OBES SURG (2016) 26:737–742
DOI 10.1007/s11695-015-1807-3

ORIGINAL CONTRIBUTIONS

Routine Postoperative Monitoring after Bariatric Surgery in Morbidly Obese Patients with Severe Obstructive Sleep Apnea: ICU Admission is not Necessary

Amin B. Goucham[1] · **Usha K. Coblijn**[1] · **Helga B. Hart-Sweet**[2] · **Nico de Vries**[3] · **Sjoerd M. Lagarde**[4] · **Bart A. van Wagensveld**[1]

Published online: 26 July 2015

Abstract
Background and Study Aim Obstructive sleep apnea (OSA) occurs in 70–80 % of bariatric surgery patients. Patients with severe OSA (apnea/hypopnea index (AHI) >30/h) are postoperatively admitted to an intensive care unit (ICU) for continuous monitoring, to prevent complications. The aim of this study was to assess the necessity of routine postoperative monitoring at an ICU of severe OSA patients after bariatric surgery, attempting to prevent and detect cardiorespiratory complications.
Methods Patients undergoing bariatric surgery from November 2010 to July 2013 were entered into a database. Minimal follow-up was 1 month. Poly(somno)graphy (P(S)G) was routinely performed. Patients with severe OSA were admitted to the ICU for the first postoperative night. Oxygen saturation was continuously measured. The database was reviewed regarding patient characteristics, CPAP use, re-intubations, desaturations (saturation <90 % and severe <85 %), and complications.
Results Severe OSA was present in 151 of the 794 patients, and all 151 were admitted to the ICU. Thirty who underwent revisional surgery were excluded. Forty-seven percent was male, median age was 51 years (27.0–68.0), and median body mass index (BMI) was 46.6 (kg/m^2) (34.0–77.6). No deaths, re-intubations, or cardiopulmonary complications occurred. Eighty-two (67.8 %) patients used continuous positive airway pressure (CPAP). Twenty-one (17.4 %) patients experienced desaturations with a median of 2.0 (1–8). Six patients (5.0 %) had one episode of severe desaturation.
Conclusion Patients with severe OSA and adequate CPAP use are at low risk of cardiopulmonary complications after (laparoscopic) bariatric surgery. Routine admission to an ICU might be superfluous. However, continuous digital oximetry remains essential.

Keywords Bariatric surgery · Anesthesia · Sleep apnea · Monitoring · Intensive care unit, ICU · Desaturations · Complications

✉ Usha K. Coblijn
usha.coblijn@gmail.com

Amin B. Goucham
amingoucham@gmail.com

Helga B. Hart-Sweet
h.hart@slaz.nl

Nico de Vries
n.devries@slaz.nl

Sjoerd M. Lagarde
sjoerdlagarde@hotmail.com

Bart A. van Wagensveld
b.vanwagensveld@slaz.nl

1 Department of Surgery, Sint Lucas Andreas Ziekenhuis, Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands

2 Department of Anesthesiology, Sint Lucas Andreas Ziekenhuis, Amsterdam, The Netherlands

3 Department of Otolaryngology, Sint Lucas Andreas Ziekenhuis, Amsterdam, The Netherlands

4 Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands

Introduction

Obesity is a major health problem with serious medical, psychological, and socioeconomic consequences all over the world [1–3]. Obstructive sleep apnea (OSA) is an important comorbidity that improves dramatically after bariatric surgery [4]. However, OSA is considered a risk factor for postoperative events after general anesthesia. Desaturation (10.7 vs

5.6 %) can be regarded as one of the first symptoms of such a negative adverse event like respiratory failure (2.0 vs 0.7 %), cardiac events (3.8 vs 1.7 %), intensive care unit (ICU) transfer (5.1 vs 1.6 %) stroke, and mortality (adjusted hazard ratio 2.0) [5, 6].

OSA is a disease characterized by recurrent airway collapse. In obese patients, it is thought that an important part of the pathophysiology is caused by the local fatty tissue deposition in the neck which results in reduction of the lumen of the upper airway [7]. Due to the subsequent restricted airflow, patients can become hypoxic which can lead to cardiac arrest and other ischemic complications [8].

The prevalence of OSA in the bariatric population ranges from 71 to 91 % [9, 10]. The apnea/hypopnea index (AHI) represents the combined number of apneas and hypopneas that occur per hour of sleep. An AHI of 5–15 was graded as mild, 15–30 as moderate, and ≥30 as severe OSA. Of those with OSA, 33.1 % are diagnosed with severe OSA [11].

Bariatric surgery is the only long-term effective treatment for weight loss [2]. Ten years after bariatric surgery, weight loss (25 % of total weight for gastric bypass) was still apparent, whereas patients receiving conservative treatment regain their baseline weight. There is also a significant reduction in obesity-related comorbidities such as type 2 diabetes [12, 13].

In many institutions, patients with severe OSA are admitted at the ICU, medium care unit, or under intensive monitoring at the general surgical ward after bariatric surgery [14]. The growing demand for bariatric surgery, however, creates an increasing logistical strain on costly critical care resources. Evidence justifying postoperative ICU admission is scarce. Several studies show that routine ICU admission is not required, and continuous monitoring by means of pulse oximetry or capnography alone may be sufficient [15, 16]. The American Society of Anesthesiologists has put forth recommendations for the perioperative care of patients with OSA. These recommendations are, however, not evidence based since research is scarce [17]. To minimize cardiopulmonary complications, continuous positive airway pressure (CPAP) is frequently used perioperatively. CPAP reduces hypoxemia and should decrease postoperative hypoxemic complications [18].

Still, many institutes do not use protocols regarding this issue, and therefore, an evidence-based approach is in order [19].

This study aimed to assess the necessity of routine postoperative monitoring at an ICU of severe OSA patients after bariatric surgery, attempting to prevent and detect cardiorespiratory complications.

Methods

From November 2010 to July 2013, 794 morbidly obese patients underwent bariatric surgery and were entered into a consecutive database. Patients underwent laparoscopic Roux-en-Y gastric bypass (LRYGB), laparoscopic adjustable gastric banding (LAGB), or laparoscopic sleeve gastrectomy (LSG). Thirty of the 151 patients who had severe OSA and were admitted at the ICU were excluded due to a previous bariatric surgery and were excluded from analysis to avoid potential bias.

Data collection for this study was approved by the institution's ethics committee. Patients were considered eligible when the International Federation for the Surgery of Obesity (IFSO) criteria for bariatric surgery were met [20]: a body mass index (BMI) of 40 kg/m^2 or more, or between 35 and 40 kg/m^2 together with significant comorbidity (for example, type 2 diabetes, high blood pressure, or OSA). One patient with a BMI of 34.0 kg/m^2 was accepted due to a severe comorbid disease (including severe OSA) that would benefit weight loss.

Preoperative screening in all patients consisted of psychological evaluation, physical examination including assessment of the upper airway, and additional tests such as laboratory tests or imaging if necessary. All patients underwent esophagogastroduodenoscopy including testing for *Helicobacter pylori*. Due to the very high prevalence of OSA in morbidly obese patients, preoperative screening for OSA was routinely performed by means of poly(somno)graphy (P(S)G). The severity of OSA was determined according to the AHI. Manual scoring was used to determine AHI.

Patients with moderate OSA (AHI >15) were prescribed continuous positive airway pressure (CPAP), and patients with severe OSA (AHI >30/h) were additionally admitted to the ICU for a 24-h postoperative observation.

Patients were treated for OSA with CPAP at home prior to surgery and the treatment was continued postoperatively. Supplemental oxygen with a maximum of 5 l was administered per nasal cannula when necessary, and oxygen saturation was continuously measured using pulse oximetry. Oxygen (O_2) saturation levels were monitored, and an alarm sounded when saturation levels dropped below 88 %. Desaturation was defined as <90 % and severe desaturation as <85 %. All desaturations were automatically collected by the electronic patient records and subsequently reviewed. CPAP compliance was regarded as proper use when its usage was witnessed and documented in a patient's chart by the nursing staff.

As thrombosis prophylaxis, nadroparine 0.6 ml daily was prescribed, starting 1 day prior to surgery until discharge. For postoperative analgesia, paracetamol 1000 mg three times daily was prescribed and, if necessary, diclofenac 50 mg three times daily. If not sufficient, morphine 10 mg subcutaneously up to six times in 24 h was administered. Patient-controlled analgesia was never used. In the postanesthesia care unit (PACU), morphine is titrated until a tolerable level of pain is achieved, usually less than four on a visual analogue scale (zero is no pain and ten is the worst possible pain) [21]. The database was retrospectively reviewed to investigate patient demographics, comorbidities, CPAP compliance, re-intubations, desaturations and severe desaturations, complications, and mortality.

Statistical analysis was performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL). A histogram was used to test whether the data was normally distributed; if normally distributed, the analysis of continuous variables was carried out using the independent sample *T* test; otherwise, the Mann-Whitney *U* was used. Logistic regression analysis was used to calculate the odds ratio and confidence interval for predictive variables. Baseline variables which were categorical were analyzed with the chi-square test. A *p* value smaller than 0.05 was considered significant. The rule of three was used to approximate the rate of major complications or fatal events in the absence of observed events.

Results

One hundred and fifty-one (19 %) of the 794 analyzed patients had severe OSA and were admitted to the ICU for the first postoperative night according to protocol. Thirty (19.9 %) patients were excluded from the analysis because they underwent revisional procedures. One hundred and ten patients underwent LRYGB (90.9 %), three underwent LAGB (2.5 %), and eight underwent LSG (6.6 %). Of the 121 patients analyzed, patient characteristics are shown in Table 1.

Median hospital stay was 2.2 nights (1–9). All patients were observed in the ICU for one night except for one patient who was observed for two nights because she did not use her CPAP mask postoperatively and developed hypercapnia which was subsequently treated with CPAP. This patient was 62 years with an AHI of 66 and a BMI of 49.5 with an extensive medical history of frequent hospital and IC admissions for impending respiratory failure due to chronic obstructive pulmonary disease.

Twenty-one (17.4 %) patients experienced one or more desaturations (O_2 below 90 %). Median number of desaturations below 90 % O_2 during ICU admission was 2.0 (1–8). Six patients (5.0 %) had one episode of severe desaturation (O_2 below 85 %). One female patient experienced one episode with six severe desaturations which was treated with CPAP. This patient was 27 years with an AHI of 34, a BMI of 61.3, and no comorbidities. A BMI of 60 kg/m^2 and higher was significantly associated with desaturations <85 % (Table 2).

Eighty-two (67.8 %) patients were CPAP compliant. All non-compliant patients (32.2 %) received oxygen per nasal cannula. There was no association between desaturations and the use of CPAP (Table 2). Median O_2 supplementation was 3 l (range 0–5). No significant association between desaturations and increased AHI could be demonstrated (Table 2).

The 30-day complication rate was 9.1 % (Table 3). Two anastomotic leaks occurred. No in-hospital deaths, re-intubations, cardiopulmonary complications, or wound infections occurred.

Table 1 Baseline characteristics

Number of patients	121
Male (%)	47
Median BMI (kg/m^2)	46.6 (34.0–77.6)
Median age (years)	51.0 (27.0–68.0)
Median AHI (per hour)	50.0 (10.0–149.0)
CPAP compliance (%)	67.8

BMI body mass index, *AHI* apnea/hypopnea index, *CPAP* continuous positive airway pressure

Discussion

This study found that in patients with severe OSA who were monitored at the ICU, no OSA-dependent adverse events occurred. No relation between a high AHI and desaturations could be established. No cardiopulmonary complications occurred in the patients admitted to the ICU. No major interventions were required for desaturations or even for the severe ones. Subsequently, the complication rate was below 2.5 %, comparable with patients without OSA as found by a prospective, observational cohort study by the Longitudinal Assessment of Bariatric Surgery Consortium. They found that the estimated percentage of patients with postoperative complications (deep-vein thrombosis or venous thromboembolism; re-intervention by percutaneous, endoscopic, or operative technique; or failure to be discharged from the hospital within 30 days after surgery) ranges from approximately 3 % among patients who did not have a history of OSA to 5 % among patients who had a history of OSA [22].

The present studies' strength compared to previously published studies is that P(S)G was performed in all patients who underwent bariatric surgery, unless previously assessed with a

Table 2 Predictive variables

Desaturation	Variable	Odds ratio	95 % Confidence interval	Sig.
<90 % O_2	CPAP use (Y/N)	0.980	0.868–1.105	0.980
<90 % O_2	AHI ≥30	1.010	0.991–1.029	0.327
<85 % O_2	BMI ≥60	8.720	1.346–56.512	0.023

CPAP continuous positive airway pressure, *AHI* apnea/hypopnea index, *BMI* body mass index

Table 3 Thirty-day complications

Complication	Number of patients
Bleeding	3
Marginal ulcer	1
Internal herniation	1
Dysphagia	1
Anastomotic leakage	2
UTI or pneumonia	3

UTI urinary tract infection

known AHI. Therefore, no selection bias based on OSA presence occurs. In a previous study, it was shown that medical history, BMI, and neck circumference cannot reliably predict the presence of OSA [11].

Unfortunately, one of the limitations of the present study is the lack of power to detect differences between patients with and without OSA or CPAP usage. Since the rate of complications was low, it cannot be concluded that no adverse events occurred. Still, the results presented are comparable with the aforementioned studies.

In an effort to eliminate as much confounding factors as possible, all patients who had previous bariatric surgery were excluded as an increased risk of postoperative complications in revisional surgery exists [23, 24].

In addition to severe sleep apnea, a BMI >60 kg/m^2 is also associated with transfers to the ICU [25]. In this study of Helling et al., no association between pulmonary comorbidity (both OSA and ICU transfers for other pulmonary comorbidities) and complications was found. However, it was shown that a BMI above 60 kg/m^2 combined with severe OSA is significantly associated with desaturations <85 %. However, only seven patients were available for analysis and no interventions were necessary.

In this study, routine P(S)G was part of the screening prior to bariatric surgery identifying all patients with (severe) OSA. The presence of a high AHI (>30 h) as a predictor for ICU admittance was assessed, but no significant association between desaturations <90 % and AHI could be found. Presumably because compliant CPAP use effectively lowers the AHI.

All CPAP-dependent patients were instructed to bring their appliance to the hospital when admitted for surgery. No association between desaturations and CPAP use was found. It is hypothesized that this is caused by low patient compliance. Of most patients using CPAP, compliance was not preoperatively determined. A retrospective cohort study showed a CPAP compliance of only 59.5 % [26]. Many patients consider the use of CPAP uncomfortable. The mask is pulled off during the night unnoticed or it may dislocate during sleep causing air to escape. Another explanation could be that oxygen therapy of less than 5 l was sufficient for the treatment of hypoxemia. A recent meta-analysis comparing oxygen therapy and CPAP showed that both oxygen therapy and CPAP improved saturation equally in non-surgical patients [27]. Because of the abovementioned limitations, it is not possible to determine the effect of CPAP on the amount or the severity of desaturations.

According to protocol, patients are instructed to use their CPAP appliance during ICU admittance, but non-usage was tolerated if the oxygen saturation level, continuously measured, was sufficient. Literature concerning the risk of OSA or CPAP usage on the development of anastomotic leakage lacks ambiguity. Although Fernandez et al. discovered that OSA is a risk factor for the development of anastomotic leakage, diagnostics of OSA is not described, nor treatment of patients with OSA [28]. Vasquez and Hoddinott hypothesized that if patients are not used to breathing with their CPAP device, air might be forced inside the gastrointestinal tract causing bowel distension and pressure on the newly formed, vulnerable anastomosis [29]. However, other studies state that the risk of anastomotic leakage is not increased in patients who use a CPAP mask [16, 30]. With regard to sleeve gastrectomy and positive airway pressure, no literature could be identified. The present study is too small to conclude if positive airway pressure could be used as the pylorus is preserved and a consequently higher pressure on the sleeve's staple line is created compared to gastric bypass surgery. In this study, 67.8 % of the patients at the ICU were postoperatively treated with CPAP. In the patient group treated with CPAP, as well in the one treated only with nasal oxygen, one leakage at the side of the gastrojejunostomy occurred.

Since CPAP use is characterized by poor and difficult compliance due to intolerability of the facial mask in many patients and desaturations still occur, continuous pulse oximetry remains indicated. However, admission at the ICU can be debated if necessary or too cautious as this study shows a low risk on OSA-related complications and unnecessary ICU admissions are costly.

Postoperative use of opioids might cause respiratory depression leading to desaturations [31]. Due to the retrospective nature of this study, it was not possible to quantify the use of morphine. Patient-controlled analgesia was never used and morphine was administered with reserve.

Shearer et al. monitored CPAP-dependent patients using continuous pulse oximetry in a non-ICU setting. CPAP was only used if nasal oxygen was not sufficient. Two out of 192 patients were in need of CPAP due to low oxygen saturation. No patients were admitted to the ICU for additional respiratory support [15]. Although the present study is not sufficient to conclude the standard administration of a standard amount of oxygen to severe OSA patients for the first postoperative night, it could be considered. One of the other limitations in extrapolating our data is in the type of care patients receive in the ICU since this is different from the care at a general surgical ward. Benefits of an ICU compared to the general surgical ward are a noisier environment, and one responsible nursing individual who may wake patients before the desaturation becomes severe compared to one nurse on four or eight patients. Minor interventions, e.g., an increase of oxygen flow till 5 l, were not documented. A prospective study to assess the role of minor interventions and the influence of standard administration of oxygen to severe OSA patients in a monitored floor setting is needed.

Conclusion

These results show that patients with severe OSA who use CPAP adequately are at a very low risk of cardiac and pulmonary complications after laparoscopic bariatric surgery. The lack of major interventions needed for desaturations suggests that routine admission to an ICU might be superfluous and can be regarded as not necessary. However, continuous digital oximetry combined with monitoring remains essential, especially as adequate CPAP compliance is difficult to guarantee.

AHI, apnea hypopnea index; *BMI*, body mass index; *CPAP*, continuous positive airway pressure; *ICU*, intensive care unit; *IFSO*, International Federation of Surgery for Obesity and Metabolic disorders; *LAGB*, laparoscopic adjustable gastric band; *LRYGB*, laparoscopic Roux-en-Y gastric bypass; *LSG*, laparoscopic sleeve gastrectomy; *OSA*, obstructive sleep apnea; O_2, oxygen; *P(S)G*, poly(somno)graphy

Disclosure Statement Amin Goucham, Usha Coblijn, Helga Hart-Sweet, Nico de Vries and Bart van Wagensveld report no conflict of interest. SM Lagarde is supported by Koningin Wilhelmina Fonds (KWF, Dutch Cancer Society) Fellowship, UVA 2013-5853. This does not create a conflict of interest.

Human and Animal Rights and Informed Consent For this type of study, formal consent is not required; the study was approved by the local medical ethics committee. For this type of study, informed consent was not required. No identifying details are presented.

References

1. Schigt A, Gerdes VE, Cense HA, et al. Bariatric surgery is an effective treatment for morbid obesity. Neth J Med. 2013;71(1):4–9.
2. Colquitt JL, Pickett K, Loveman E, et al. Surgery for weight loss in adults. Cochrane Database Syst Rev. 2014;8:CD003641.
3. Caballero B. The global epidemic of obesity: an overview. Epidemiol Rev. 2007;29:1–5.
4. Ravesloot MJ, Hilgevoord AA, van Wagensveld BA, et al. Assessment of the effect of bariatric surgery on obstructive sleep apnea at two postoperative intervals. Obes Surg. 2014;24(1):22–31.
5. Kaw R, Chung F, Pasupuleti V, et al. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. Br J Anaesth. 2012;109(6):897–906.
6. Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353(19):2034–41.
7. Strollo Jr PJ, Rogers RM. Obstructive sleep apnea. N Engl J Med. 1996;334(2):99–104.
8. Shepard Jr JW. Hypertension, cardiac arrhythmias, myocardial infarction, and stroke in relation to obstructive sleep apnea. Clin Chest Med. 1992;13(3):437–58.
9. Frey WC, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. Obes Surg. 2003;13(5):676–83.
10. Hallowell PT, Stellato TA, Schuster M, et al. Potentially life-threatening sleep apnea is unrecognized without aggressive evaluation. Am J Surg. 2007;193(3):364–7.
11. Ravesloot MJ, van Maanen JP, Hilgevoord AA, et al. Obstructive sleep apnea is underrecognized and underdiagnosed in patients undergoing bariatric surgery. Eur Arch Otorhinolaryngol. 2012;269(7):1865–71.
12. Picot J, Jones J, Colquitt JL, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess. 2009;13(41):1–357.
13. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357(8):741–52.
14. El SH, Backman S, Christou N, et al. Use of critical care resources after laparoscopic gastric bypass: effect on respiratory complications. Surg Obes Relat Dis. 2008;4(6):698–702.
15. Shearer E, Magee CJ, Lacasia C, et al. Obstructive sleep apnea can be safely managed in a level 2 critical care setting after laparoscopic bariatric surgery. Surg Obes Relat Dis. 2013;9(6):845–9.
16. Grover BT, Priem DM, Mathiason MA, et al. Intensive care unit stay not required for patients with obstructive sleep apnea after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2010;6(2):165–70.
17. Gross JB, Bachenberg KL, Benumof JL, et al. Practice guidelines for the perioperative management of patients with obstructive sleep apnea: a report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. Anesthesiology. 2006;104(5):1081–93.
18. DeMaria EJ, Carmody BJ. Perioperative management of special populations: obesity. Surg Clin North Am. 2005;85(6):1283–9. **xii**.
19. Memtsoudis SG, Besculides MC, Mazumdar M. A rude awakening—the perioperative sleep apnea epidemic. N Engl J Med. 2013;368(25):2352–3.
20. IFSO. IFSO: are you a candidate. http://www.ifso.com 2015 January 1 [cited 2015 Jan 14].
21. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798–804.
22. Flum DR, Belle SH, King WC, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med. 2009;361(5):445–54.
23. Tran TT, Pauli E, Lyn-Sue JR, et al. Revisional weight loss surgery after failed laparoscopic gastric banding: an institutional experience. Surg Endosc. 2013;27(11):4087–93.
24. Coblijn UK, Verveld CJ, van Wagensveld BA, et al. Laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy as revisional procedure after adjustable gastric band—a systematic review. Obes Surg. 2013;23(11):1899–914.
25. Helling TS, Willoughby TL, Maxfield DM, et al. Determinants of the need for intensive care and prolonged mechanical ventilation in patients undergoing bariatric surgery. Obes Surg. 2004;14(8):1036–41.

26. Richard W, Venker J. den HC, Kox D, van den Berg B, Laman M, et al. Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2007;264(9):1081–6.
27. Mehta V, Vasu TS, Phillips B, et al. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. J Clin Sleep Med. 2013;9(3):271–9.
28. Fernandez AZ, de Maria EJ, Tichansky DS, et al. Experience with over 3,000 open and laparoscopic bariatric procedures. Surg Endosc. 2004;18:193–7.
29. Vasquez TL, Hoddinott K. A potential complication of bi-level positive airway pressure after gastric bypass surgery. Obes Surg. 2004;14(2):282–4.
30. Jensen C, Tejirian T, Lewis C, et al. Postoperative CPAP and BiPAP use can be safely omitted after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2008;4(4):512–4.
31. Chung SA, Yuan H, Chung F. A systemic review of obstructive sleep apnea and its implications for anesthesiologists. Anesth Analg. 2008;107(5):1543–63.