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ORIGINAL ARTICLE

Atrial fibrillation after esophagectomy: an indicator of postoperative morbidity

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Abstract
Purpose. The relevance of new-onset atrial fibrillation (AF) after esophagectomy remains poorly defined. This study's primary goal is to better define the incidence, clinical patterns, and outcomes associated with the development of AF after esophagectomy.
Methods. The study is a retrospective review of patients undergoing esophagectomy at a single academic center between May 1996 and December 2007. Patients with new-onset AF were evaluated by univariate and multivariate analyses for risk factors associated with AF onset and outcomes.
Results. New-onset AF was noted in 32 of 156 (20.5%) patients after esophagectomy. Most (16/32, 50%) developed AF within 48 h, and 28 of 32 (87.5%) developed new AF within 72 h of surgery. Pulmonary complications were more frequent in patients with AF than those without AF (59.4% vs. 15.3%, $P < 0.01$) and usually immediately preceded or occurred concurrently with AF. Anastomotic leaks were significantly more common in patients with AF than those without (28.1% vs. 6.45%, $P < 0.01$) and were identified, on average, 4.2 days after the onset of AF. In the multivariate analysis, anastomotic leaks, pulmonary complications, and number of complications were significantly associated with AF. Although 60-day survival was worse for patients developing AF ($P < 0.01$), multivariate analysis suggests that non-AF complications were the independent predictor of mortality.
Conclusion. New-onset AF after esophagectomy is associated with anastomotic leaks, pulmonary complications, and decreased 60-day survival. Although pulmonary complications typically occurred coincident with the onset of AF, anastomotic leaks were usually diagnosed 4 days after AF onset. New postesophagectomy AF should prompt vigilance for the presence of other concurrent complications.

Key words Esophagectomy · Atrial fibrillation · Anastomotic leak

Introduction

The incidence of esophageal malignancy is increasing in the United States.[1,2] The mainstay of curative treatment for esophageal carcinoma is surgery. Regardless of the surgical approach (transhiatal, minimally invasive, Ivor-Lewis), esophagectomy remains a high-risk procedure with considerable morbidity and significant mortality.[3] Major morbidities associated with esophagectomy include pulmonary complications, anastomotic leak, wound infection, and dysrhythmia. Atrial fibrillation (AF) is one of the most common complications associated with esophagectomy, occurring in more than 20% of patients in some reports.[4–6] Importantly, new-onset postoperative AF may be associated with other complications and increased mortality.[4–19] Because new-onset

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AF often requires readmission and/or prolongs stay in our surgical intensive care unit, we hypothesized that new-onset AF might be a preventable complication of esophagectomy. Before embarking on a prophylaxis trial, we sought to determine the incidence of new-onset AF after esophagectomy and define risk factors and consequences of its development.

Methods

We performed a retrospective review of all patients undergoing esophagectomy at the James Cancer Center and the Ohio State University Medical Center from May 1996 through December 2007. Patients included in this study had primary squamous cell carcinoma or adenocarcinoma of the esophagus or the gastroesophageal junction. Exclusion criteria included (1) those with a previous history of AF (paroxysmal, persistent, or chronic); (2) pregnant women; (3) prisoners; and (4) patients <18 years of age. The institutional review board approved this study.

Recorded clinical parameters included patient demographics, medical co-morbidities and surgical history, drugs of abuse, tobacco and ethanol use, preoperative radiation therapy, hospital and intensive care unit (ICU) length of stay (LOS), follow-up information, and 60-day survival data. Additional detailed chart review included clinical physician/nursing progress notes, physician orders, electrocardiograms (ECGs), operative records, pathology reports, and radiography and laboratory results. Medication data collected included the use of preoperative β-adrenergic antagonists, calcium channel antagonists, angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors (statins). Information regarding postoperative epidural analgesia, postoperative non-AF dysrhythmias, time to AF resolution, administration of amiodarone, β-adrenergic antagonists, or diltiazem for rhythm conversion and/or rate control was also recorded.

The surgical approach for esophagectomy was determined by the operating surgeon based on lesion location and preoperative staging. Approaches included transhiatal esophagectomy, minimally invasive esophagectomy, or Ivor-Lewis esophagectomy. Most cases utilized esophageal replacement with a gastric conduit, with occasional use of an interposition of colon or jejunum. Anastomoses were performed either in the neck or thorax, depending on the approach.

Clinical endpoints included new-onset postoperative AF, patient morbidity (including anastomotic leaks and pulmonary complications), mortality, ICU LOS, hospital LOS, and postoperative survival at 60 days. The definition of an anastomotic leak was based on the presence of one or more of the following criteria: (1) radiographic contrast extravasation on postoperative imaging study (i.e., computed tomography, contrast esophagraphy); (2) documented anastomotic defect on postoperative endoscopic evaluation; and/or (3) clinically apparent leak as evidenced by drain and/or chest tube output.

Recorded pulmonary complications included acute respiratory distress syndrome (ARDS), aspiration/pneumonitis, pneumonia, pneumothorax/hemothorax, pleural effusion, respiratory failure (inability to readily liberate the patient from mechanical ventilatory support), chylothorax, reintubation, radiographically proven pulmonary embolus, mucus plugging, and tracheobronchial injury. Other recorded complications included myocardial infarction (MI), wound infection, wound dehiscence, acute renal failure (ARF), anastomotic stricture, deep venous thrombosis (DVT), vocal cord paralysis, *Clostridium difficile* colitis, multiorgan system failure (MOSF), and sepsis/septic shock.

Atrial fibrillation was defined as an irregularly irregular atrial rhythm without discernible P waves on any ECG tracing with or without symptoms/hemodynamic manifestations that occurred within 30 days of surgery. Identification of postoperative AF was obtained from the physician/nurse daily notes, telemetry recordings, and/or ECG. Baseline cardiac rhythm was ascertained from 12-lead ECG performed within 24 h before the esophagectomy procedure. Additional verification of the presence or absence of preoperative AF was conducted by reviewing each patient's preoperative outpatient records. Preoperative therapy with β-adrenergic antagonists (β-blockers) was routinely continued postoperatively, unless contraindicated. Patients on calcium channel antagonists preoperatively had their pharmacotherapy resumed on the first postoperative day unless clinically contraindicated. Endoscopy examinations, barium contrast evaluations, and/or computed tomography (CT) scans were used to investigate and document suspected anastomotic leaks and strictures.

Statistical analyses were performed using SPSS Version 17 software (SPSS, Chicago, IL, USA). Continuous data were analyzed using Student's *t*-test and analysis of variance (ANOVA) methodologies. Fisher's exact or χ^2 tests were utilized to analyze categoric data. Multivariate logistic regression was performed to determine advanced interactions between clinical variables. Inclusion of individual variables in the multivariate logistic regression was based on statistical significances of alpha <0.20 in the initial univariate analyses, with 14 variables meeting such criteria (see Table 3, below). Survival analysis for AF and non-AF groups was performed

Table 1 Procedure types by incidence of AF and associated cumulative non-AF morbidity

Procedure	No. of patients	Patients with AF	Non-AF morbidity: overall	Non-AF morbidity: AF group	Morbidity: non-AF group
Transhiatal esophagectomy	81 (51.9%)	17/81 (21.0%)	49/81 (60.5%)	12/17 (70.6%)	37/64 (57.8%)
Ivor-Lewis esophagectomy	59 (37.8%)	12/59 (20.3%)	30/59 (50.8%)	10/12 (83.3%)	20/47 (42.6%)
Minimally invasive esophagectomy	16 (10.3%)	3/16 (18.8%)	8/16 (50.0%)	3/3 (100%)	5/13 (38.5%)
Significance (*P*)		NS	NS	NS	NS

AF, atrial fibrillation

Table 2 Characteristics of patients with postoperative AF compared with those without AF

Characteristic	AF group	Non-AF group	*P*
No. of patients	32 (20.5%)	124 (79.5%)	NA
Age (years), mean ± SD	63.7 ± 9.4	59.8 ± 10.8	<0.05
Sex (M:F)	30:2	115:9	NS
ICU LOS (days)	10.1 ± 9.9	3.0 ± 6.8	<0.01
Hospital LOS (days), mean ± SD	19.2 ± 11.6	16.4 ± 16.0	NS
Hospital mortality	6/32 (18.8%)	0	<0.01
Epidural analgesia	20/32 (62.5%)	83/124 (66.9%)	NS

ICU, intensive care unit; LOS, length of stay; NA, not applicable

using Kaplan-Meier/log rank (Mantel-Cox) methodology. Statistical significance was set at alpha = 0.05.

Results

A total of 156 patients underwent esophagectomy (145 men, 11 women) during the study period. Despite a mean patient age of 60.7 years (range 31–80 years), none of the 156 patients had a previously documented history of AF. The in-hospital mortality for the study sample was 6 of 156 (3.9%) and overall morbidity was 93 of 156 (59.6%). Transhiatal esophagectomy was performed in 81 patients, Ivor-Lewis esophagectomy in 59 patients, and minimally invasive esophagectomy in 16 patients (Table 1).

A total of 32 of the 156 (20.5%) patients had new-onset postoperative AF. Most patients (16/32, 50%) developed AF on postoperative day (POD) 2, and 28 of the 32 (87.5%) developed AF by POD 3. It is important to note that none of the patients with AF developed acute MI, as evidenced by lack of cardiac enzyme elevations during the subsequent cardiac workup. The incidence of AF appears independent of the esophageal resection technique, with AF occurring in 21.0% of the transhiatal approach patients, 20.3% of the Ivor-Lewis group, and 18.8% of the minimally invasive group (Table 1). Patients with AF were significantly older than those without AF (63.7 ± 9.4 vs. 59.8 ± 10.8 years, $P < 0.05$) (Table 2).

Interestingly, AF was usually associated with one or more other complications, and isolated AF occurred in only 7 of the 32 (21.9%) patients. AF and one additional complication occurred in 7 (21.9%) patients, AF and two additional complications occurred in 6 (18.8%) patients, and AF plus three or more complications occurred in 12 (37.5%) patients. The presence of non-AF complications and the number of non-AF complications were significantly associated with both postoperative AF and postoperative mortality in the univariate analysis (Table 3). Multivariate analysis suggested that as the number of non-AF complications increases so does the risk for postoperative AF, and the coexistence of AF and non-AF complications is associated with worsened mortality (Table 3).

The most common morbidities associated with AF were anastomotic leaks and pulmonary complications (Table 4). Patients with AF had a much higher incidence of anastomotic leaks than those without AF by univariate analysis (28.1% vs. 6.5%, $P < 0.01$), and AF preceded identification of anastomotic leaks by a mean of 4 days [95% confidence interval (CI), 1.1–7.3 days]. Importantly, of all those with a leak, 9 of 17 (~53%) had new-onset AF. Despite a significant univariate association between AF and anastomotic leaks, multivariate analysis did not corroborate this relation.

When looking at the relation between pulmonary complications and AF, univariate analyses showed that the presence of any pulmonary complication (atelectasis, pleural effusion/pneumothorax, respiratory failure/ARDS) is significantly more frequent in patients with AF than those without AF (all $P < 0.04$). Unlike anastomotic complications, however, these either precede or occur concurrently with AF. Multivariate analysis

Table 3 Univariate and multivariate analyses of risk factors associated with postesophagectomy atrial fibrillation and mortality

	Factors associated with atrial fibrillation			Factors associated with mortality		
	Univariate (*P*)	Multivariate (*P*)	OR	Univariate (*P*)	Multivariate (*P*)	OR
Miscellaneous risk factors/associations						
Atrial fibrillation	n/a	n/a	n/a	<0.001	n/s	n/s
Diltiazem use	n/s	n/s	n/s	<0.001	n/s	n/s
Patient age	n/s	n/s	n/s	n/s	n/s	n/s
SICU length of stay	<0.001	n/s	n/s	<0.001	n/s	n/s
Complications overall						
Presence of any non-AF complication	0.008	n/s	n/s	<0.001	0.023	11.648
No. of non-AF complications	<0.001	<0.001	3.671	<0.001	n/s	n/s
Nonpulmonary complications						
Anastomotic leak	0.002	0.047	4.608	n/s	n/s	n/s
Urologic complication	0.046	n/s	n/s	n/s	n/s	n/s
Wound dehiscence	n/s	n/s	n/s	0.026	n/s	n/s
Pulmonary complications						
Any pulmonary complication	<0.001	0.044	5.917	n/s	n/s	n/s
Atelectasis	0.005	n/s	n/s	0.001	n/s	n/s
Effusion, hemo/pneumothorax	0.034	n/s	n/s	n/s	n/s	n/s
Pneumonia	n/s	n/s	n/s	n/s	n/s	n/s
Acute respiratory failure/ARDS	0.008	n/s	n/s	0.001	n/s	n/s

n/a, not applicable; n/s, not statistically significant; OR, odds ratio for the multivariate analysis; ARDS, adult respiratory distress syndrome
All variables listed had $P < 0.20$ in the univariate analysis

Table 4 Comparison of morbidities among patients with postoperative AF to those without AF

Variable	AF group ($n = 32$)	No AF group ($n = 124$)	*P*
Pulmonary complications (ARDS, PTX, pneumonia, aspiration pneumonitis, pleural effusion, respiratory distress/failure, reintubation)	19 (59.4%)	19 (15.3%)	<0.01
Anastomotic leak	9 (28.1%)	8 (6.5%)	<0.01
Other complications (MI, wound infection, wound dehiscence, ARF, anastomotic stricture, DVT, vocal cord paralysis, *Clostridium difficile* colitis, MOSF)	6 (18.8%)	24 (19.4%)	0.13

PTX, pneumothorax; MI, myocardial infarction, ARF, acute renal failure; DVT, deep venous thrombosis; MOSF, multiorgan system failure

showed that anastomotic leak, number of non-AF complications, and the presence of any pulmonary complication were independently associated with AF (Table 3). Of interest, most leaks occurred at the cervical anastomotic site (12/17, 71%), with the remaining leaks occurring in the chest (5/17, 29%)—an anatomical distribution that is generally consistent with overall case-type proportions in this study (Table 1).

Other complications, including MI, wound infection, wound dehiscence, ARF, DVT, vocal cord paralysis, *Clostridium difficile* colitis, and MOSF collectively were not significantly different between patients with and without AF (18.8% vs. 19.4%, $P > 0.05$). Neither univariate nor multivariate analyses demonstrated any of these complications to be associated with new AF or mortality.

Overall mortality for the entire study sample was 6 of 156 (3.9%). Development of AF after esophagectomy was associated with significantly increased mortality [6/32 (18.8%) vs. 0/124 (0%)] for non-AF patients ($P < 0.01$). Although all six deaths occurred in the AF group, none was directly attributed to AF. Kaplan-Meier survival analysis showed that AF was associated with significantly worse 60-day survival [log rank (Mantel-Cox), $P < 0.001$] (Fig. 1). Despite these univariate associations between AF and mortality, multivariate analysis shows that AF is not an independent risk factor for mortality. Multivariate analysis suggests that the presence of non-AF complications are associated with increased mortality (Table 3), although leak alone was not an independent risk factor for mortality. Specifically, the mortality group was characterized by a median of 2.5 non-AF complications per patient (range one to five complications). Among non-AF complications in the mortality group, 2 of 6 (33%) patients had anastomotic leaks, 2 of 6 (33%) had wound-related complications,

and 3 of 6 (50%) had one or more pulmonary complications. There was no difference in mortality between the surgical approaches.

In terms of resource consumption, the development of new-onset AF after esophagectomy was associated with significantly longer ICU stays (10.1 ± 9.9 days vs. 3.0 ± 6.8 days; $P < 0.001$). However, the mean hospital LOS (19.2 ± 11.6 days vs. 16.4 ± 16.0 days; $P = 0.350$) was not significantly different between AF and non-AF groups (Table 5).

Among other variables, the rates of new-onset AF in patients who received β-blocking agents, calcium channel antagonists, ACE-I, and/or HMG-CoA inhibitors preoperatively were not significantly different than patients not receiving these medications (data not shown). Likewise, postoperative epidural analgesia did not appear to influence the development of new-onset AF. In addition, time to resolution of AF was not different for amiodarone, β-blocker, or diltiazem treatment.

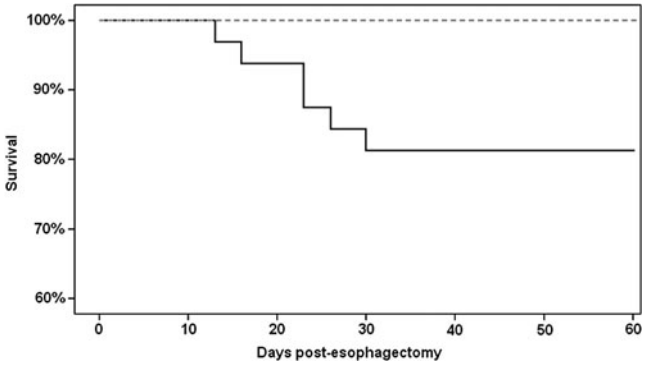

Fig. 1 Sixty-day survival curves. Patients with atrial fibrillation (AF) (*solid line*) had significantly worse survival than patients without AF (*dashed line*) determined by Mantel-Cox (log-rank) testing: $P < 0.001$. As shown, all deaths occurred during the first 30 postoperative days

Discussion

Our results show that new-onset AF following esophagectomy is associated with pulmonary complications, anastomotic leaks, and possibly increased mortality. More than 20% of the patients in this study had new-onset postoperative AF, which is within the previously reported range (10%–25%) from similar studies.[5,20,21] Consistent with previous reports, half of all AF cases occurred on POD 2, with nearly 90% of new-onset AF manifesting by POD 3.[4,20] Recent literature has suggested that prevention of AF with medical prophylaxis might reduce the incidence of new-onset postoperative AF and possibly reduce the ICU LOS after thoracic surgery.[6] We therefore hypothesized that new-onset AF after esophagectomy might behave similarly and might be similarly prevented. Prior to embarking on a clinical trial to test this hypothesis, we thought it prudent to determine the incidence, risk factors, and consequences of new-onset AF following esophagectomy.

Although several previous studies have reported the frequency of anastomotic leaks after esophageal resections (range 6%–50%),[9–14] few studies have defined a relation between new-onset postoperative AF and anastomotic leaks. Despite a significant univariate association between AF and anastomotic leaks, the multivariate analysis did not corroborate this relation—a finding consistent with previously published large series.[4–6] It is important to emphasize that approximately 28% of patients with new-onset AF after esophagectomy had an anastomotic leak and that it took, on average, 4

Table 5 Clinical endpoints and resource consumption

Variable	AF ($n = 32$)	No AF ($n = 124$)	P
28-Day mortality	6/32 (18.8%)	0	<0.001
ICU stay (days), mean ± SD	10.1 ± 9.9	3.0 ± 6.8	<0.001
Hospital stay (days)			
Mean ± SD	19.2 ± 11.6	16.4 ± 16.0	0.350
Median	15.5	11.0	
Time to SR after AF onset (days)[a]			
Overall mean ± SD	4.7 ± 5.7		
Overall median	3.0		
Temporal relation between AF ($n = 32$) and diagnosis of complication			
Anastomotic leak	4.2 ± 4.1		
Pulmonary complication	–0.7 ± 5.7		
Others	3.8 ± 5.1		

ICU, intensive care unit; SR, sinus rhythm
[a]Includes only 26 of 32 patients with AF who converted to sinus rhythm in hospital

days after the onset of AF for diagnosis. The converse relation is equally strong, and patients with leaks had a >50% incidence of new-onset AF. Despite this association, our results do not allow determination of whether AF is caused by leaks or, conversely, if AF might contribute to anastomotic failure from decreased cardiac output. Whichever the case, early diagnosis and treatment may improve clinical outcomes, and we suggest that new-onset AF after esophagectomy should alert the surgeon to the possibility of an anastomotic leak.

The relation between pulmonary complications and AF is well established,[4–6,10,13,14] and AF is one of the principal complications seen following surgical procedures involving the lungs and/or the pleural surfaces.[6,7] Not surprisingly, pulmonary complications preceded or were concurrent with the onset of AF after esophagectomy in the current report. Given the contiguous relation between the operative field and either pulmonary or pleural surfaces during esophagectomy, it is possible that this also contributes to AF, especially if these surfaces are contaminated by gastrointestinal contents during a leak. Because of the temporal relation between pulmonary complications and new-onset AF in the current report, we suspect that most AF is a consequence, not a cause, of pulmonary complications.

The relation between new-onset AF and mortality after esophagectomy does not appear causal. Our univariate analyses showed that mortality and 60-day survival are significantly associated with the development of new-onset AF. In fact, all deaths in this study occurred in the AF group, accounting for approximately one in five patients with AF. Despite this fact, new-onset AF after esophagectomy rarely occurred alone but was usually associated with non-AF complications, and these non-AF complications appear by multivariate analysis to be an independent risk factor for mortality (Table 3). Of interest, half of the deaths in this study were in patients with pulmonary complications, corroborating the previously published relation between pulmonary factors, postesophagectomy AF, and mortality.[5,14] Moreover, our study shows that none of the deaths in the AF group were directly attributable to AF, which is also consistent with previous reports.[4,20] This is further confirmed by multivariate analysis, which showed that AF alone is not an independent risk factor for mortality. We therefore conclude that AF following esophagectomy is "guilty by association" and not directly contributory to mortality in this patient population.

Determining whether to institute prophylactic treatment to prevent postesophagectomy AF was one of our primary interests. The obvious benefit of prophylaxis might be prevention of readmission to the ICU or a shortened ICU LOS because postoperative AF is not routinely managed outside the ICU in our institution. At first glance, the reported incidence in the current as well as previous studies could justify strategies to attempt to limit this fairly frequent postoperative complication.[6,20,22] Our major concern with this strategy is that new-onset AF might be an early warning of anastomotic leak in some patients, and that effective AF prophylaxis might mask this early indicator of leak or other complications. Furthermore, with aggressive treatment, most of these AF episodes resolved within 3–5 days independent of the pharmacological agent chosen for treatment, which is consistent with resolution of AF in other noncardiac postoperative populations.[23] Thus we are reluctant to recommend treatment to prevent new-onset AF following esophagectomy outside of a clinical trial.

We also sought to determine whether any particular factors might predict patients at risk for developing postoperative AF. Previous studies have examined the effects of age, sex, surgical approach, epidural analgesia, HMG-CoA inhibitors, and nonsteroidal antiinflammatory drugs on the likelihood of developing AF postoperatively.[4,5,14,16,19,24] In these reports, male sex and older patient age (>65 years) were significantly associated with postoperative AF.[4,6,20] Although our univariate analysis showed age to be a risk factor for postoperative AF, patient sex was not a risk factor in the present study, and neither was it an independent risk factor by multivariate analysis. Similar to previous studies, the incidence of AF in the current study was not significantly different between the three surgical approaches. Preoperative treatment with β-blockers also did not appear to influence postoperative AF occurrence significantly.

This study has several limitations. They include its retrospective nature (with biases inherent to the retrospective study design), potential patient selection/population bias (our institution is a tertiary referral center), and any potential biases associated with different surgical techniques across the operating surgeons. Although patient characteristics in the current study are consistent with those from previously published series,[4,5,14] the study sample is relatively small and confined to a single institution. Although our sample is large enough to determine our primary endpoints, it may not be of adequate size to detect subtle treatment-related differences between the AF and non-AF groups (i.e., effects of pharmacotherapy, fluid administration, determination of the interaction between AF and less common postoperative complications). Lastly, it must be emphasized that the relation between AF and the incidence of anastomotic leaks presented here is associative and largely phenomenological. Consequently, it is not possible to conclude that there are any causative relations between AF, anastomotic leaks, and other clinical variables studied. The

most reliable method of further defining such relations would be to perform a prospective study of AF in post-esophagectomy patients.

Conclusion

New-onset AF is a common complication following esophagectomy that is frequently associated with non-AF complications including anastomotic leaks and pulmonary complications. The univariate association of AF with mortality appears to be a consequence of concurrent non-AF complications on multivariate analysis. Due to the high overall incidence of AF in patients with leaks, along with the finding that AF precedes leak diagnosis by several days, we suggest that AF might be considered an early warning sign of leak that warrants judicious anastomotic evaluation. Consequently, we are reluctant to recommend routine prophylaxis for AF following esophagectomy outside of a clinical trial.

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The authors have no conflicts of interest to declare.

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