ORIGINAL ARTICLE

Immediate Extubation After Pediatric Liver Transplantation: A Single-Center Experience

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The care of pediatric liver transplant recipients has traditionally included postoperative mechanical ventilation. In 2005, we started extubating children undergoing liver transplantation in the operating room according to standard criteria for extubation used for general surgery cases. We reviewed our single-center experience to determine our rates of immediate extubation and practice since that time. The records of 84 children who underwent liver transplantation from 2005 to 2011 were retrospectively reviewed. The immediate extubation rate increased from 33% during 2005-2008 to 67% during 2009-2011. Immediate extubation did not result in an increased reintubation rate in comparison with delayed extubation in the intensive care unit (ICU). Patients undergoing immediate extubation had a trend toward a shorter mean ICU stay as well as a significantly decreased overall hospital length of stay. Our findings suggest that there is a learning curve for instituting immediate extubation in the operating room after liver transplantation and that the majority of pediatric liver recipients can safely undergo immediate extubation. *Liver Transpl 21:57-62, 2015*. © 2014 AASLD.

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In 1997, studies reported an increasing frequency of immediate extubation of adult liver transplant recipients in the operating room.[1,2] Subsequent studies showed no increase in reintubation rates, decreased postoperative days in the intensive care unit (ICU), and decreased associated costs with immediate extubation.[2] Despite this increase in the fast-tracking of adult liver transplant recipients, common management in pediatric liver transplantation has continued to include postoperative ventilation.[3] A recently presented abstract examining the Studies of Pediatric Liver Transplantation database demonstrated that among the 25 centers queried, those centers with an overall shorter hospital stay and lower costs had a shorter duration of postoperative intubation (2.7 days) in comparison with other centers (6.5 days). The authors concluded that early extubation may result in a decreased length of stay.[4] In 2005, we began immediately extubating pediatric liver transplant recipients if all team members were comfortable with that plan. The current study sought to (1) examine our rates of immediate extubation, (2) identify factors associated with immediate extubation or postoperative ventilation, and (3) evaluate postoperative outcomes after this practice change.

PATIENTS AND METHODS

Approval for the study and a waiver for consent were obtained from the institutional review board. We performed a retrospective review of the medical records of all pediatric liver transplant recipients from January 2005 through December 2011 at our institution. Patients with preoperative ventilator requirements were subsequently excluded from the analysis. Three patients were included in the data set twice for

Abbreviations: BMI, body mass index; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease; PN, parenteral nutrition.

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retransplantation. To evaluate the effects of our practice change over time, transplant patients were divided into 2 time periods: I (2005-2008) and II (2009-2011).

Anesthesia was provided by a member of a small, consistent transplant anesthesia team. Intraoperative anesthetic management was not standardized, but most patients were anesthetized with a balanced anesthetic technique with an opioid (fentanyl or sufentanil), a volatile anesthetic (isoflurane), and a muscle relaxant. Extubation criteria included the following: appropriate mental status, adequate pain control, normothermia, complete neuromuscular reversal, adequate airway reflexes, adequate respiratory rate, tidal volume and oxygenation on minimal ventilator settings, hemodynamic stability, no surgical concerns regarding ongoing bleeding or vascular patency, successful abdominal wall closure without concern about the development of abdominal compartment syndrome, and no scheduled return to the operating room (an incomplete biliary anastomosis or abdominal wall closure or an expected need for intervention within 24 hours). All patients were transferred to the ICU postoperatively, and similar criteria were used for the extubation of those who remained on mechanical ventilation upon their arrival at the ICU.

Preoperative patient data [sex, age, body mass index (BMI), weight, height, primary diagnosis, preoperative location, and Model for End-Stage Liver Disease (MELD)/Pediatric End-Stage Liver Disease (PELD) score] were evaluated. Intraoperative characteristics (graft type, operative time, administered resuscitation products, and vasopressor use) and postoperative outcomes (reintubation, ICU length of stay, and total hospital length of stay) were also evaluated. A data analysis was performed for each time period. Other than analyses of the yearly extubation rate, all categorical analyses were performed with Fisher's exact test. Normally distributed data were compared with an unpaired *t* test and analysis of variance, and nonparametric data were compared with the Wilcoxon rank sum test. $P \leq 0.05$ was considered significant. All analyses were performed in JMP Pro 64-bit 10.0.0 (SAS Institute, Inc., Cary, NC).

The yearly rate of immediate extubation after transplantation from 2005 to 2011 was analyzed with the Pearson χ^2 test for trends to assess whether the rate had changed with time. Then, using a log-linear model with a binomial distribution, we determined whether the longitudinal trend was significant by the likelihood ratio test and the years in which the rate of immediate extubation differed in comparison with 2005. Statistical analysis was performed with IBM SPSS Statistics 21.0 (IBM, Armonk, NY). Two-tailed *P* values ≤ 0.05 were considered statistically significant.

RESULTS

Eighty-six patients were identified who underwent liver transplantation from January 2005 to December 2011 at our institution. Two patients were excluded

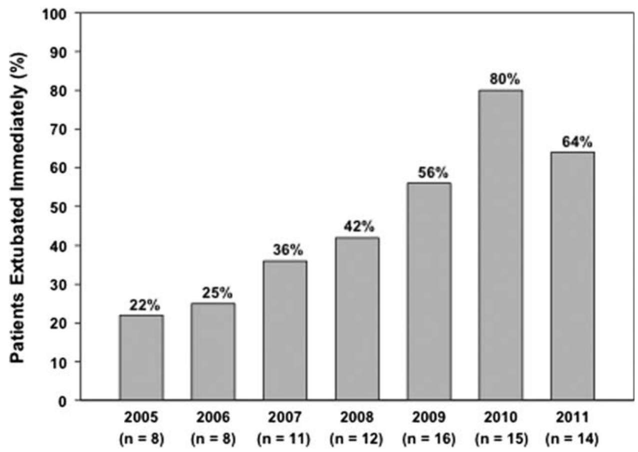

Figure 1. Yearly rate of immediate extubation after transplantation: 2005-2011. There was a significant trend over time of increasing immediate extubation after liver transplantation (likelihood ratio test = 10.14, $P < 0.001$).

because of preoperative ventilation requirements. Thirty-nine patients underwent transplantation in time period I (2005-2008), and 45 patients underwent transplantation in time period II (2009-2011). Among the 84 total patients eligible for analysis, 44 patients were immediately extubated postoperatively in the operating room, and 40 patients remained intubated postoperatively. Three patients underwent retransplantation and were, therefore, included twice. One patient was extubated after both transplants (5 years apart). The other 2 patients underwent immediate extubation after their first transplants, but both remained intubated after retransplantation. The rate of immediate extubation increased from 33% in time period I to 67% in time period II ($P = 0.002$).

The Pearson χ^2 test for trends indicated a significant association between immediate extubation and the year of transplantation from 2005 to 2011 ($P < 0.05$). The rates are shown throughout the 7-year period in Fig. 1. Logistic regression confirmed a highly significant overall time-based trend (likelihood ratio test = 10.14, $P < 0.001$) and also indicated that, in comparison with transplants performed in 2005, the increased rate of immediate extubation was statistically significant in 2010 ($P < 0.01$) and 2011 ($P < 0.05$).

Patient Characteristics

Patient characteristics were compared for the 2 time periods. Patients in time period II were older (median: 3.6 versus 1.4 years, $P < 0.05$), had higher BMIs (median: 17.1 versus 15.8), were taller (median: 99.0 versus 74.3 cm, $P < 0.05$), and weighed more (median: 17.3 versus 9.3 kg, $P < 0.05$) but otherwise had demographics comparable to those of patients who underwent transplant during time period I. Although more patients less than 1 year of age underwent transplantation in the first time period (n = 19) versus the second (n = 9), a larger percentage of these patients were

TABLE 1. Patient Characteristics: Comparison Between Time Periods

Characteristic	2005-2008	2009-2011	*P* Value
Male sex [n (%)]	23 (57.5)	20 (44.4)	0.28
Age (years)*	1.4 (0.6-2.5)	3.6 (1.1-9.8)	<0.05
BMI (kg/m^2)*	15.8 (14.8-17.7)	17.1 (15.9-19.0)	<0.05
Recipient weight (kg)*	9.3 (5.6-11.7)	17.3 (7.9-25.9)	<0.05
Recipient height (cm)*	74.3 (61.0-81.2)	99.0 (66.5-124.1)	<0.05
Diagnosis [n (%)]			0.28
Biliary atresia	13 (32.5)	18 (40.0)	
Cirrhosis, other	5 (12.5)	1 (2.2)	
Malignancy	8 (20.0)	5 (11.1)	
Metabolic	5 (12.5)	9 (20.0)	
PN-related liver disease	5 (12.5)	4 (8.9)	
Other	4 (10.0)	8 (17.8)	
Preoperative ICU [n (%)]	8 (20.0)	4 (8.9)	0.21
Laboratory MELD/PELD score*	15 (3.3-27.5)	8 (−1.0 to 23.0)	0.21
Graft type [n (%)]			0.74
Whole	14 (35.0)	16 (35.6)	
Living	1 (2.5)	1 (2.2)	
Split	15 (37.5)	21 (46.7)	
Multiorgan	10 (25.0)	7 (15.6)	

*The data are presented as medians and interquartile ranges.

extubated in period II versus period I at the conclusion of surgery (67% versus 33%, respectively). No significant difference in sex, diagnosis, preoperative ICU location, laboratory MELD/PELD score, or graft type was found between the 2 time periods (Table 1).

Time Period I (2005-2008)

The immediate extubation rate during this period was 33%. There were no differences between patients immediately extubated and those who were not with respect to sex, age, size, diagnosis, preoperative ICU location, or MELD/PELD score. Intraoperative factors such as the length of surgery, amount and type of resuscitation products transfused, and vasopressor requirements were comparable between those extubated and those maintained on ventilation support postoperatively. All multiorgan graft recipients (n = 10) remained intubated during this period. After immediate extubation, 1 of 13 patients (7.7%) was reintubated within 3 days, and 3 of 26 patients (11.5%) in the nonextubated group required reintubation after delayed extubation in the ICU. No significant differences in the ICU stay or the total length of stay were found between patients who underwent immediate extubation and those who remained intubated after transplantation (Table 2).

Time Period II (2009-2011)

During this period, 67% of the recipients underwent immediate extubation. The extubated and ventilated groups were comparable with respect to sex, age, weight, height, preoperative ICU location, and MELD/PELD score. Significant differences in preoperative diagnoses were seen between the groups ($P < 0.05$). Patients with parenteral nutrition (PN)–related liver disease remained intubated postoperatively, whereas patients with cirrhosis secondary to another etiology, malignancy, or metabolic disease were more likely to be extubated in the operating room. Compared with patients who were extubated in the operating room, patients who were not extubated tended to receive greater amounts of blood (median: 73.0 versus 33.9 cc/kg, $P < 0.05$), fresh frozen plasma (median: 44.5 versus 22.8 cc/kg, $P = 0.05$), or platelets (median: 64.3% versus 22.6%, $P < 0.05$) during this time period. Although recipients of multiorgan transplants were never extubated during period I, 43% of multiorgan recipients were extubated during this period. Immediate extubation was not associated with an increased risk of reintubation within the first 3 postoperative days. During this period, only 1 of 45 patients (2.2%) was reintubated after immediate extubation for acute hemodynamic and respiratory decompensation of unknown origin. None of the postoperatively ventilated patients required reintubation after extubation in the ICU. Extubated patients tended to require fewer days in the ICU [median: 2 versus 3 days, $P = 0.16$ (not significant)] and did have a significantly shorter total hospital length of stay (median: 17.0 versus 28.5 days, $P < 0.05$; Table 2).

DISCUSSION

Since 1997, reports have confirmed an increasing frequency of early extubation (fast-tracking) after extensive surgery.[1,2,5] Increasing attention paid to resource utilization and costs have been driving factors for

TABLE 2. Comparison of Immediately Extubated and Ventilated Patients by Time Period

	2005-2008		2009-2011		
Characteristic	Extubated (n = 13)	Not Extubated (n = 26)	Extubated (n = 31)	Not Extubated (n = 14)	*P* Value
Male sex [n (%)]	7 (53.8)	15 (57.7)	13 (41.9)	7 (50.0)	0.75
Age (years)*	1.3 (0.5-1.8)	1.2 (0.6-4.0)	3.6 (1.1-10.2)	3.1 (1.1-8.8)	0.54
BMI (kg/m^2)*	15.6 (15.4-17.2)	16.0 (14.4-19.0)	17.5 (15.6-19.2)	17.1 (16.3-18.9)	0.85
Recipient weight (kg)*	9.5 (5.52-10.875)	8.9 (5.4-14.3)	17.6 (8.5-25.8)	13.6 (6.9-26.0)	0.57
Recipient height (cm)*	76.2 (59.2-80.4)	70.8 (61.0-95.0)	102.0 (66.6-134.7)	86.5 (65.5-120.4)	0.36
Diagnosis [n (%)]					<0.05
Biliary atresia	6 (46.2)	7 (26.9)	10 (32.3)	8 (57.1)	
Cirrhosis, other	1 (7.7)	5 (19.2)	4 (12.9)	0 (0.0)	
Malignancy	2 (15.4)	5 (19.2)	6 (19.4)	0 (0.0)	
Metabolic	3 (23.1)	4 (15.4)	9 (29.0)	2 (14.3)	
PN-related liver disease	0 (0.0)	5 (19.2)	0 (0)	4 (28.6)	
Other	1 (7.7)	0 (0.0)	2 (6.5)	0 (0.0)	
Preoperative ICU [n (%)]	2 (15.4)	6 (23.1)	2 (6.5)	2 (14.3)	0.57
Laboratory MELD/ PELD score*	11 (6.5-23.5)	18 (2.8-31.5)	7 (−1.0 to 22.5)	10.0 (−1.0 to 27.0)	0.63
Graft type [n (%)]					0.27
Whole	8 (61.5)	5 (19.2)	13 (41.9)	3 (21.4)	
Living	1 (7.7)	0 (0.0)	1 (3.2)	0 (0.0)	
Split	4 (30.8)	11 (42.3)	14 (45.2)	7 (50.0)	
Multiorgan	0 (0.0)	10 (38.5)	3 (9.7)	4 (28.6)	
Operative length (hours)*	7.7 (7.1-8.5)	8.3 (7.8-9.4)	7.0 (5.9-8.8)	7.3 (6.6-8.9)	0.5
Resuscitation products (cc/kg)					
Crystalloid*	82.0 (43.2-96.9)	67.8 (49.0-101.8)	69.8 (42.6-140.0)	61.5 (28.5-87.9)	0.31
Packed red blood cells*	48.4 (35.0-62.6)	83.0 (29.3-230.9)	33.9 (20.3-55.6)	73.0 (34.2-150.1)	<0.05
Albumin*	37.4 (0.0-50.9)	33.8 (0.0-56.0)	14.1 (0.0-31.3)	23.1 (0.0-43.8)	0.42
Fresh frozen plasma*	48.4 (24.0-75.5)	101.5 (15.8-162.4)	22.8 (0.0-47.0)	44.5 (25.1-109.3)	0.05
Platelets [n (%)]	5 (38.5)	13 (50.0)	7 (22.6)	9 (64.3)	<0.05
Pressors > 1 [n (%)]	0 (0.0)	4 (15.4)	6 (19.4)	6 (42.9)	0.15
Reintubation within 3 days [n (%)]	1.0 (7.7)	3.0 (11.5)	1 (3.2)	0 (0.0)	1.00
ICU length of stay (days)*	3.0 (2.0-6.0)	3.8 (2.3-10.0)	2.0 (1.0-3.0)	3.0 (1.0-6.5)	0.16
Total length of stay (days)*	19.0 (12.0-20.0)	22.0 (11.5-57.0)	17.0 (10.0-20.5)	28.5 (19.0-55.25)	<0.05

*The data are presented as medians and interquartile ranges.

minimizing prolonged postoperative ventilation.[3,6] These studies have shown that this practice is safe in select patients without an increase in reintubation rates, and they suggest that early extubation is cost-effective and does not compromise patient outcomes.[1,2,5,7-9] Immediate postoperative extubation of select adult liver transplant recipients is now commonly performed at many institutions.[3]

Despite these changes, the management of pediatric liver transplant recipients has continued traditionally to include postoperative ventilation. Concerns about graft function, vessel patency, depressive effects of analgesia, preexisting malnutrition, graft-recipient mismatch, and emotional difficulties among pediatric patients have been cited as reasons that patients are not extubated at the conclusion of surgery.[10] Ulukaya et al.[6] first described early extubation in 30% (n = 40) of pediatric liver transplant recipients according to standard extubation criteria used in other pediatric surgery cases. They used an anesthetic regimen that included nonhepatically metabolized remifentanil and cisatracurium; this allowed a "predictable and rapid recovery" after liver transplantation, with no patients requiring reintubation.[6] O'Meara et al.[3] reported a 76% immediate extubation rate (n = 34) among a select group of liver transplant recipients, which they described as "elective" without clarification of what differentiated these patients from "nonelective" patients, and they found that a small recipient size, the transplantation of split grafts, the presence of preexisting respiratory disease, and retransplantation were not factors precluding successful immediate extubation. They also used remifentanil and cisatracurium because of the pharmacokinetic advantage. They reported only 1 reintubation secondary to transfusion-related acute lung injury.[3]

In 2005, we began extubating pediatric liver transplant recipients in the operating room. This initiative for early extubation was based on our opinion that early extubation could be safe and feasible in our patient population. Within a few years of instituting this practice, rates of immediate extubation increased from 0% before 2005 to nearly 65% in 2011 (Fig. 1). Among the patients who were not extubated in the later period (2008-2011), only 2 patients had documented reasons for remaining intubated: an open abdomen in one patient and decreased ventilator compliance after abdominal closure in another patient. We have found that early extubation in the operating room is safe without an associated increase in reintubation rates, and it has the potential benefit of decreased ICU and total hospital stays. The demographics of our cohort are comparable to those of the national cohort of pediatric patients in the 2011 report from the Scientific Registry of Transplant Recipients. The most common etiologies for liver disease from 2009 to 2011 in the Scientific Registry of Transplant Recipients report include cholestatic disease (47%), malignancy (14%), and metabolic liver disease (13%). In periods I and II, we had the following distribution: biliary atresia, 33% and 40%; malignancy, 18% and 13%; and metabolic liver disease, 18% and 24%.[11]

Unlike previously published studies, our patients did not receive remifentanil and cisatracurium, and this indicates that the choice of anesthetic drugs may be less important for successful immediate postoperative extubation than the team's embrace of the concept of early extubation. Thus, the increasing rate of immediate extubation likely reflects the increasing comfort level of the clinicians involved and an increasing willingness to move beyond the previously prevailing bias. This is evident in our increasing early extubation rates after 2005, with a constant disease severity in our recipients across the 2 time periods. Although this was untested in the current study, we hypothesize that the presence of a small, involved anesthesiology group in frequent communication with their surgical counterparts and a commitment to moving beyond previously held biases played a role in promoting this practice change.

In our study, certain factors that were no longer significant in the second period appeared to have a statistically significant association with remaining intubated in the first period. Factors such as the amounts of red blood cells, plasma, and platelet transfusions were not found to be absolutely predictive of the decision to keep patients intubated. For example, 1 multivisceral graft recipient received blood (120 cc/kg), fresh frozen plasma (94 cc/kg), and platelet transfusions and was successfully extubated in the operating room after surgery. The long-held belief that a large volume of transfused blood precludes successful early extubation may not be applicable to all cases because, in our experience, patients were successfully extubated at the conclusion of surgery despite large-volume transfusions. In addition, multiorgan transplant recipients, arguably a population undergoing operations of increasing complexity, remained intubated in the early period, but they were equally likely to be immediately extubated in the second period. At our institution, receiving a multivisceral transplant did not preclude extubation in appropriate patients.

Our study has obvious limitations because of its retrospective nature. The statistical analysis of such retrospective data may suggest that certain factors are associated with avoiding immediate extubation; however, we do not endorse the use of these factors as criteria for the decision to extubate after liver transplantation. On the basis of data from time period I, if we had relied specifically on the associated factors for nonextubated patients, then we would have limited the number of patients who were successfully extubated over the ensuing years. Instead, we relied on the clinical judgment of the anesthesiologists and the surgeons and found that these associated factors should not necessarily be used as parameters to avoid immediate extubation.

The aim of our study was not to determine factors that should guide decision making for immediate extubation. Instead, we wanted to demonstrate a high success rate with immediate extubation after pediatric liver transplantation. Even though this has been reported more extensively in the adult literature, the practice of immediate extubation has not been reported as widely in the pediatric literature, and it appears not to be standard practice among many centers in the United States (according to personal communications with surgical and anesthesia peers).

This study is limited by its design because of its observational and retrospective nature, and further large-scale, prospective work may be required to establish factors associated with successful early extubation. This study demonstrates to us that at this institution, factors previously considered to be contraindications to extubation were not associated with the failure of early extubation or the need for reintubation. Even factors that were significantly associated with remaining intubated in this series in the earlier time period did not reliably preclude extubation over time. This study has shown that, as with any other surgical and anesthetic procedure, extubation after liver transplantation has a learning curve among practitioners. With the decision to extubate immediately after transplantation on the basis of the judgment of the anesthesiology and surgical teams, a near-logarithmic increase in the rate of extubation from 2005 to 2011 was evident (Fig. 1).

Because of our ongoing experience so far, all pediatric liver transplant recipients at our institution are now considered for immediate extubation. We continue to avoid immediate extubation in these settings: (1) open abdomen/temporary closure, (2) anticipation of a return to the operating room within the next 24 hours, (3) significant volume overload symptomatic of impaired pulmonary gas exchange or swelling compromising the airway, (4) severe hemodynamic instability with escalating vasopressor requirements, (5) encephalopathy with preoperative ventilation or compromised airway protection, and (6) pretransplant ventilatory dependence. Otherwise, all other patients are considered for immediate extubation.

Our results confirm that immediate extubation in the operating room after pediatric liver transplantation is safe in the majority of patients and does not compromise patient outcomes. This practice may lead to decreased ventilator-associated morbidity, ICU and hospital stays, and associated costs.

REFERENCES

1. Neelakanta G, Sopher M, Chan S, Pregler J, Steadman R, Braunfeld M, Csete M. Early tracheal extubation after liver transplantation. J Cardiothorac Vasc Anesth 1997; 11:165-167.
2. Mandell MS, Lockrem J, Kelley SD. Immediate tracheal extubation after liver transplantation: experience of two transplant centers. Anesth Analg 1997;84:249-253.
3. O'Meara ME, Whiteley SM, Sellors JM, Luntley JM, Davison S, McClean P, et al. Immediate extubation of children following liver transplantation is safe and may be beneficial. Transplantation 2005;80:959-963.
4. Kelly ME, Bucuvalas J, Andrews W, Mitchell J, Anand R, Yin W, Magee J, Mazariegos G, Horslen S. Improving value after pediatric liver transplant: discharge practices of high-performing centers. Am J Transplant 2013; 13(suppl 5):47.
5. Mandell MS, Stoner TJ, Barnett R, Shaked A, Bellamy M, Biancofiore G, et al. A multicenter evaluation of safety of early extubation in liver transplant recipients. Liver Transpl 2007;13:1557-1563.
6. Ulukaya S, Arikan C, Aydogdu S, Ayanoglu HO, Tokat Y. Immediate tracheal extubation of pediatric liver transplant recipients in the operating room. Pediatr Transplant 2003;7:381-384.
7. Mandell MS, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: influence of early extubation. Liver Transpl 2002;8:676-681.
8. Mandell MS, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: patient attributes that determine early transfer to surgical wards. Liver Transpl 2002;8:682-687.
9. Zeyneloglu P, Pirat A, Guner M, Torgay A, Karakayali H, Arslan G. Predictors of immediate tracheal extubation in the operating room after liver transplantation. Transplant Proc 2007;39:1187-1189.
10. Kelly DA. Diseases of the Liver and Biliary System in Children. 2nd ed. Malden, MA: Blackwell Publishing; 2004.
11. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2011 Annual Data Report. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012.