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1 Optoelectronic plethysmography in clinical practice and research: 2 a review 3

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34 **Running head**

35 OEP in clinical practice and research

36 **Keywords**

37 Optoelectronic plethysmography; breathing; Mechanics of breathing; respiratory volumes; chest wall
38 kinematic; lung volumes.
39

40 **Abstract**

41 BACKGROUND: Optoelectronic plethysmography (OEP) is a non-invasive motion capture
42 method to measure chest wall movements and estimate lung volumes. .

43 OBJECTIVES: Provide an overview of the clinical findings and research applications of OEP in the
44 assessment of breathing mechanics across populations of healthy and diseased individuals.

45 METHODS: A bibliographic research was performed with the terms “opto-electronic
46 plethysmography”, “optoelectronic plethysmography” and “optoelectronic plethysmograph” in 50
47 Digital Library and Bibliographic Search databases resulting in the selection of 170 studies.

48 RESULTS: OEP has been extensively employed in studies looking at chest wall kinematics and
49 volume changes in chest wall compartments on healthy subjects in relation to age, gender, weight,
50 posture and different physiological conditions. In infants, OEP has been demonstrated to be a tool
51 to assess disease severity and the response to pharmacological interventions. In COPD patients
52 OEP has been used to identify that patients can dynamically hyperinflate or deflate their lungs
53 during exercise. In neuromuscular patients respiratory muscle strength and chest kinematics has
54 been analysed . A wide-spread application of OEP is in tailoring post-operative pulmonary
55 rehabilitation as well as in the monitoring of volume increases and muscle contributions during
56 exercise.

57 CONCLUSIONS: OEP is an accurate and validated method of measuring lung volumes and chest
58 wall movements. OEP is an appropriate alternative method to monitor and analyse respiratory
59 patterns in children, adults and patients with respiratory diseases. OEP may be used in the future
60 to contribute to improvements in the therapeutic strategies for respiratory conditions.

61 **1. Introduction**

62 **1.1. Overview**

63 In clinical practice and scientific research, the evaluation of chest wall kinematics during breathing
64 and the assessment of thoraco-abdominal volumes allow an additional perspective on the study of
65 different pathologies and can direct medical treatment during rehabilitation. From the middle of
66 the 20th century the scientific community started to study the respiratory system as a model [1–3]
67 and founded its analysis on mechanical models of the different parts composing the system [3–6].
68 Mead et al. published a series of scientific papers in which the possibility of measuring lung
69 volume variations by the measure of thoracic and abdominal wall displacement was described [7–
70 9]. These studies led to hundreds of studies on respiratory mechanics in the 1980s with works of
71 Mead et al. [10,11], Macklem et al. [4], Peslin et al. [6,12] and others who contributed to the
72 understanding of the respiratory drive and the mechanisms of pulmonary ventilation, and to the
73 determination of how the ventilatory pump acts on respiratory structures.

74 The real technological breakthrough occurred in 1990 with Pedotti et al., who was the first to use a
75 system based on motion analysis technology that provided the theoretical possibility of measuring
76 and monitoring the movement of a number of points by photo-reflective markers [13,14]. The
77 ELITE system was the first motion analysis system used for the assessment of non-invasive
78 optoelectronic breathing mechanics [14–16]. Since 2000 a growing number of studies have used
79 optoelectronic plethysmography (OEP) to i) assess breathing pattern, ii) measure asynchronies in
80 breathing strategies in patients with various pathologies, iii) to investigate the healthy breathing
81 biomechanics.

82 **1.2 Aim and Methods**

83 This paper provides an overview of the clinical findings and research applications of OEP in the
84 non-invasive assessment of breathing in a population of healthy and diseased individuals and in a
85 wide age range. In March 2016, a search in 50 Digital Library and Bibliographic Search databases
86 (e.g., SCOPUS® , PubMed® and Google Scholar®) with the terms “opto-electronic
87 plethysmography”, “optoelectronic plethysmography” and “optoelectronic plethysmograph” was
88 performed. 220 studies were found overall. After reading the titles and abstracts, those which
89 referred to OEP were included, totalizing 156 papers. After reading the full texts of these studies,
90 14 more studies were found by manual search. Thus, a total of 170 studies on OEP were selected.

91

92 **2. Working Principle: from 3D markers trajectories to breathing**

93 **volumes**

94 OEP is a motion analysis system, which measures the changes of the chest wall during breathing
95 by modeling the thoraco-abdominal surface. The OEP working principle is based upon the general
96 principles of three dimensional motion capture [17] (Fig. 1). OEP reconstructs the chest wall
97 surface and then volume by placing a number of markers on the skin (Fig. 1). In a general clinical
98 setting 6 and 10 mm diameter hemispherical or spherical markers are used [34]. For standing
99 evaluations commonly an 89 marker protocol is used (as shown in Figure 1, considered the “full
100 marker” protocol) [18–24]. A 52 marker protocol can be used to assess subjects in the supine
101 position, for example in the monitoring of breathing in intensive care [25–27]. A 24 marker
102 protocol has been used to collect the upper and lower chest wall movements in the breathing

103 analysis of newborn babies [28,29]. Furthermore, a recent study validated a new 52 marker based
104 three-compartment model of the chest wall to record spontaneous sleeping in infants [30].

105
106 A number of infrared (IR) camera (four [14,31–33] to eight [27,34,35]) capture the scene and track a
107 number of IR-reflective markers within a previously calibrated volume [36] defining the recording
108 workspace [37]. A dedicated workstation (Fig. 1) synchronizes input and output information to
109 and from cameras; an ad-hoc designed software in the workstation computes the marker 3D
110 trajectories integrating the information collected from each camera. Then a geometrical model is
111 applied: a closed surface is defined starting from connecting each triplet of markers to form a
112 triangle. From each closed surface, the volume contained into this surface is calculated.

113 For each triangle - identified by three markers - the area (S) and the direction of normal vector (\vec{n})
114 are calculated and from the volume contained in this surface can be calculated using the Gauss
115 theorem [14,38] as in Eq.(1):

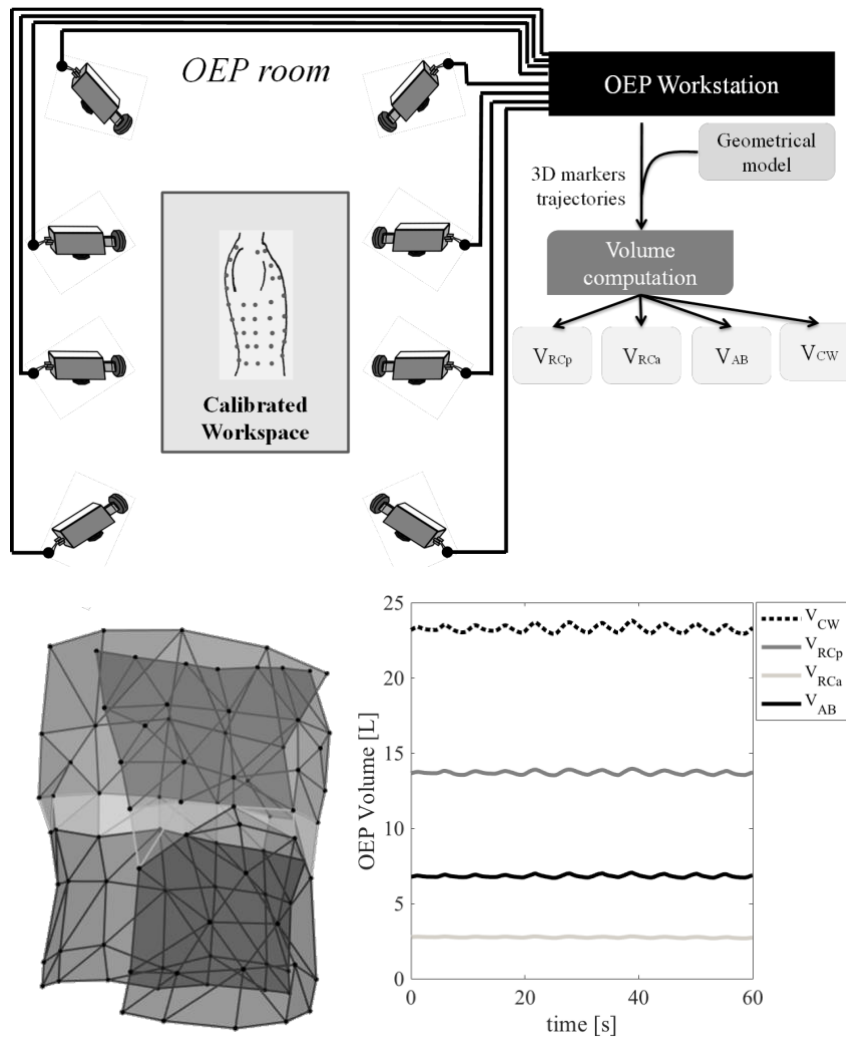
$$116 \quad \int_S \vec{F} \cdot \vec{n} dS = \int_V dV = V \quad (1)$$

117 where \vec{F} is an arbitrary vector, S is a closed surface, V is the volume enclosed by S and \vec{n} is the
118 normal unit vector on S .

119 The OEP chest wall model can be divided into three compartments, composed of the pulmonary
120 rib cage (RCp), the abdominal rib cage (RCa), and the abdomen (AB) as highlighted in Fig.1. The
121 three-compartment model allows the following phenomena to be considered that *i*) RCp and RCa
122 are exposed at different pressures during the inspiration, *ii*) the diaphragm acts directly only on
123 RCa, and *iii*) non-diaphragmatic inspiratory muscles act largely on RCp and not on RCa [7].
124 Regarding the abdomen, AB volume change is defined as the volume swept by the abdominal wall

125 [7,24,39], and it is the result of the conjunct action of the diaphragm and expiratory abdominal
 126 muscles.

Figure 1: Schematic of OEP working principle; 3D human chest wall reconstructed starting from 89 markers: blue, green and red surfaces represent the pulmonary rib cage (RCp), the abdominal rib cage (RCa) and the abdomen (AB), respectively. The rib cage (RC) volume is considered as the sum of RCp and RCa volumes. The plot shows the three compartmental volumes and the total chest wall volume during 60s of OEP data collection in one healthy subject.



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130 3. OEP applicability: what does OEP measure?

131 3.1 Chest wall kinematics

132 OEP is a reliable tool for the analysis of chest wall (CW) kinematics partitioned into RC_p, RC_a, and
133 AB, for both the left and right side (also known as hemithoraxes). Results obtained from the
134 breath-by-breath analysis of compartmental volumes can be further processed to assess if the
135 thoracic-abdominal movement of the CW is synchronous, thus if RC (where $RC=RC_p+RC_a$) and
136 AB are moving in phase. When the two compartments move in opposite directions paradoxical
137 movement occurs [40]. Konno et al. described one of the first models of movement of the chest
138 wall [7]: on healthy subjects volume variations of the rib cage must be equal and opposite to
139 volume variations of the abdomen and the two compartments must move in phase. Several
140 methods were designed in order to describe the synchrony of the thoracic-abdominal movement,
141 also based upon ultrasound [41]. The most commonly used indexes are *i*) the phase angle analysis
142 and Lissajous loop evaluation [42–48] *ii*) the Cross-Correlation Function [49], *iii*) the paradoxical
143 inspiratory (PI) and expiratory time (PE) [50], *iv*) the inspiratory and expiratory phase ratio, *v*) the
144 total phase ratio [50].

145 3.2 Breathing volumes

146 The difference between the end-inspiratory volume and the end-expiratory volume is computed
147 for each compartment, obtaining compartmental volumes. For each compartment, OEP gives
148 information about the tidal volume (V_T) [51], end-expiratory and end-inspiratory volume
149 [39,52,53].

150 OEP can also indirectly compute the following pulmonary volumes: Expiratory Reserve Volume
151 (ERV), Inspiratory Reserve Volume (IRV), Forced Expiratory Volume in the first second (FEV1)
152 [54,55], Vital Capacity (VC) and Inspiratory Capacity (IC)[56].

153 **3.3 Breathing time assessment**

154 By-breath analysis of compartmental volumes allows study of the respiratory cycle. The following
155 variables are computed in order to analyse the respiratory cycle: inspiratory time (T_i), expiratory
156 time (T_e), and total time of the respiratory cycle (T_{tot}), inspiratory time in relation to the total time
157 (T_i/T_{tot}), minute ventilation (MV), mean inspiratory flow (VC_{cw}/T_i) and mean expiratory flow
158 (VC_{cw}/T_e) [50].

159 **4. OEP performance: validity, accuracy and reliability**

160 The accuracy of OEP has been assessed in different ways. OEP is typically able to detect linear
161 marker displacements higher than $30\mu\text{m}$, which was assessed to be its threshold for detecting
162 linear movement [57]. This results in a volume threshold around 9mL for typical adults. The effects
163 of number of cameras (i.e., 4, 6, 8) and marker size (i.e., spherical, 6 mm and 12 mm diameters) on
164 OEP accuracy in linear displacement have been evaluated: increasing the number of cameras
165 generally increases OEP accuracy if spherical 6mm markers are used [57]. On the other hand, OEP
166 accuracy in dynamic volume estimation appears not to be influenced by the magnitude of the
167 thorax's movement [58]. The OEP volume accuracy investigated by a volume calibration device in
168 the range of 0-2.78L is always better than 6.0% of measured volume. The OEP volume standard
169 deviation for a known volume change delivered via a volume calibration device ten times was
170 $\pm 2.7\text{mL}$, in the range of 0-2.78L [59].

171 The validity of OEP in measuring respiratory volume variations was performed by the comparison
172 between V_{CW} changes estimated by OEP, and lung volume variations measured by spirometers
173 and pneumotachometers as gold standard instruments [60]. OEP validity has been evaluated in
174 healthy seated and standing subjects with the 89 marker protocol in different experimental
175 situations (e.g., quiet breathing, incremental exercises). The maximum difference between
176 spirometer and OEP measurements was reported to be <4% in all studies. V_{CW} measurements of
177 OEP, spirometry and pneumotachography are highly correlated, with the mean discrepancy lower
178 than 5%, in constrained postures like supine and prone position in healthy subjects during quiet
179 and deep breathing [61].

180 Intra-rater and inter-rater reliability of OEP have been evaluated at rest and during submaximal
181 exercise on a cycle ergometer. OEP showed an Intra-class Correlation Coefficient higher than 0.75
182 and a coefficient of variation always lower than 10% [62].

183 **5. Breathing evaluation of healthy subjects**

184 In the last decade, OEP has been extensively employed in studies looking at CW kinematics and
185 volume changes in the three CW compartments on healthy subjects in relation to age, gender,
186 weight, posture and different physiological conditions, such as coughing and laughing.

187 In pre-term and term infants, OEP has been demonstrated as a good tool to assess lung volume
188 and compartmental changes and relative compartmental distribution [28]. The main advantage of
189 this technology is that subject collaboration is not necessary. Typically, an easier marker protocol
190 (24 markers on the anterior thoraco-abdominal surface) is used for such analysis. The non-invasive
191 bedside evaluation of the respiratory status with OEP is especially useful in critically ill neonates
192 to assess disease severity and the response to pharmacological interventions [63] as well as to
193 guide mechanical respiratory support (e.g., high-frequency oscillatory ventilation) [64].

194 In adulthood, OEP has been applied to study for the first time how the influence of posture and
195 age can affect breathing variables (e.g., volumes, compartmental contribution to the V_T , breathing
196 frequency). Aliverti et al. [16] demonstrated that during quiet breathing the RCa volume changes
197 are higher in prone position; and AB volume changes have the opposite behaviour; they are
198 decreased when subjects are layed down. Volume data collected during deep breathing on healthy
199 adults demonstrated that the distribution of compartmental breathing volumes is posture-
200 independent. The volume changes in both hemithoraxes are similar as demonstrated by Nozoe et
201 al. [65]. Moreover, Wang et al. demonstrated that the motion of all three CW compartments is
202 highly correlated with diaphragmatic movement distance in the inspiratory phase, during both
203 quiet and deep breathing REF. In particular, the AB movement is closely correlated with
204 diaphragmatic movement in supine position [66]. The progressively increased inclination of the
205 trunk (from seated to supine position) determines a progressive reduction of RC displacement, V_T ,
206 and MV and a progressive increase of AB contribution to the V_T [67]. In a recent study Souza
207 Mendes et al. demonstrated that posture, gender, and age influence both the breathing pattern and
208 the thoracoabdominal motion [68].

209 The influence of age on ventilatory kinematics and the mechanisms adopted by the elderly
210 population to overcome age-related physiological changes has been studied by Muniz de Souza et
211 al. [69]. They showed that in the elderly, during moderate inspiratory resistance, the pattern is
212 deep and slow. With respect to the influence of gender, different results have been found in the
213 literature. On one hand, Romei et al. showed that female subjects are characterized by smaller
214 dimensions of the RC compartment and during quiet breathing by lower V_T , minute ventilation
215 and AB contribution to V_T than males [67]. On the other hand, Binazzi et al. demonstrated no
216 gender differences in breathing pattern or CW kinematics when normalised to size-related vital
217 capacity (VC). Moreover, Muniz de Souza et al. investigated with OEP differences in AB

218 kinematics between young and elderly women during different inspiratory efforts [69]. It was
219 shown that in the elderly, during moderate inspiratory resistance, the breathing pattern is deep
220 and slow.

221 Barcelar et al. investigated how both lung function and thoraco-abdominal volume variations
222 during quiet breathing are altered in obese women [70]. Obesity significantly reduced V_{RCp} and
223 increased V_{AB} compared with normoweight. Additionally, the increased mass of AB modifies the
224 position and the shape of the diaphragm, making this muscle more cranially displaced and its
225 fibres lengthened.

226

227 New insights have been found with the OEP in the field of laughing and coughing. Filippelli et al.
228 highlighted that fits of laughter consistently lead to sudden and substantial decrease in lung
229 volume in all the CW compartments and remarkable dynamic compression of the airways [71].
230 Moreover, Cossette et al. showed that flute support entails antagonistic contraction of non-
231 diaphragmatic inspiratory muscles that tends to hold the RC at higher lung volume by collecting
232 for the first time volume data with OEP on young professional flutists [72]. OEP has been used to
233 investigate the influence of cough on CW kinematics in healthy adults by Smith et al. and Lanini et
234 al. [19,73]. The operating volume was found to be the most important determinant of cough peak
235 flow and volume expelled in healthy individuals [73]. A noticeable RC distortion ensues during
236 coughing if the action of the muscle force acting on the RCa is not commensurate with the force
237 acting on the RCp [19].

238 One study investigated the effect on the chest wall of the incentive spirometry in healthy adults
239 [74] and Chihara et al. analysed the chest wall kinematics and respiratory muscle recruitment in
240 seven healthy men during rebreathing of a hypercapnic-hyperoxic gas mixture [74]. The latter
241 study showed that the end-inspiratory lung volume increase in V_{cw} was mainly achieved by

242 increasing end-inspiratory volumes of the RC_p and RC_a reflecting the inspiratory RC muscle
243 contribution to recruit the IRV. Findings reported by Illi et al. likely indicate that all inspiratory
244 muscles fatigued simultaneously rather than in succession and that inspiratory RC muscles did not
245 take over diaphragmatic work in the course of prolonged normocapnic hyperpnoea [75].

246 The comprehensive literature analysis reported in this section demonstrates that OEP can be
247 considered both a reliable system for the basic physiological and pathophysiological studies
248 thanks to its non-invasiveness measurements and unnecessary of subject cooperation during the
249 evaluations and an attractive tool for evaluating breathing under a wide variety of circumstances
250 in health.

251 **6. Evaluation of Chronic Obstructive Pulmonary Disease**

252 Although the origins of dyspnoea and exercise intolerance in COPD are complex and
253 multifactorial, “dynamic hyperinflation” (DH), which is mainly due to expiratory flow limitation
254 (EFL) and gas accumulation/retention (usually termed “air trapping”), is presumably the most
255 important factor in limiting exercise and contributing to dyspnoea by causing restrictive
256 constraints onto volume expansion [76]. OEP has been used to confirm the hypothesis that COPD
257 patients can dynamically hyperinflate or deflate lung/CW compartments during exercise. In one
258 such study, Aliverti et al. found that the patients with severe COPD showed DH during
259 incremental exercise; patients with a greater expiratory flow reserve at rest, instead, adopted the
260 more “normal” approach to reducing EEV_{cw} when they exercised [52].

261 It remains nevertheless unclear if reduced lung volume contributes to relieving dyspnoea and
262 improving exercise tolerance in COPD patients [77]. When Aliverti et al. used OEP to analyse the
263 effect of nebulised salbutamol on endurance exercise time in subjects with severe airway
264 obstruction, they described two different response patterns to bronchodilation therapy: while the

265 less hyperinflated patients showed reduced End-Expiratory Lung Volume (EELV) after active
266 treatment, the more severely hyperinflated ones continued to allow EEV_{AB} to rise during exercise
267 [78]. Georgiadou et al. described an increase in exercise dyspnoea both in individuals who
268 progressively hyperinflated the chest wall as well as in those who did not [53].

269 A lack of correlation between the degree of DH and exercise-induced dyspnoea has led to the
270 hypothesis that abnormalities in chest wall motion, in particular, the paradoxical (inward)
271 inspiratory movement of the lower rib cage, play a critical role in the onset of dyspnoea and
272 exercise intolerance in COPD patients. OEP measurements have shown that although
273 hyperinflated patients are especially likely to display abnormalities in RC motion, a paradoxical
274 movement of the RCa is not entirely explained by static lung or dynamic RC hyperinflation [79–
275 81].

276 Pursed-Lip Breathing (PLB), which involves nasal inspiration followed by exhalation through
277 partially closed lips, has recently been used to assess volume changes in CW compartments and
278 onset of dyspnoea in COPD patients. Bianchi et al. utilized OEP measurement to analyse the
279 displacement of the CW and its compartments and of the RC and AB during supervised PLB
280 manoeuvre in a group of patients with mild to severe COPD [82]. Compared to spontaneous
281 breathing, the patients practicing PLB exhibited a significant reduction in end-expiratory lung
282 volume (EEV) of the CW (EEV_{CW}) and a significant increment in end-inspiratory lung volume
283 (EIV) of the CW (EIV_{CW}).

284 The hypothesis that RC distortion plays a role in the onset of breathlessness during exercise in
285 COPD patients raises the question if rehabilitation programs can reduce abnormalities in CW
286 motion in these patients, thereby restoring exercise capacity and relieving breathlessness.

287 Gagliardi et al. recently used OEP to evaluate the V_{CW} , V_{RC} and V_{AB} in COPD patients before and
288 after a 24-session exercise program that included education, breathing retraining, unsupported

289 arm exercise, and cycling. Study results showed that exercise training *i)* had no effect on
290 operational thoraco-abdominal volumes, *ii)* contributed to dyspnoea relief by improving patients'
291 ventilatory profile, *iii)* increased tolerance to the dynamic restriction of CW volumes, and *iv)*
292 improved RC distortion, albeit only to a small extent [83].

293 By using the OEP, Bruni et al. evaluated the effect of oxygen therapy on dyspnoea, CW dynamic
294 hyperinflation, and RC distortion in a group of COPD individuals [84]. At isotime during exercise,
295 while breathing supplemental oxygen, dyspnoea relief was associated with a decrease in
296 ventilation regardless of whether patients distorted the RC, dynamically hyperinflated, or deflated
297 the CW. In the light of these results, the authors concluded that dyspnoea, CW dynamic
298 hyperinflation, and RC distortion were not interrelated phenomena and that benefit from oxygen
299 therapy was unrelated to its possible effect on RC distortion or dynamic CW hyperinflation.

300 When Coutinho Myrrha et al. analysed chest wall volumes and breathing patterns in COPD
301 patients at rest and during inspiratory loaded breathing (ILB) [85], they found that the AB was the
302 main compartment responsible for V_T during both situations. The authors noted that the COPD
303 patients overcame the load imposed by ILB and improved V_T by changing the inspiratory V_{CW}
304 without modifying the predominant mobility of the AB at rest and without affecting the EEV_{CW} .

305 Table I summarized all the study utilizing OEP in the evaluation of patients with COPD.

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314 **Table 1:** Studies utilizing OEP in the evaluation of patients with COPD (DH= Dynamic
 315 Hyperinflation; EELV= End-Expiratory Lung Volume; ILB= Inspiratory Loaded Breathing; PLB=
 316 Pursed-Lip Breathing, MDRT=Manual Diaphragm Release Technique, EEV_{CW}=end-expiratory lung
 317 volume (EEV) of the CW).

Authors – year	Pathology stage, Sample characteristics	Topic	Findings
Aliverti et al. [52] – 2004	Clinically stable, n=20	Pathogenesis of DH during incremental exercise	Response pattern may vary according to disease severity
Aliverti et al. [78] – 2005	Severely obstructed, n=18	Effect of salbutamol on endurance exercise	Less hyperinflated patients show reduced EELV
Vogiatzis et al. [73] -2005	Clinically stable, n=20	Change in VT pattern during recovery from exercise	Presence of two patterns during exercise: early and late hyperinflation.
Georgiadou et al. [53] – 2007	Severely obstructed, n=20	Influence of chest wall volumes on dyspnoea during exercise	EEVCW attenuation in “hyperinflators” doesn’t reduce dyspnoea
Bianchi et al. [86] – 2007	Mild to severe obstruction, n=30	Volume changes in chest wall compartments during PLB	Symptom relief associated to decreased end-expiratory volumes of the chest wall and abdomen in more severely obstructed
Bruni et al. [84] – 2012	Clinically stable, n=15	Effect of oxygen therapy on dyspnoea, chest wall DH, and rib cage distortion	Benefit unrelated to a possible effect on rib cage distortion or dynamic chest wall hyperinflation
Coutinho Myrrha et al. [85] – 2013	Clinically stable, n=13	Chest wall volumes and breathing patterns during ILB	Increment in VT of the chest wall as a result of higher EEVCW during ILB
Gagliardi et al. [83] – 2014	Severely obstructed, n=14	Effect of exercise program on chest wall volume, and exercise-induced dyspnoea	No effect on thoraco-abdominal volumes; improved rib cage distortion
Rocha et al. [87] – 2015	Clinically stable with age > 60 y.o., n=20	Effect of MDRT on improvement of diaphragmatic mobility	MDRT significantly improved diaphragmatic mobility over the course of treatments and significantly improved the 6-minute walk distance over the treatment course

Borges-Santos et al. [88] – 2015	Clinically stable, n=54: n=17 no symptoms, n=12 anxiety symptoms, n=13 depressive symptoms, n=12 both symptoms	Relationship between the presence of symptoms of anxiety or depression with breathing pattern and thoracoabdominal mechanics at rest and during exercise in COPD	Patients with symptoms of depression report more dyspnoea. No impact of anxiety and depression on breathing pattern and thoracoabdominal mechanics.
Lima et al. [89] - 2016	Meta-analysis considering 6 studies	The effects of a constant load or incremental cycle ergometer tests on dyspnoea and CW volumes	Euolumic COPD patients respond more favourable with less dyspnoea to constant load and incremental protocol.

319

320 7. Use of OEP in Intensive Care Units

321 The OEP system has been used to evaluate the effect of invasive and non-invasive ventilatory
322 strategies on V_T and thoraco-abdominal synchrony and to monitor CW mechanics and the
323 distribution of V_{CW} variations in patients undergoing Mechanical Ventilation (MVe). Aliverti et al.
324 found that volumes measured using OEP in patients with acute lung injury and acute respiratory
325 distress syndrome (ALI/ARDS) receiving continuous positive pressure ventilation (CPPV) or
326 pressure support ventilation (PSV) were highly correlated with measurements taken using
327 spirometry and pneumotachography [29]. They also assessed accuracy of the
328 compartmentalization procedure (RCp, RCa, and AB) by calculating compartmental volume
329 changes during isovolume manoeuvres and concluded that OEP is able to provide relevant data on
330 the distribution of CW volume variations in ventilated patients.

331 Dellacà et al. set out to investigate the efficacy of OEP in assessing PEEP-induced variations of
332 lung gas volume in mechanically ventilated, paralyzed patients with Acute Respiratory Failure
333 [90]. The authors measured the EEV_{CW} breath-by-breath by OEP before, during, and after the PEEP
334 increase/decrease and compared its variations with the corresponding EELV ones measured using

335 the helium dilution technique. The regression line between EELV changes measured by helium
336 and EEV_{CW} changes measured by OEP was found to be quite close to the identity line and the
337 difference was not related to their absolute magnitude.

338 Finally, OEP was used to study lung volume distribution during the administration of Neurally
339 Adjusted Ventilator Assist (NAVA) ventilation, which assists spontaneous breathing
340 proportionally to diaphragmatic electrical activity, compared to administration of PSV at different
341 levels of support [91]. Although NAVA and PSV similarly reduced the abdominal contribution to
342 V_T , subject-ventilator synchronization was better during NAVA with respect to PSV and the
343 difference between the two modes in regional ventilation distribution was not significant.

344 **8. OEP in the neuromuscular disease evaluation**

345 Muscular diseases are characterized by progressive loss of muscle strength, resulting in cough
346 ineffectiveness with its deleterious effects on the respiratory system. Assessment of cough
347 effectiveness is, therefore, a prominent component of the clinical evaluation and respiratory care in
348 these patients. Table 2 shows the main findings from studies performed on patients with
349 neuromuscular diseases.

350 OEP has been used to investigate pulmonary volumes, respiratory muscle strength, peak cough
351 flow and CW kinematics in neuromuscular patients. A recent review suggests the use of OEP as a
352 non-invasive method to study the thoraco-abdominal kinematics in children with neuromuscular
353 diseases [92]. Subjects with these conditions are unable to reduce EE_{CW} volume, and exhibit greater
354 RC distortion during cough. Peak cough flow is negatively correlated with RC distortion (the
355 greater the former, the smaller the latter), but is not correlated with respiratory muscle strength
356 [93]. So this suggests that insufficient deflation of CW compartments and marked RC distortion
357 resulted in cough ineffectiveness in these neuromuscular patients.

358 In patients with Duchenne Muscular Dystrophy (DMD), OEP highlighted that the CW motion
359 during spontaneous breathing in awake conditions and in the supine position is an important
360 indicator of the degree of respiratory muscle impairment in DMD [26]. Moreover, the contribution
361 of abdominal volume change is a strong indicator of diaphragm impairment [94] such that it could
362 discriminate between efficient and inefficient coughs [95,96]. However AB contribution is not only
363 an important marker of the progression of the disease but is also an early indicator of nocturnal
364 hypoxaemia [26]. Although, even in other dystrophic diseases as Becker's Muscular Dystrophy
365 (BMD), Facioscapulohumeral dystrophy (FSHD) and Limb-girdle dystrophy patients (LGMD),
366 OEP is able to reveal mild initial modifications in the respiration, which could be helpful for
367 functional and new therapeutic strategy evaluation. Moreover, OEP has been used on spinal
368 muscular atrophy (SMA) patients with the aim to investigate if the RC motion was similar in mild
369 SMA (with onset of lower limbs muscular weakness after 3 years) and healthy subjects [27,97].

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392 **Table 2:** Studies utilizing OEP in the evaluation of patients with neuromuscular diseases (DMD=
 393 Duchenne Muscular Dystrophy, NH=nocturnal hypoxemia, MV=minute volume, BMD=Becker's
 394 muscular dystrophy, FSHD=Facioscapulohumeral dystrophy, LGMD=Limb-girdle dystrophy
 395 Myotonic, SMA= Spinal muscular atrophy)
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Authors – year	Pathology, Sample characteristics	Aim	Findings
Lo Mauro et al. [26] – 2010	DMD patients at different stages of the disease, n=66	To investigate if V_{AB} contribution to V_T should be considered an early indicator of respiratory impairment in DMD	<ul style="list-style-type: none"> • In the supine position, the average contribution of V_{AB} to V_T progressively decreased with age. • NH patients showed significantly lower contribution of V_{AB} changes.
Romei et al. [98] – 2012	DMD, n=40	To determine if V_{RC} and V_{AB} can be helpful to distinguish between those patients who are in the early stages of NH development and those who do not yet.	<ul style="list-style-type: none"> • In supine position during the slow VC manoeuvre, ventilator parameters are significantly lower in DMD patients. • In seated position, DMD patients showed lower MV than healthy subjects during quiet breathing.
D'Angelo et al. [99] – 2011	DMD patients (4 groups according to age), n=114	To identify early markers of respiratory insufficiency and rule out the role of pharmacological and surgical therapies in DMD	<ul style="list-style-type: none"> • A subgroup of adolescent DMD patients showed differences in AB contribution to V_{CW} related to the time spent with low oxygen saturation during night, despite similar spirometric parameters. • The inadequate pre-inspiration and insufficient expiratory flow, particularly of the RC muscles seemed to be the cause underlying the progressive inefficient cough typical of the natural course of the disease.
Bonato et al. [100]-2011	DMD patients, n=40	To investigate the relation between the reduction of VC and inspiratory muscles weakness and the ability to breath autonomously	Relationship between the CW variations and the saturations showed differences in AB contribution to V_{CW} variations related to the time spent with low oxygen saturation during night, despite similar spirometric parameters.

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<ul style="list-style-type: none"> • Lo Mauro et al. [95] - 2014 • Lo Mauro et al. [96] - 2012 	DMD patients, n=36 (3 groups according to the peak cough flow)	To investigate if thoraco-abdominal operating volumes during coughing determine the effectiveness of cough in DMD patients	<ul style="list-style-type: none"> • During the inspiration preceding cough, patients with efficient cough showed normal volume variations whereas patients with intermediate cough efficiency showed low AB volume variation. • Patients with inefficient cough were characterized by reduced total and compartmental CW volumes during the inspiration preceding cough and reduced AB contribution to V_T during quiet breathing.
D'Angelo et al. [94]- 2012	DMD, n=45: <ul style="list-style-type: none"> • with Spinal Fusion, n=15, <ul style="list-style-type: none"> • with severe scoliosis (Cobb angle $>20^\circ$), n=22 • with mild scoliosis Cobb angle $<20^\circ$), n=8 	To compare the rate of decline in respiratory function in 3 groups of non-ambulant DMD patients, divided on the basis of Cobb angle and Spinal fusion	The decline of V_{AB} contribution to the CW in the DMD patients who underwent spinal fusion is far less evident and steep that the one indicated by the FVC and it occurs in a longer period of time.
Lanini et al. [93] - 2008	<ul style="list-style-type: none"> • BMD, n=3 • FSHD, n=1 • LGMD, n=2 • Myotonic dystrophy, n=2 • Healthy subjects, n=12 	To test the hypothesis that operating forces on the CW may impact on distribution of inspired gas volume to RC compartments, resulting in RC distortion and decrease in cough effectiveness.	The cough peak flow was negatively correlated with the distortion of the CW, but not with respiratory muscle strength.
D'Angelo et al. [101] - 2011	<ul style="list-style-type: none"> • LGMD, n=38 • BMD, n=20 • FSHD, n=30 • Healthy subjects, n=20 	To study the CW behaviour in a large population of patients affected with LGMD, BMD and FSHD.	<ul style="list-style-type: none"> • Both IC and VC were significantly lower in LGMD and FSHD patients than in healthy subjects. • BMD patients showed slightly lower values of IC and normal values of VC. • AB contribution was reduced in wheelchair bound patients with LGMD and FSHD in the seated

			position.
Bourdarham et al. [25] – 2013	<ul style="list-style-type: none"> • Myotonic Dystrophy, n=6 • Acid Maltase deficiency, n=5 • Mitochondrial Myopathy, n=1 • DMD, n=1 • Spinal muscular atrophy, n=1 • Neuralgic amyotrophy, n=6 	To determine whether OEP accurately evaluated VC in patients with respiratory muscle dysfunction of variable severity, including those with paradoxical AB movements.	In subjects with various degrees of restrictive respiratory disease VC evaluated with spirometry and OEP showed a strong positive correlation and relatively good agreement.
LoMauro et al. [27] - 2014	<ul style="list-style-type: none"> • SMA, n=18 • Healthy subjects, n=18 	To study how CW kinematics and respiratory muscles change in relation to SMA severity.	In mild SMA and intermediate SMA, RC motion was significantly reduced and sometime paradoxical during quiet breathing in supine position.
Lissoni et al [97] - 1998	<ul style="list-style-type: none"> • SMA type II, n=9 • Healthy subjects, n=13 	To analyse CW kinematics during spontaneous breathing (healthy subjects) and during spontaneous breathing and while using mechanically assisted ventilation (SMA patients).	CW kinematic analysis may be helpful for choosing the ventilation parameters to optimize therapeutic benefits.
Lissoni et al. [102] - 1996	<ul style="list-style-type: none"> • SMA, n=12 • Healthy subjects, n=13 	To analyse thoraco-abdominal volume changes when breathing spontaneously and when breathing deeply.	kinematic analysis can be helpful in determining differences in regional lung mobility and risk for nocturnal ventilatory dysfunction in children with SMA.

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400 9. Outcome assessment after thoracic surgery

401 Thoracic surgery deeply affects CW kinematics, mainly in the early post-operative period. Patients
402 who underwent surgical procedures involving the CW may benefit from pulmonary rehabilitation
403 (PR) in order to restore correct function of respiratory muscles [103]. OEP represents a suitable tool
404 to identify muscular dysfunctions related to chest surgery.

405 Lung transplantation (LT) represents the most burdensome CW dynamics' alteration surgical
406 procedures. Wilkens et al. utilized OEP to measure CW volumes of 39 patients, affected by COPD,
407 idiopathic pulmonary fibrosis (PF) and cystic fibrosis (CF), waiting for LT, and sixteen
408 transplanted subjects [104]. Three distinctive breathing patterns were observed to cope with the
409 disease, which includes higher V_T due to increased EIV for COPD and increased respiratory rate
410 without V_T changes for CF and PF patients. Chronic adaptations of the ventilatory pump to
411 advanced lung diseases seem to be reversible, as the authors demonstrate that lung transplantation
412 restores a normal breathing pattern regardless of the underlying disease. Nosotti et al. focused the
413 attention on the rearrangement of the V_{CW} and its compartments CF patients receiving a double LT
414 [105]. Results showed that 2 months after surgery TLC, FRC and RV significantly decrease, mainly
415 due to the reduction in AB amplitude and to lesser extent in RCp displacement. Based on these
416 findings, the authors argued that with a healthy lung the diaphragm restores its normal curvature,
417 thus decreasing the abdominal distension.

418 OEP has been used to reveal post-operative ventilatory asymmetries. De Groote et al. analysed
419 how two lungs with different mechanical properties may influence CW dynamics. Imbalances in
420 the extent and rate of inflation or deflation between native and transplanted lung could be
421 explained by different changes in the volume of the two hemithoraxes (due to hyperinflation of the
422 native lung), by displacement of the mediastinum, or by a combination of both. Changes in the
423 volume of each hemithorax were measured by OEP during CO₂-induced hyperpnoea and forced
424 expiration in male patients who have undergone single LT for emphysema [106]. The authors
425 reported similar volumes of the two hemithoraxes at both FRC and TLC, thus showing that the
426 unequal volumes of the native lung and the graft are accommodated by displacement of the
427 mediastinum rather than by volume distortion.

428 A wide-spreading application of OEP is in tailoring post-operative pulmonary rehabilitation (PR).
429 Several studies have pointed out the efficacy of PR for COPD patients but less evidence exists for
430 surgical conditions. In Bastianini et al. [54], patients receiving superior lobectomy for non-small
431 cell lung cancer underwent CW kinematic assessment before and immediately after surgery, as
432 well as after 2 weeks of PR. FEV₁ and FVC were found to be decreased between the pre-surgery
433 (PreS) phase and the post-surgery phase (PostS) and partially recovered post-rehabilitation
434 (PostR). Notably the authors reported a significant negative correlation between FEV₁ measured
435 during PreS and the FEV₁ decreasing from PreS to PostR. The above-mentioned findings agree
436 with the results of Cesario et al., although a lower improvement in the latter study was observed
437 after 4-week PR [107]. In another study aimed at testing an OEP system as a diagnostic tool to
438 assess the efficacy of asymmetric PR, Bastianini et al. assessed V_T variations of the six
439 compartments (the left and right sides of RCp, RCa and AB) in patients undergone left or right
440 superior lobectomy, in preS, postS and postR phases [108]. Even though PR did not improve the
441 overall volumes, the V_T of the non-operated side increased between preS and postR. This
442 indicates PR was more effective on the non-operated side, which then compensates the
443 contralateral one. The negative effect of chest wall tumours on global CW mechanics during quiet
444 breathing and exercise has been confirmed by Elshafie et al. in recent study on a patient with
445 unilateral extra-thoracic chest wall sarcoma. They demonstrated that surgery reverses this
446 abnormality, but only at rest [109].

447 **10. Evaluation of other health conditions**

448 OEP has been used in several clinical applications to study different pathological conditions. Due
449 to the large number of studies in each category, the main scientific findings are summarised in
450 Table 3, and only the main applications are briefly described in this section.

451 OEP has been used to study thorax and CW deformity, in children with pectus excavatum
452 [110,111] with Osteogenesis Imperfecta type III and type IV (connective tissue disorder
453 characterized by bone fragility, multiple fractures, and significant CW deformities) [107] and in
454 adults with ankylosing [112,113] and to evaluate the effect of posture on breathing kinematics in
455 subjects with spinal cord injury [55]. OEP has also been used to investigate V_T differences between
456 paretic and healthy sides during quiet breathing, voluntary hyperventilation and hypercapnic
457 stimulation in post-stroke patients with hemiparesis [21]. One study analyzed the ventilator
458 breathing pattern in patients with late onset glycogen storage disease type II. This is an autosomal
459 recessive lysosomal storage disease due to glucosidase alpha acid deficiency, a slowly progressive
460 disease predominantly affecting skeletal and respiratory muscles [114]. Frazão et al. used the OEP
461 to assess the outcome of a respiratory rehabilitative treatment using PEP-Mask in Parkinson
462 patients [115].

463 In patients with chronic heart failure plus cardiomegaly, significant differences in the regional
464 distribution of RC volumes were found among patients with heart failure associated with
465 cardiomegaly and healthy controls [116]. Barcelar et al. demonstrated, with the use of the OEP, in
466 obese women ($BMI > 40\text{kg/m}^2$) not only lung but also CW function is altered [70].

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480 **Table 3:** Studies utilizing OEP in the evaluation of other pathological conditions (VC=Vital
 481 Capacity, MV=minute volume, FVC=functional ventilatory capacity, IC=inspiratory capacity, ERV=
 482 expiratory reserve volume,).
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Authors – year	Pathology, Sample characteristics	Findings
<ul style="list-style-type: none"> • Binazzi et al. [110] – 2012 • Redlinger et al. [111] – 2011 	Pectus Excavatum, <ul style="list-style-type: none"> • n=24 • n=119 	<ul style="list-style-type: none"> • The V_{CW}, V_{RCp}, V_{RCa} and V_{AB} at rest are similar in patients with PE and in healthy subjects. During maximal respiration, PE patients had a significant increase in the volume within the RCa compared with healthy ones. • Patients with PE demonstrated significantly decreased midline marker excursion at the level of the pectus defect.
LoMauro et al. [40] – 2012	Osteogenesis Imperfecta type III and type IV, n=22	<ul style="list-style-type: none"> • Pectus carinatum characterizes Osteogenesis Imperfecta type III patients and alters respiratory muscles coordination, leading to CW and RC distortions and an inefficient ventilator pattern.
<ul style="list-style-type: none"> • Ferrigno et al. [112] – 1998 • Romagnoli et al. [113] – 2004 	Ankylosing spondylitis <ul style="list-style-type: none"> • n=17 • n=6 	<ul style="list-style-type: none"> • During rebreathing, CW expansion increased (AB component increased more) to a similar extent in patients with ankylosing spondylitis to that unhealthy subjects. • RC inspiratory peak and muscle pressure was significantly lower in patients than in controls subjects, but not the AB.
Bouardham et al. [117] – 2013	Unilateral diaphragm weakness, n=13	<ul style="list-style-type: none"> • OEP detected asymmetric ventilation in all patients diagnosed with unilateral diaphragm weakness and in no patients without this diagnosis. • OEP is an effective non-invasive alternative that is preferred by the patients over diaphragm compound muscle action potentials response and lateral twitch transdiaphragmatic pressure
Meric et al. [118] – 2016	Late-onset Pompe disease, n=11	<ul style="list-style-type: none"> • AB contribution and V_{AB} during the VC manoeuvre are reliable and non-invasive indices of diaphragmatic function in Pompe disease

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Remiche et al. [114] – 2013	Late onset Glycogen storage disease type II, n=10	<ul style="list-style-type: none"> • Higher MV in supine position were found in patients with diaphragmatic weakness (supine FVC fall higher than 25%) respect patients without diaphragmatic weakness (supine FVC change lower or equal to 25%). • In seat and in supine position, patients were characterized by reduced CW IC and by a poor ability to mobilize the AB, being both AB IC and AB ERV significantly lower than in control subjects.
Lanini et al. [21] – 2003	Hemiplegia due to a cerebrovascular accident, n=8	<ul style="list-style-type: none"> • V_T of paretic and healthy sides were similar during quiet breathing • Hemiparetic stroke produces asymmetric ventilation with an increase in carbon dioxide sensitivity and a decrease in voluntary ventilation on the paretic side
Frazão et al. [115] – 2014	Parkinson Patients, n=15	<ul style="list-style-type: none"> • The study did not find significant difference for AB compartment contribution between Parkinson's patients and healthy subjects during quiet breathing even with Parkinson's showed higher V_T values.
Brandão et al. [116] – 2012	Chronic heart failure plus cardiomegaly patients, n=19	<ul style="list-style-type: none"> • Left side of the RCa is characterized by lower displacement during inspiratory loaded breathing. • Regional distribution differences in V_{CW} are correlated with other functional parameters, namely left ventricular ejection fraction and dyspnoea.

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486 11. OEP in Exercise Science

487 The function of the respiratory system during exercise is usually assessed by via the analysis of
488 expired air to calculate breathing frequency, tidal volume, minute ventilation, oxygen
489 consumption and carbon dioxide production. These methods are commonly used and are valuable
490 in the quantification of fitness status and diagnosis of a range of cardiovascular and respiratory
491 diseases [119].

492 Until recently the movement of the chest and abdomen during exercise has not been considered in
493 neither the understanding of optimal breathing pattern nor in relation to exercise respiratory
494 diseases. The assessment of chest and abdomen wall movement during exercise may also assist in
495 the understanding of breathing pattern disorders and exercise-triggered dysfunctional breathing
496 [120].

497 Dickinson et al. have previously reported that using breathing technique and inspiratory muscle
498 training has been successful in eliminating exercise respiratory symptoms during high intensity
499 exercise in an elite athlete, however the absence of a method to track chest and abdomen wall
500 movements meant it was impossible to quantify any changes in breathing mechanics [121].

501 Investigations into the use of OEP to assess the movement of the chest and abdomen during
502 exercise is emerging. Initial reports suggest end-inspiratory lung volume increases during exercise
503 are mainly achieved by increasing end-inspiratory volumes of the RCp and RCa reflecting the
504 inspiratory RC muscle contribution [122]. Initial work from Layton et al using OEP suggests that
505 during exercise females have less contribution from V_{AB} and greater contribution of V_{RCp} when
506 compared to males [123,124]. Table 4 provides an overview of the studies that have used OEP to
507 evaluate breathing pattern and CW movement during exercise.

508 Further investigations using OEP during exercise will assist our understanding of the relationship
509 between respiratory and locomotor muscle fatigue, posture and CW movement. These types of
510 investigations can then aid the delivery of specific therapy and breathing training programmes
511 targeted towards reducing exercise respiratory symptoms and optimising chest and abdomen wall
512 movement during exercise.

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516 **Table 4:** Studies that have used OEP to evaluate chest wall movement and breathing pattern
 517 during exercise. (FVC=Functional Vital Capacity, EIV_{CW} = End-inspiration chest wall volume,
 518 EEV_{CW} = End-expiration chest wall volume, V_{CW}= total chest wall volume variations, EEV_{RCp} = End-
 519 expiration pulmonary rib cage volume, EIV_{RCp} = End-inspiration pulmonary rib cage volume, V_{AB}=
 520 abdominal volume, ET=endurance-trained athletes, UT=untrained athletes)
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Authors – year	Sample characteristics	Aims	Findings
Vogiatzis et al. [125] – 2005	n=15 (10 males, 5 females)	To investigate the pattern of response in operational lung volumes and relative contribution of respiratory muscle groups between men and women of similar fitness.	<ul style="list-style-type: none"> • Men exhibited significantly greater operational lung volumes than women during symptom-limited exercise. • During the incremental exercise EIV_{CW} is progressively increased and EEV_{CW} is decreased and that both genders utilised primarily the muscles of the rib cage compartment rather than those of the abdomen.
Layton et al. [123] –2011	n=18 ET (11 males, 7 females) n=14 UT (9 males, 5 females)	To determine how increased ventilatory demand impacts ventilatory kinematics and if there is any difference in the total chest wall volume variations (V _{CW}) of male and female endurance-trained athletes (ET) compared to untrained individuals (UT) during exercise.	<ul style="list-style-type: none"> • With peak exercise, female ET did not change EEV_{CW} or EEV_{RCp} while female UT significantly decreased both parameters. • ET have significant increases in EIV_{RCp}, while UT do not. • Women demonstrated less contribution of the V_{AB} and greater contribution of V_{RCp} when compared to men. • Men demonstrated similar contribution of the V_{RCp} and the V_{AB}.
Layton et al. [124] – 2013	n=16 ET n=14 UT	To compare measurements of V _T by OEP and spirometry during a maximal cycling exercise test	Discrepancy of -2.4±3.9% between the two methods during maximal exercise and -2.0±7.2% during submaximal exercise

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525 **11. Conclusions**

526 OEP is an innovative non-invasive tool of measuring different compartments of the chest wall and
527 thus lung volume variations. OEP has been shown to be a valuable and accurate assessment tool
528 that can provide crucial information about chest wall mechanics across the respiratory field.

529 The high accuracy and validity of the OEP to measure volume variations assessed in different
530 populations and experimental protocols allow to successfully use this tool in newborns and
531 children, healthy and pathological subjects; OEP allows the study of both breathing volumes and
532 biomechanical indexes for a better comprehension of the work of breathing without interferences
533 using invasive instrumentation.

534 Despite the fact that OEP has been used in research, the large number of markers strongly
535 discourage its employment in the daily clinical practise as an alternative tool for traditional flow-
536 based instrument to assess respiratory parameters. In fact, the markers placement can be tedious
537 and complicated, especially in subjects in which the landmarks are difficult to identify. Markers
538 placement is also time-consuming and therefore requires dedicated staff. In order to make OEP
539 more practical for an applied patient setting, future investigations should focus on reducing the
540 marker set or integrate OEP into wearable technology.

541 Moreover, at the moment the cost of an eight-cameras system OEP is very high, however softwares
542 to compute breathing volumes from markers have recently been described in literature and they
543 will be profitably used with all high-resolution commercial motion capture systems.

544 OEP may be used in the future to assist in the understanding of breathing patterns in respiratory
545 conditions that are difficult to diagnose objectively e.g. dysfunctional breathing, and therefore it
546 may have the potential to contribute to an improvement in therapeutic strategies.

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