapse aside, during breathing at low lung volume levels, there is also an enhanced velocity of air flow in the smaller airways compared with the flow in the same airways at higher lung volumes. This is because the ‘traffic jam’ of distal resistance, caused by the larger volume of gas converging on the more central airways, causes a reduction in the speed of flow in the peripheral airways at higher lung volumes. At lower lung volumes, there is less distal congestion so flows and secretion clearance in the peripheral airways are enhanced [8].

Secretions in the peripheral airways vibrate with a high frequency, and as they move more centrally, this vibration will reduce in frequency. In response to this feedback, the subject will need to change the volume at which they are breathing the functional tidal volume from the ERV to the IRV, breathing through low lung volume levels to middle and high lung volume levels. This is the phase known as ‘collect’.

Functional tidal breathing is progressed through middle and high lung volume levels in order to efficiently transport the secretions centrally; at progressively higher lung volumes, flow velocity is more rapid and secretions are transported more effectively in these specific levels of airway. Velocity increases as breathing is adjusted in this way because the driving pressure is increased via elastic recoil. Velocity is also enhanced by the decreasing cross-sectional diameter of the more central airways as gas converges in this area.

The final phase of evacuation voids secretions from the central airways or trachea into the mouth. For this, a huff or controlled cough may be performed [8]. The purpose of breathing at different lung volume levels is to enhance the velocity in specific types of airway, so that secretions can be transported more efficiently from the periphery to the mouth. However, it is important to note that at whichever lung volume the patient is breathing, flow is occurring in all generations of the bronchial tree simultaneously, and therefore secretions will be moving at all levels throughout the AD cycle (low lung volume through to high lung volume breathing). For this reason, AD should not be thought of as three entirely separate phases, but as if the secretions were being transported continuously on a ‘conveyor belt’ [8].

When teaching AD or instructing a patient during a treatment session, it is important to remember that flow-related airway collapse may occur more readily at low lung volumes as the transmural pressure is less [5]. Transmural pressure expresses a value of pressure at the inside wall of a structure relative to the pressure outside. All airways can be compressed by the reversal of the normal transmural pressure gradient; this includes airways with cartilaginous structure and those with no structural rigidity, i.e. those beyond the 11th generation of the bronchial tree [15]. These smaller airways are held open by traction exerted on them by the elastic recoil of the lung tissue in which they are embedded. They will be collapsed by a much smaller reversal of the transmural pressure gradient than cartilaginous airways. Similarly, airways become even more collapsible if there is decreased elastic recoil within the lung structure [15]. Therefore, care when balancing the expiratory forces is needed, especially when breathing into ERV, and more so in the presence of severe pathology.

The enhanced flows seen when breathing in an AD style are probably of more significance to those with pressure-dependent airway collapse as they cannot achieve the usual high flows seen during forced expiration.

Evidence for AD

A literature search using the keywords ‘chest physiotherapy’, ‘airway clearance techniques’ and ‘autogenic drainage’ was undertaken using Medline (1950 to June 2006), Pubmed and the Cochrane Library (no lower date restriction to June 2006). A hand search was used to follow up references from the retrieved studies. The search revealed few clinical trials investigating the use of AD. This research was mainly conducted on subjects with cystic fibrosis, except for one trial [16] that examined the effects of treatment on a sample of patients with chronic obstructive pulmonary disease. In total, seven randomised controlled trials were found, all of which had a small sample size. One retrospective audit examining changes in the use of airway clearance techniques over a 2-year period was also found [17]. The main characteristics of the clinical trials are described in Table 1.

The studies testing AD generally compared different treatments. This, combined with variations in age range, gender, disease severity classification and stability, makes comparison between the studies difficult.
### Table 1
Summary of the characteristics of autogenic drainage trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Interventions compared</th>
<th>Design/duration</th>
<th>Sample size</th>
<th>Subject age (years)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Disease severity</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindemann et al. [19]</td>
<td>Modified AD and PEP AD, PEP and cough</td>
<td>2-day crossover RCT</td>
<td>20</td>
<td>9–12</td>
<td>Unknown</td>
<td>CF</td>
<td>Unclassified and clinically stable</td>
<td>Sputum weight</td>
</tr>
<tr>
<td>Pfleger et al. [21]</td>
<td>AD, PEP and cough</td>
<td>5-day crossover RCT</td>
<td>14</td>
<td>9–22</td>
<td>5 male, 9 female</td>
<td>CF</td>
<td>Unclassified</td>
<td>Sputum weight, lung function testing</td>
</tr>
<tr>
<td>Giles et al. [18]</td>
<td>AD with PD, vibration and clapping</td>
<td>2-day crossover RCT</td>
<td>10</td>
<td>12–42</td>
<td>7 male, 3 female</td>
<td>CF</td>
<td>Unclassified</td>
<td>Sputum weight, lung function testing</td>
</tr>
<tr>
<td>Miller et al. [20]</td>
<td>AD and ACBT with PD</td>
<td>2-day crossover RCT</td>
<td>16</td>
<td>11–32</td>
<td>10 male, 8 female</td>
<td>CF</td>
<td>6 mild, 6 medium, 5 severe and clinically stable</td>
<td>Sputum weight, lung function testing, lung scintography, ventilation studies, visual analogue score</td>
</tr>
<tr>
<td>App et al. [22]</td>
<td>AD and flutter</td>
<td>10-week crossover RCT</td>
<td>14</td>
<td>17–41</td>
<td>Male and female, number of each unknown</td>
<td>CF</td>
<td>Unclassified and clinically stable</td>
<td>Sputum weight, lung function testing, sputum rheology</td>
</tr>
<tr>
<td>Davidson et al. [23]</td>
<td>PEP, AD and percussion with PD</td>
<td>6 months</td>
<td>18</td>
<td>?</td>
<td>?</td>
<td>CF</td>
<td>Unclassified</td>
<td>Lung function testing</td>
</tr>
<tr>
<td>Savci et al. [16]</td>
<td>AD and ACBT with PD</td>
<td>4-week pragmatic RCT</td>
<td>30</td>
<td>44–76</td>
<td>All male</td>
<td>COPD</td>
<td>Classified and clinically stable</td>
<td>Lung function testing, arterial blood gas analysis, 6-minute walking test with Borg scale</td>
</tr>
</tbody>
</table>

PEP, positive expiratory pressure; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; AD, autogenic drainage; ACBT, active cycle of breathing techniques; PD, postural drainage; RCT, randomised controlled trial.
Three of the trials were 2-day randomised crossover designs \[18–20\], one was a 5-day randomised crossover design \[21\], one was a 10-week crossover design \[22\], one was a 6-month crossover design \[23\], and one was a 4-week parallel randomised controlled trial \[16\]. In a crossover trial, the sample acts as its own control, whereas with a parallel design, the researchers must ensure that there are no significant differences in the demographics of the groups. This was not done for severity of disease in the AD parallel design trial \[16\].

Results of the brief trials could be attributed to random daily events, whereas a trial of longer duration might give a more reliable account of physiotherapeutic effects, as well as being able to demonstrate possible longer-term effects. A problem encountered in crossover trials is that of patient preference for one particular treatment or greater familiarity, which cannot be eradicated as it is often not possible to blind patients to the type of intervention they receive. Descriptions from the studies indicate that the subjects self-treated, but clarification about whether a therapist was involved should also be included. Due to the lack of methodological detail, it would be difficult to reproduce any of the studies.

As with any clinical trial testing a physiotherapeutic intervention, methods are designed to reduce confounding factors, e.g. standardising treatment duration or frequency. This is necessary to preserve the internal validity of the study and can be seen within the AD trials. However, the scientific clinical protocol may no longer resemble clinical practice in these circumstances, and one should interpret results with caution. Also, in the case of the AD studies, these scientific clinical protocols varied in detail, thus reducing study comparability. The length of the treatment varied between trials, from 20 minutes \[19\] up until ‘the lungs are clear’ \[18\]. In addition, there was variation in the frequency of treatment; Miller et al. \[20\] described two sessions per day, and the other trials only included one session per day.

All the AD study protocols were similar in that they compared the effectiveness of airway clearance techniques within a group of patients, leading to the assumption that perhaps one is better than the others. This, however, seems to be an unreasonable assumption given that patients seen in clinical practice will have differing pathophysiological changes within their lungs, therefore requiring the airway clearance technique that theoretically best addresses their problem or that which is the most effective for that individual. Therefore, it could be proposed that this type of study has little clinical value or relevance.

Subjects in the studies by Pfleger et al. \[21\], Giles et al. \[18\] and Miller et al. \[20\] were taught AD by trained therapists, but this information is not included for the other studies. Miller et al. \[20\] acknowledged that their subjects were already familiar with the active cycle of breathing techniques (ACBT), which was being compared with AD, but the usual regimen of the other trial samples was not reported. If subjects were performing AD for the first time (which is assumed as the subjects needed teaching), it seems reasonable to assume that they may not be as proficient in performing AD as ACBT. Also of great importance in these studies is the description of the technique being taught. Pfleger et al. \[21\], Giles et al. \[18\] and Miller et al. \[20\] gave accurate descriptions of the AD technique; Lindemann et al. \[19\], Davidson et al. \[23\] and App et al. \[22\] did not state such details, and Savci et al. \[16\] gave a slightly confusing definition that leaves the reader in some doubt about whether it was AD that was actually used and compared within the study. At this point, it is also appropriate to highlight criticism of the Miller et al. study \[20\], which raised concern about whether or not AD had been compared with ACBT, as the descriptions of ACBT given by Miller et al. \[20\] were thought to lack accuracy \[24\].

All of the studies incorporated more than three different outcome measures except for that of Lindemann et al. \[19\], who relied entirely on sputum weight, and Davidson et al. \[23\], who used lung function testing (the exact tests were unspecified). Cystic fibrosis obstruction occurs mainly in the peripheral airways, and measurements that reflect clearance from these areas are the most appropriate \[25\]. Of the five studies that used specified lung function tests, all used forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV\(_1\)); however, these tests are effort dependent and are not specific to small airways disease \[25\]. The use of peak expiratory flow rate by Savci et al. \[16\] is also inappropriate as this measurement is also effort dependent. Giles et al. \[18\], Savci et al. \[16\] and Miller et al. \[20\] all used the forced expiratory flow (FEF\(_{25–75}\)) test, which is more appropriate for measuring peripheral airway clearance. In addition, Pfleger et al. \[21\] measured residual volume and airway resistance in order to gauge peripheral clearance. Other outcomes used were lung scintigraphy \[20\], a visual analogue score to assess the patients’ preferred technique \[20\], percutaneous oxygen saturation levels \[18\], sputum rheology \[22\], arterial blood gas analysis, the Borg scale and the 6-minute walk test \[16\]. Indeed, quite a range of outcomes was employed. However, each of these different outcomes was only used in a single trial, and only those used more frequently (sputum weight and lung function testing) can allow comparisons between the trials.

The results of Lindemann et al. \[19\] demonstrated an increase in sputum weight. Pfleger et al. \[21\] performed a 5-day crossover trial comparing positive expiratory pressure alone, AD alone, positive expiratory pressure followed by AD, AD followed by positive expiratory pressure, and cough. FVC and FEV\(_1\) increased significantly, and residual volume and total lung capacity decreased significantly after positive expiratory pressure alone and positive expiratory pressure then AD. FVC also increased significantly after AD. AD and positive expiratory pressure gave the lowest and highest sputum weights, respectively, and cough alone cleared the least sputum, but there were no significant differences between any of the treatments. Giles et al. \[18\] demonstrated increased oxygen saturation levels during and after AD, but
this decreased with postural drainage, percussion and vibration. No significant difference was seen on lung function testing, and sputum weights were described as similar. Miller et al. [20] demonstrated no change in oxygen saturation levels and no significant difference in pulmonary function testing, sputum weight, heart rate, lung scintography and a patient preference survey. App et al. [22] demonstrated no significant difference in lung function tests or sputum weight, but did report significantly lower sputum viscosity. It is not possible to comment on the effects of treatments in Davidson et al.’s trial [23] as the outcome measures were not specifically stated. Savci et al. [16] stated that both AD and ACBT were effective for mucus transport based on the improvement in certain outcomes following the intervention period. Specifically, they found statistically significant improvements in FVC, FEV$_1$, peak expiratory flow, FEF$_{25-75}$, partial pressure of arterial carbon dioxide, 6-minute walk test and Borg score in the AD group. In the ACBT group, FVC, peak expiratory flow, partial pressure of arterial oxygen and the 6-minute walk test improved significantly. Although there were differences between the pre- and post-treatment measurements, some of the tests were inappropriate (as discussed previously) or relate more specifically to ventilation, which could be affected by other factors. The studies discussed are generally not very comparable in terms of methods, with unsurprisingly conflicting results. Also, due to the poor quality of the research, only one of the studies [20] met the criteria for inclusion in the meta-analysis by Thomas et al. [26].

The initial search also uncovered a retrospective audit published in 2004 [17] concerning the physiotherapeutic treatment of 249 hospitalised children, aged 2–17 years, with cystic fibrosis in an Australian centre. The audit was performed to assess differences occurring in the physiotherapy management of these children with the progression of time. The physiotherapy records of the patients were first examined in 1998 and again in 2000. New patients presenting within the time frame who met the inclusion criteria were also included. Results revealed a significant decrease in the use of postural drainage (PD) with head tilt down, and also in AD; an increase in modified PD with no head tilt down and positive expiratory pressure; and no difference in exercise or use of flutter (oscillating positive expiratory pressure). There were no significant differences in the sample demographics for the two years examined, and the authors felt that the observed changes in management could not be due to changes in sample characteristics but represented a change in treatment trend. However, the authors stated that a large number of the new patients in 2000 were very young (under 12 years of age), and on examining the protocol at the centre involved, they would not have been taught AD but would have performed another airway clearance technique. It is possible that such an influx of new patients may have changed the proportions of patients performing AD, whilst a change in demographics of a significant amount between 1998 and 2000 was undetectable. Any change, therefore, was due to protocol rather than therapist or patient preference.

Many reviews of airway clearance techniques have been performed over the last 20 years. Some of the more recent include a meta-analysis by Thomas et al. [26], Cochrane reviews by Main et al. [27] and Van der Schans et al. [28], and review papers by Hess [29], Pryor [30] and Lapin [31]. All found a lack of high-level evidence for the use of any airway clearance technique, and reached different conclusions and recommendations due to the inclusion of studies demonstrating varying methodological rigor. Thomas et al. [26] found that providing some intervention gave more favourable results than when there was no intervention. Main et al. [27] found that there was no advantage of conventional chest physiotherapy over other airway clearance techniques. Van der Schans et al. [28] found that airway clearance techniques have short-term benefits. Hess [29] found that there is not enough high-quality evidence to support any airway clearance technique; a conclusion with which Pryor [30] agreed, stating that choice of treatment should be based upon preference. Lapin [31] conducted a review of the physiological basis for AD and ACBT, and the supporting evidence. He found that the physiological rationale supported the use of AD in several disease states, but the evidence base was lacking. He recommended that further research is needed, and until this is done, the clinician must employ the airway clearance technique that elicits the best outcome for the individual case.

Conclusion

With little guidance available on which technique to use and in whom, clinical decisions are often based on tradition, experience and knowledge, and resources. After investigating the physiological basis of AD, it appears that patients with excess or retained secretions, and in whom dynamic airway collapse occurs, may benefit. If a gentle expiratory approach is taken with these patients, it would appear, from evidence provided in flow-volume loops, that a higher velocity of air flow is achieved. If the aim of treatment is to improve these flows in order to move secretions, then AD should theoretically be effective for this purpose. The types of patient who may benefit are those in whom more forceful expiratory techniques have little effect and those in whom energy conservation and relaxation are desirable, such as patients presenting with cystic fibrosis or chronic obstructive pulmonary disease. With a lack of high-quality evidence, there is no guidance available about which airway clearance techniques should be used, and further research in this area is needed. When treating a patient, consideration should be given to the airway clearance technique that is most effective for the particular case, and to the patient’s preference (if this means the difference between providing some intervention and providing no intervention). It is important to remember that many patients are embarking on, or are already involved in, long-term treatment, and their role in the decision-making process should be integral.
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References

[31] Lapin CD. Airway physiology, autogenic drainage and active cycle of breathing. Respir Care 2001;47:778–85.