Fluid and electrolyte balance after major thoracic surgery by bioimpedance and endocrine evaluation

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**Objective:** Weight gain with oedema formation is a complication of major surgical procedures with an incidence as high as 40%. Fluid retention is not always clinically evident and it is reported despite fluid-restriction regime. The causes are several and not totally clear.

**Methods:** In 49 patients submitted to lobectomy with systematic lymph node dissection for lung cancer, we measured preoperatively and on the postoperative days 1, 2, 4 and 7, body weight, fluid balance, brain natriuretic peptide (BNP) and bioimpedance analysis (BIA)-derived parameters resistance (R) and reactance (Xc). Results: The postoperative course was characterised by significant changes. Mean increase in body weight was 2.7 kg ((1.9—3.4); p < 0.001) on postoperative day 2. Most of the patients had a negative basal fluid balance (~244 ml (~520 to ~50)), whereas, on postoperative day 2, we observed a positive and significant change (~968 ml (646—1456), p < 0.001)). Total body R and Xc fell on the first day (p < 0.001), anticipating the changes in weight and fluid balance. BNP increased on day 1, immediately after surgery, and remained significantly above basal values for the entire observation period (p < 0.001), in the absence of clinical signs of heart failure. Conclusion: The three methods used consistently showed a significant fluid retention over the course of the study. BIA was an easy, reproducible and non-invasive method for the estimation and early detection of fluid retention. Increase in BNP may be related to the systemic reaction to stress and to the decreased effects [7], the activation of the stress response to the surgical injury [6] and one-lung ventilation [8]. However, postoperative fluid retention is reported despite fluid-restriction regime. Undoubtedly, there are other factors, not sufficiently investigated, that could cause this event.

**Keywords:** Pulmonary surgical procedures; Fluid balance; Brain natriuretic peptide (BNP); Bioimpedance analysis (BIA)
Consequently, the aim of this observational study was to evaluate, in patients submitted to pulmonary lobectomy for lung cancer, the amount of weight gain due to postoperative fluid retention using conventional methods, bioimpedance and neuroendocrine markers.

2. Materials and methods

2.1. Study protocol

We prospectively evaluated from 1 April to 1 August 2009 all patients affected by lung cancer and scheduled to lobectomy with systematic lymph node dissection. A total of 49 consecutive patients were enrolled in the study. All had good performance status, defined according to the Eastern Cooperative Oncology Group scale as a performance status <2 [11,12]. The local ethics committee approved the study, and written informed consent was obtained from all patients.

The primary end point of this study was to assess fluid retention after acute stress due to major thoracic surgery. Other secondary end points were predefined to evaluate the feasibility and performance of bioimpedance to quantify fluid imbalance, and to evaluate the time course of BNP after surgery.

The preoperative evaluation included detailed history and physical examination, cardiopulmonary evaluation, total body computed tomography (CT), fiberoptic bronchoscopy and positron emission tomography/computed tomography (PET-CT). Weight, body mass index (BMI), haematological and biochemical profile, brain natriuretic peptide (BNP) and bioimpedance analysis (BIA) were recorded preoperatively (value 0) and on the postoperative day (POD) 1 (value 1), 2 (value 2), 4 (value 3) and day 7 (value 4). The day of surgery was counted as intra-operative time and postoperative day 0. Because of the observational nature of this study, no set guidelines for intra-operative and postoperative intravenous fluid management were imposed, and all patients were treated in accordance with the established practice of fluid-restriction regime. Intra-operative fluid administration was controlled by the anaesthesiologist, and by the surgical team thereafter, depending on the clinical course of the patients and on the losses of blood, fluids, drains, urine output and cardiovascular signs. The patients remained fasted from midnight on the preoperative day. Loss due to fasting and perspiratio insensibilis was recorded in the intra-operative fluid balance and estimated at 80 ml per fasting h as reported by literature [4].

Oral ingestion began on the day after operation. The volume and type of fluid administered during surgery and the total fluid intake (oral plus IV infusion) were recorded daily. Fluid balance was calculated from the day of operation up to POD 7. Body weight was recorded every day in the morning with the same scale.

As reported in literature [1], some patients accumulate large fluid volumes in the postoperative period without developing clinically overt oedema. For this reason, we decided not to assess oedema during the course of the study.

2.2. Bioelectrical impedance analysis (BIA)

A small, undetectable, alternating current is passed through the body and bioimpedance analysis (BIA) measures the resistance to flow of the current. BIA consists of two components: tissue resistance ($R$) and reactance ($X_c$). It is inversely related to fluid volume and directly related to the square of the conducting length [13], and, using validated equations, it allows measurement of preoperative fluid depletion and postoperative fluid overload [9].

BIA measurements were performed at the bedside, after a minimum of 30 min supine rest, according to standard, tetrapolar, whole-body (hand–foot) techniques using a single-frequency (50 kHz) analyser (BIA-101; Akern–RJL Systems, Florence, Italy). The distance between hand and foot electrodes was recorded at baseline and used in all subsequent measurements. Subjects were instructed to remove any metal item before measurements. BIA measurements were performed in the morning of the preoperative day, and postoperatively on the first, second, fourth and seventh day. $R$ and $X_c$ values were used to estimate TBW, according to validated equations [14].

2.3. BNP measurements

In our study, the levels of BNP were determined before surgery, and on PODs 1, 3 and 7. Venous blood (4 ml) was obtained from each patient and transferred to tubes containing ethylene diamine tetraacetic acid (EDTA), then stored at $-20 \, ^\circ \mathrm{C}$ until determination. Plasma concentrations of BNP were measured using a chemiluminescent enzyme immunoassay kit (TRIAGE BNP; Biosite Incorporated, San Diego, CA, USA). The minimum quantity of human BNP detectable with this system is 1.0 pg ml$^{-1}$. The intra-assay and inter-assay coefficients of variation (CVs) of the test were 3.1% and 4.5%, respectively.

2.4. Statistical analysis

Outcome variables were analysed using a mixed-effects linear model for repeated measures that included baseline values and daily fluid intake as covariates. Missing data were handled using the last observation carried forward (LOCF) methodology. We also tested for the contribution, if any, of age, sex, BMI, haematocrit, serum albumin concentration and duration of anaesthesia as potential explanatory covariates. Non-normally distributed variables were log-transformed before the analysis. Results are given as mean and 95% confidence intervals (95%CI) or mean and range, as appropriate. All statistical tests were two-tailed and evaluated at the 5% significance level with Sidak’s adjustment for multiple comparisons.

3. Results

The mean age of 34 males and 15 females enrolled in the study was 66 years (63–68 years). The main clinical characteristics of these patients are listed in Table 1.

All patients underwent a pulmonary lobectomy and systematic node dissection with curative intent through a
standard posterior-lateral thoracotomy. A lower lobectomy was performed in 20 patients, a middle in three, a bilobectomy in five and an upper lobectomy in 21.

Two procedures were associated with bronchial sleeve resection; one with en bloc chest wall resection and one with resection of first and second ribs.

There were 22 adenocarcinomas, 13 squamous cell carcinomas, six large cell carcinomas, three carcinoids, three bronchioloalveolar carcinomas, one squamous-sarcomatoid and one adenosquamous carcinoma Pathological tumour, node, metastasis (TNM) staging was determined according to the guidelines of the American Joint Committee on Cancer [15], and was as follows: 18 patients had stage Ia, nine had stage Ib, five had stage Ila, five had stage IIb and 12 IIIa.

Postoperative pain relief was accomplished by paravertebral analgesia and by continuous intravenous (IV) infusion of morphine using a silicone elastomeric pump from POD 0 to day 4 or 5. The intra-operative courses were uneventful; all patients were promptly extubated at the end of operation. Estimated mean intra-operative blood loss was 274 ml (range 50—1100 ml). No blood transfusions were required and none of the patients required intensive care unit stay. The procedures were performed under general anaesthesia with selective one-lung ventilation; mean duration of anaesthesia was 260 min (range 180—480 min).

There was no mortality and there were three cases of major morbidity: one acute renal failure, one pulmonary embolism and one prolonged air leak. There were five minor morbid events: four atrial fibrillations and one limited alveolar consolidation. None of the patients in this study had a prolonged period of pyrexia.

The mean preoperative body weight was 71.1 kg (67.6—74.4). The largest weight increase was observed on POD 2 (+2.7 kg (1.9—3.4); \( p < 0.001 \) vs baseline). From day 3, postoperative weights decreased moderately, but, on day 7, they were still above (+1.24 (0.5—2.2); \( p = 0.001 \) vs baseline) preoperative values (Fig. 1). Body-weight changes were not related to age, sex, BMI and duration of anaesthesia.

Fluid balance from the intra-operative period to POD 7 is shown in Fig. 1. The mean value of fluids infused (saline or crystalloids) during the day of operation was 2500 ml (range 2000—6000 ml). On POD 1, oral liquid feeding was started, and, on the following day, free diet was introduced. The mean value of the global fluid intake (oral plus IV infusion) was 1764 ml (range 3500—750 ml), 2700 ml (range 4400—400 ml), 2520 (range 5700—600 ml) and 2190 (range 3600—500 ml) on POD 1, 2, 4, and 7, respectively. We found a highly significant positive correlation (\( r = 0.4532, p < 0.001 \)) between fluid balance and fluid intake (Fig. 2). Fluid balance (after adjustment for intake) was negative at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>[95% confidence interval]</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>65.6 (62.9—68.4)</td>
</tr>
<tr>
<td>% Male</td>
<td>69% (56%—83%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.4 (162.4—166.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.1 (67.6—74.6)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.3 (25.1—27.5)</td>
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<tr>
<td>Duration of anaesthesia (min)</td>
<td>265.8 (244.8—286.7)</td>
</tr>
<tr>
<td>BIA — resistance (R) (ohms/m)</td>
<td>540.4 (516.3—564.5)</td>
</tr>
<tr>
<td>BIA — reactance (Xc) (ohms/m)</td>
<td>43.4 (40.6—46.2)</td>
</tr>
<tr>
<td>Hb (g/l)</td>
<td>13.5 (13.1—13.9)</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>40.9 (39.3—42.5)</td>
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<tr>
<td>Albumin (g/l)</td>
<td>4.1 (4.0—4.2)</td>
</tr>
<tr>
<td>Total proteins (g/l)</td>
<td>6.8 (6.6—7.0)</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>38.5 (35.8—41.2)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8 (0.7—0.9)</td>
</tr>
<tr>
<td>Na⁺ (mEq/l)</td>
<td>141.2 (140.4—142.0)</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>42.8 (25.7—60.0)</td>
</tr>
</tbody>
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BMI: body mass index; BIA: bio-impedance analysis; R: resistance; Xc: reactance; Hb: haemoglobin; Ht: haematocrit; BUN: blood urea nitrogen; BNP: brain natriuretic peptide.

Fig. 1. Body weight (left panel), fluid balance (middle panel), and BNP (right panel) time course. The dashed line denotes the upper limit of normal range.

Table 1. Baseline characteristics. Values are means or percentages as appropriate.
(−244 ml (−520 to −50) ml) and moved to positive values on day 2 (+968 ml (646–1456), p < 0.001 vs baseline). During the subsequent days, the average fluid balance remained above baseline, and, on day 7, the mean difference was still positive (+708 ml (352–1023) ml; p < 0.001 vs baseline).

As shown in Fig. 1, the preoperative average BNP level was in the normal range (0–100 pg ml\(^{-1}\)). The postoperative evolution of BNP showed an early and highly significant increase on day 1 (+101 pg ml\(^{-1}\) (50–153); p < 0.001 vs baseline). The value remained above basal values up to day 4 (+89 pg ml\(^{-1}\) (19–160); p = 0.007 vs baseline) with a biphasic trend; there was an early significant increase on day 1, immediately after surgery, and late phases on day 4. BNP was close to basal levels by the end of the observation period (p = 0.233 vs baseline). None of the patients developed signs or symptoms of heart failure during the PODs.

We found no correlation between BIA parameters and fluid intake (Fig. 2). Fig. 3 shows the time course of \(R\) and \(X_c\). A sharp drop of these values was already evident on day 1 (\(R = 81\) ohms (−100 to −20); p < 0.001 vs baseline; \(X_c = 10\) ohms (−13 to −8); p < 0.001 vs baseline), anticipating subsequent changes in body weight and fluid balance. Nadir values of both \(R\) and \(X_c\) were observed on day 2. Subsequently, \(R\) and \(X_c\) showed an increasing trend, but they remained below baseline values until the end of the observation period (\(R = 49\) ohms (−49 to −28); p < 0.001 vs baseline; \(X_c = 7\) ohms (−10 to −3); p < 0.001 vs baseline).

Finally, although we noted significant changes over time of haemodilution markers (haematocrit, p < 0.001; serum albumin, p < 0.001), these were not significantly related to weight gain (p = 0.109 and p = 0.260 for haematocrit and albumin, respectively) (Fig. 4).

4. Discussion

Our data confirm the generalised tendency to accumulate large volumes of fluids in the postoperative days. Fluid retention with weight gain is evident despite a negative intra-operative fluid balance, peroperative strict fluid restriction, early mobilisation and an encouraged intake of oral fluids as part of a normal diet. Besides conventional methods of clinical assessment, both BNP and BIA are early informative and sensitive markers of this condition. Fluid
retention has been so far evaluated after major abdominal surgery. In this setting, fluid retention was associated with increased morbidity including prolonged ileus, sepsis and delayed recovery time [3—5]. Following lung resection, the increase of water in the interstitial space can severely impair gas diffusion. Early detection of fluid retention may reduce the risks associated with this condition.

In major thoracic surgery, fluid imbalance is hazardous because the incidence of post-pneumonectomy pulmonary oedema may be as high as 12—15% [8]. The acute stress response to major surgery can determine a severe inflammatory response syndrome and profound changes in the endocrine, neuroendocrine and immune system responses, as well as significant changes in organ function [16,17], leading to fluid retention [6,17,18]. Taken together, the net effect is an increased catabolism with increased substrate availability for energy production, and sodium and water retention to maintain fluid volume and haemodynamic stability [6,17]. Sodium and water are retained avidly in the first few days, and convalescence and recovery are heralded by a return of the capacity to excrete any salt and water overload acquired during the earlier phase [19]. All these facts support the concept that parts of intra-operatively administered fluids are redistributed into the interstitial and intracellular spaces, which undergo reabsorption in the postoperative period [20].

As reported by ‘British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients’ [21] and by Brandstrup [4], daily weighing is considered the most reliable method to estimate fluid balance in surgical patients with fluid replacement being based on clinical observation of fluid loss.

In our experience, the three methods used to assess fluid gain consistently showed a significant fluid retention over the course of the study. However, conventional assessment of daily fluid balance and body-weight changes may be cumbersome and inaccurate in a typical clinical setting. Daily fluid balance may be inaccurate due to perspiratio insensibilis, poor quantitation of oral fluid intake and/or urine collections. Daily weighing may be cumbersome or even unfeasible in the early PODs due to the presence of chest drains and difficulties in maintaining an upright position. Thus, quantitative and non-invasive methods to estimate TBW might be useful in clinical practice to monitor patients susceptible of fluid compartmentalisation after major surgery. BIA is a bedside tool allowing non-invasive, early, informative and convenient assessment of fluid retention independent of intake. The time course of BIA in our study is consistent with the results reported by Itobi et al. following major abdominal surgery [1]. Besides, as reported by the Danish Study Group on Peri-operative Fluid Therapy [5], BIA is a more sensitive indicator of fluid overload than body weight and clinical examination.

BNP is a well-known biomarker of fluid overload. Its association with heart failure, atrial fibrillation [22,23] and other cardiac or infective complications following pulmonary resection [24] is well documented. Elevated BNP levels are associated with primary pulmonary hypertension and this marker can distinguish heart failure from other causes of dyspnoea more accurately than left-ventricular (LV) ejection fraction and ANP level [10]. Recently, a compensatory role of BNP after pulmonary resection has been described [25], but its clinical significance in patients undergoing pulmonary resection for lung cancer is not completely elucidated. In our patients, preoperative BNP was within the normal range, whereas, in the postoperative observation, plasma BNP rapidly increased and remained above the normal range for the whole study period. The overall BNP pattern appears somewhat biphasic. This is consistent with findings by Nojiri et al. [22] in a study designed to evaluate the association between BNP secretion and postoperative atrial fibrillation. They reported a biphasic BNP pattern in a series of 80 patients with lung cancer submitted to pulmonary resection (not pneumonectomy). They explained the early peak to be
caused by an increase of right-ventricular (RV) overload, with a decreased volume of the pulmonary vascular bed caused by pulmonary resection, and the late peak, due to RV and LV overloading caused by a change in the circulating fluid balance or the so-called refilling phenomenon [22].

Our findings have some limitations. The results of this observational non-randomised study should be regarded as hypothesis generating, deserving further confirmatory studies. It was a single-centre, pathophysiology-driven study conducted on a limited number of patients. We did not observe major morbidity events; thus, we could not evaluate the potential prognostic impact of our findings.

In conclusion, we found a significant postoperative weight gain due to fluid retention following lobectomy. BIA is a convenient, reproducible and non-invasive method for the estimation and early detection of fluid retention independent of total intake. The early rise of circulating BNP soon after surgery might be part of the systemic reaction to stress and fluid imbalance. The clinical and prognostic implication of fluid retention following major thoracic surgery may be relevant to patient health.

References