Immediate Postoperative Renal Function Deterioration in Cardiac Surgical Patients Predicts In-Hospital Mortality and Long-Term Survival

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Postoperative renal function deterioration is a serious complication after cardiac surgery with cardiopulmonary bypass and is associated with increased in-hospital mortality. However, the long-term prognosis of patients with postoperative renal deterioration is not fully determined yet. Therefore, both in-hospital mortality and long-term survival were studied in patients with postoperative renal function deterioration. Included were 843 patients who underwent cardiac surgery with cardiopulmonary bypass in 1991. Postoperative renal function deterioration (increase in serum creatinine in the first postoperative week of at least 25%) occurred in 145 (17.2%) patients. In these patients, in-hospital mortality was 14.5%, *versus* 1.1% in patients without renal function deterioration ($P < 0.001$). Multivariate analysis significantly associated in-hospital mortality with postoperative renal function deterioration, re-exploration, postoperative cerebral stroke, duration of operation, age, and diabetes. In patients who were discharged alive, during long-term follow-up (100 mo), mortality was significantly increased in the patients with renal function deterioration ($n = 124$) as compared with those without renal function deterioration (hazard ratio 1.83; 95% confidence interval 1.38 to 3.20). Also after adjustment for other independently associated factors, the risk for mortality in patients with postoperative renal function deterioration remained elevated (hazard ratio 1.63; 95% confidence interval 1.15 to 2.32). The elevated risk for long-term mortality was independent of whether renal function had recovered at discharge from hospital. It is concluded that postoperative renal function deterioration in cardiac surgical patients not only results in increased in-hospital mortality but also adversely affects long-term survival.

J Am Soc Nephrol 16: 195–200, 2005. doi: 10.1681/ASN.2003100875

Postoperative renal function deterioration is a serious complication after cardiac surgery with cardiopulmonary bypass (CPB) and is associated with increased in-hospital morbidity and mortality (1). The reported incidence rate of this complication ranges from 2.9 to 7.7% (1,2). Risk factors for the development of postoperative renal function deterioration include elevated preoperative serum creatinine, duration of CPB, carotid artery murmur, diabetes, increased age, poor left ventricular function, and increased body weight (3). Most studies in cardiac surgical patients focused on risk factors for postoperative renal function deterioration and its associated in-hospital morbidity and mortality. However, the long-term prognosis of patients with postoperative renal function deterioration remains unclear as data on long-term survival are not available so far. Therefore, we studied not only in-hospital mortality but also long-term survival in patients with postoperative renal function deterioration as compared with patients without postoperative renal function deterioration in a cohort of all consecutive cardiac surgical patients who underwent surgery with CPB at our institution in 1991.

Received October 22, 2003. Accepted September 28, 2004.

Published online ahead of print. Publication date available at www.jasn.org.

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Materials and Methods

Institutional approval was obtained, and the need for informed consent was waived. All consecutive adult patients who underwent elective or emergency cardiac surgery with CPB in 1991 at our tertiary care hospital entered the study. Patients who were on dialysis before cardiac surgery were excluded from further analysis ($n = 6$). Included were 843 consecutive patients, and the data of intensive care unit (ICU) charts and anesthesia records of these patients were entered into a database. The following variables were assessed.

Preoperative Data

Age, length, gender, body mass index (BMI), cerebral vascular disease (previous stroke and/or transient ischemic attack), peripheral vascular disease (exertional claudication and/or previous revascularization procedure and/or angiographic evidence of arterial obstruction), diabetes (requiring therapy with oral agent or insulin), hypertension requiring therapy, preoperative serum creatinine (serum creatinine was obtained the day before surgery and in emergency cases just before surgery), congestive heart failure, previous myocardial infarction, intra-aortic balloon counter pulsation (IABP), emergency operation, radiocontrast within 1 wk before surgery, and previous cardiac operation were assessed. The Cockroft-Gault formula was used to estimate preoperative creatinine clearance (4).

ISSN: 1046-6673/1601-0195

Intraoperative Data

Type of surgical procedure, duration of CPB, duration of operation, duration of perfusion pressure <50 mmHg, and urine output during operation were assessed.

Postoperative Data

Surgical re-exploration for bleeding or cardiac tamponade; myocardial infarction; serum creatinine at the first, second, and seventh postoperative days and at discharge from the hospital; cerebral stroke; IABP; length of stay in the ICU; dialysis; low cardiac output syndrome (cardiac index <2.2 L/min per m^2); and in-hospital mortality were assessed. Postoperative renal function deterioration was defined as an increase in the serum creatinine level in the first postoperative week of at least 25% from the preoperative level. The postoperative day of maximal renal function deterioration was assessed. In all of the patients, discharge creatinine was compared with the preoperative value, and an increase or decrease from the preoperative level was assessed.

Long-Term Follow-up Data

In April 1999, the vital status of all patients was ascertained by extracting data from the patient charts of the outpatient clinic or by contacting the general practitioner of the patient. When a patient had died during follow-up, the date of death was established.

Anesthesia, CPB, and ICU Management

Anesthesia was performed according to a set protocol (5). Nonpulsatile CPB was performed with a roller pump and membrane oxygenator (Cobe Excel, Lakewood, CO). Moderate hypothermia was used in all patients. Cold St. Thomas solution was used to maintain cardioplegic arrest. Mean arterial pressure was allowed to vary between 50 and 90 mmHg during bypass. In the ICU, patients were treated according to a set protocol targeted at a cardiac index ≥2.2 L/min per m^2 and a urine production of ≥1 ml/kg per h. Indications for initiation of renal replacement therapy were signs and symptoms of extracellular volume overload, azotemia, hyperkalemia, and uncorrectable metabolic acidosis.

Statistical Analyses

All analyses were performed using SPSS 10.0 for Windows. Data are given as mean ± SD. Univariate testing of variables between two groups was performed with the *t* test for continuous variables and the χ^2 test for discrete variables. Backward logistic multivariate analysis was used to test the independent association of in-hospital mortality with different variables. Variables with a $P < 0.1$ in the univariate analysis were included in the multivariate analysis. In the patients who were discharged alive, long-term outcome was studied with Kaplan-Meier survival analysis, and the log rank test was used to compare survival in the groups and hazard ratios (HR) and 95% confidence intervals (CI) were estimated for long-term mortality. The possible influence of postoperative renal function deterioration was analyzed by comparing survival between groups with or without a ≥25% increase in serum creatinine. In addition, the effect of an increase in serum creatinine at hospital discharge compared with the preoperative level on mortality was analyzed for the whole group and was separately analyzed in the subgroups with or without postoperative renal function deterioration. Cox regression analysis was used to test the independent association of long-term survival with different variables in the patients who survived the hospitalization. Backward variable selection was used until only significant covariates ($P < 0.05$) remained in the model. HR and 95% CI were estimated for independent risk factors. Statistical significance was accepted at a two-sided $P < 0.05$.

Results

Clinical characteristics and operative and postoperative variables of the cohort ($n = 843$) are shown in Tables 1 and 2, dichotomized according to presence or absence of postoperative renal function deterioration. Postoperative renal function deterioration, defined as an increase of 25% in serum creatinine at one or more days in the first postoperative week, occurred in 145 (17.2%) patients. The time of development of renal function deterioration was in 37.5% of the patients on the first postoperative day, in 38% of the patients on the second postoperative day, and in 24.5% of the patients on the seventh postoperative

Table 1. Baseline preoperative clinical characteristics[a]

Characteristic	No Renal Function Deterioration	Renal Function Deterioration	*P* Value
No. of patients	698	145	
Age (yr)	62.6 ± 10.6	64.7 ± 11.3	0.04
Male/female	505/193	108/37	0.6
BMI (kg/m^2)	25.6 ± 3.0	25.7 ± 2.8	0.79
Preoperative Cr (μmol/L)	101 ± 24.1	104.4 ± 39.9	0.31
Cockroft-Gault clearance (ml/min)	71.9 ± 21.7	71.5 ± 29.3	0.84
Preoperative cerebral stroke (%)	32 (4.5)	12 (8.2)	0.069
Diabetes (%)	72 (10.3)	22 (15.1)	0.091
Hypertension (%)	161 (23.1)	34 (23.4)	0.921
Peripheral vascular disease (%)	77 (11.0)	20 (13.7)	0.343
Congestive heart failure (%)	51 (7.3)	17 (11.7)	0.075
Preoperative myocardial infarction (%)	291 (41.6)	58 (40.0)	0.707
Radiocontrast <1 wk before surgery (%)	158 (22.6)	41 (28.3)	0.146
Emergency operation (%)	52 (7.4)	23 (15.8)	0.001
Preoperative IABP (%)	3 (0.4)	3 (2.0)	0.033

[a]Data are mean ± SD. BMI, body mass index; Cr, serum creatinine; IABP, intra-aortic balloon counterpulsation.

Table 2. Intraoperative and postoperative variables[a]

Variable	No Renal Function Deterioration	Renal Function Deterioration	*P* Value
No. of patients	698	145	
Type of surgery (%)			
Coronary artery bypass grafting	546 (78.2)	95 (65.5)	0.001
Valve replacement	94 (13.5)	21 (14.5)	0.75
Combined procedure	58 (8.3)	29 (20.0)	<0.001
Duration of operation (min)	210.5 ± 64.8	239.2 ± 96.4	0.001
Duration of CPB (min)	100.1 ± 42.2	123.9 ± 62.0	<0.001
Perioperative diuresis (ml/kg per h)	4.1 ± 2.6	3.9 ± 2.4	0.286
Highest postoperative Cr (μmol/L)	103.4 ± 26.2	182.9 ± 114.4	<0.001
Cr change (%)	2.7 ± 12.2	76 ± 103.0	<0.001
Hospital discharge Cr (μmol/L)	93.7 ± 21.4	111.1 ± 44.2	<0.001
LOS (d)	1.4 ± 2.5	5.2 ± 11.5	<0.001
Postoperative IABP (%)	10 (1.4)	11 (7.5)	<0.001
Re-exploration (%)	24 (3.4)	22 (15.2)	<0.001
Postoperative low output syndrome (%)	20 (2.8)	13 (9.0)	0.001
Postoperative myocardial infarction (%)	16 (2.3)	5 (3.4)	0.416
Postoperative cerebral stroke (%)	7 (1.0)	5 (3.4)	0.024
In-hospital mortality (%)	8 (1.1)	21 (14.5)	<0.001

[a]Data are mean ± SD. CPB, cardiopulmonary bypass; LOS, length of stay.

day. On univariate analysis, the groups with and without postoperative renal function deterioration were different as to age, emergency operation, preoperative IABP (preoperative characteristics; Table 1), type of surgery, duration of operation, duration of CPB, occurrence of postoperative low cardiac output state, need for postoperative IABP, and postoperative surgical revision for bleeding (intra- and postoperative characteristics; Table 2).

For the whole cohort, in-hospital mortality was 3.4% ($n = 29$). In the group with renal function deterioration, in-hospital mortality was 14.5% ($n = 21$) *versus* 1.1% ($n = 8$) in the group without renal function deterioration ($P < 0.001$). The causes of death in the group with renal function deterioration and in the group without renal function deterioration were, respectively, intractable low cardiac output state in 12 and 7 and cerebrovascular stroke in 5 and 1. In addition, in the renal function deterioration group, two patients died of sepsis, one patient died of rupture of the thoracic aorta, and one patient died of rupture of the ventricular septum. Accordingly, postoperative renal function deterioration carried an HR of 12.6 (95% CI 5.7 to 27.0) for in-hospital mortality. Renal replacement therapy was required in 6 (0.7%) patients, who all were in the postoperative renal function deterioration group. Five of these patients died during their hospital stay. Finally, patients with renal function deterioration had a nearly four times longer ICU stay than those who did not ($P < 0.001$).

Preoperative renal function, either measured by serum creatinine levels or creatinine clearance estimated by the Cockroft-Gault formula, was not significantly different between both groups (Table 1). Serum creatinine at discharge from the hospital, however, was significantly higher in the patients with renal function deterioration during the first postoperative week ($P < 0.001$). In the group with renal function deterioration, the creatinine at discharge was higher than the preoperative value in 32% of the patients, as compared with 20% in the control group ($P = 0.0032$). Logistic regression analysis revealed that in-hospital mortality was associated with renal function deterioration in the first operative week, re-exploration, postoperative cerebral stroke, duration of operation, age, and diabetes (Table 3).

To analyze the influence of postoperative renal function deterioration on long-term survival, we compared the groups of patients who were discharged alive with and without postoperative renal function deterioration. Kaplan-Meier survival analysis with a complete follow-up time of 100 mo in 99.1% of the patients revealed a significant difference in survival between patients with and without postoperative renal function deterioration ($P = 0.005$ by log rank test; Figure 1). Postoperative renal function deterioration carried an HR of 1.83 (95% CI 1.38 to 3.20) for long-term mortality. Among the patients with postoperative renal function deterioration, mortality was not different for patients in whom creatinine was still above the preoperative value at discharge, as compared with those in whom serum creatinine level had returned to the preoperative level or below (HR 1.22; 95% CI 0.64 to 2.37; Figure 2). In both the group with discharge creatinine returned to preoperative levels ($n = 84$) and the group with elevated discharge serum creatinine ($n = 40$), the risk for mortality during long-term follow-up was significantly higher compared with patients without postoperative renal function deterioration ($n = 690$; HR 1.71, 95% CI 1.17 to 3.21, and HR 2.08, 95% CI 1.35 to 5.81, respectively). Also in the group of patients without postoperative renal function deterioration ($n = 690$), no difference in mortality was found between patients who were discharged

Table 3. Independent predictive factors in logistic regression analysis for in-hospital mortality after cardiac surgery[a]

Variable	HR (95% CI)	*P* Value
Postoperative renal function deterioration	7.8 (3.1–20.0)	<0.001
Re-exploration	4.5 (1.5–13.2)	0.006
Postoperative cerebral stroke	27.7 (5.4–142.0)	<0.001
Duration of operation (min)	1.008 (1.004–1.013)	<0.001
Diabetes	3.1 (1.1–8.7)	0.032
Age (yr)	1.074 (1.017–1.133)	0.010

[a]HR, hazards ratio; CI, confidence interval.

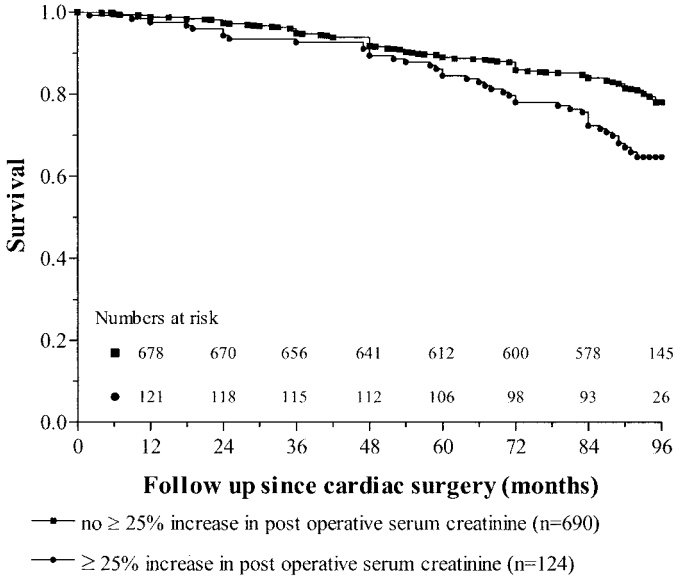

Figure 1. Kaplan-Meier survival curves for patients who were discharged alive with and without postoperative renal function deterioration.

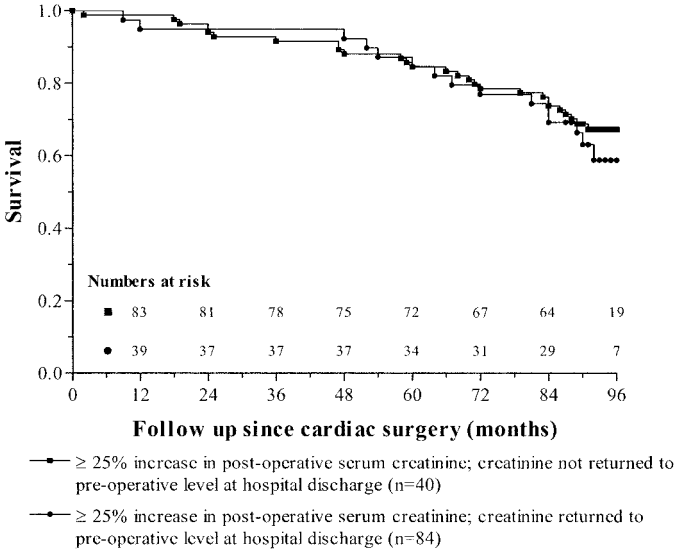

Figure 2. Kaplan-Meier survival curves for patients who had postoperative renal function deterioration and were discharged alive according to serum creatinine returned to preoperative level.

with a serum creatinine above the preoperative level and those who were discharged with a serum creatinine at or below the preoperative level (R 0.84; 95% CI 0.59 to 1.20).

Using Cox proportional hazards analysis, the association of postoperative renal function deterioration was adjusted for other possible variables associated with mortality during long-term follow up. After adjusting for the effect of age, peripheral vascular disease, operation time, and preoperative renal function estimated by the Cockroft-Gault formula (Table 4), postoperative renal function deterioration was still highly significantly associated with mortality with an HR of 1.63 (95% CI 1.15 to 2.32). Again, the association of mortality was comparable between patients who had postoperative renal deterioration and in whom discharge creatinine had improved to or below the preoperative level (HR 1.66; 95% CI 1.09 to 2.53) and those who had not returned to the preoperative level at discharge (HR 1.72; 95% CI 1.00 to 2.96). No patient developed end-stage renal failure during long-term follow-up.

Discussion

We found that postoperative renal function deterioration during the first postoperative week in cardiac surgical patients was an independent risk factor not only for in-hospital mortality but also for long-term mortality. The immediate and small decline in renal function is associated with an increased long-term mortality risk. This increased long-term mortality risk is not modified by the recovery of renal function at discharge from the hospital as evidenced by the same mortality risk in patients whose discharge creatinine had returned to preoperative value or not. Thus, perioperative renal function impairment, whether transient or not, predicts a higher long-term mortality risk in cardiac surgical patients. The association of postoperative renal dysfunction after cardiac surgery with early mortality (6–8) is in line with previous studies with a limited follow-up (6), but our study is the first to show that postoperative renal function deterioration has long-term prognostic impact as well.

The group with postoperative renal function deterioration was slightly older than the other group, but no prominent other differences in *a priori* patient factors were present, as differences in diabetes, preoperative cerebral stroke, and congestive heart failure were of only borderline significance. The main differences between the groups point toward a more serious perioperative course, both regarding severity and duration of operation and CPB as such, as well as the incidence and severity of various com-

Table 4. Independent predictive factors in Cox proportional hazards analysis for long-term mortality after cardiac surgery

Variable	HR (95% CI)	*P* Value
Postoperative renal function deterioration	1.63 (1.15–2.32)	0.006
Peripheral vascular disease	1.75 (1.18–2.59)	0.005
Preoperative creatinine clearance	0.99 (0.98–1.0)	0.005
Duration of operation (min)	1.004 (1.002–1.006)	0.001
Age (yr)	1.06 (1.04–1.09)	<0.001

plications, *e.g.*, re-exploration, IABP, and low output syndrome. These risk factors for renal function deterioration in our study are in line with other studies (9). Thus, patients with renal function deterioration have a more complicated perioperative course, associated with a higher in-hospital mortality. The perioperative complications, in particular those with impact on hemodynamic stability, may well have played a causal role in the renal function deterioration. Previous studies suggested that preoperative renal function impairment is a risk factor for postoperative renal function deterioration and mortality after cardiac surgery (1,3). In our group we did not find such an association between preoperative renal function and postoperative renal function deterioration. This finding may be due to patient selection, definition used of postoperative renal function deterioration, and perioperative patient treatment.

The incidence of postoperative renal function deterioration in our study was 17.2%, which is in line with data by Ryckwaert *et al.* (10). Of note, the criteria used for renal function deterioration can affect the reported incidence of renal function deterioration. Some studies use the change in creatinine from baseline (3) whereas others use the absolute postoperative creatinine value plus the change in creatinine (1). We defined renal function deterioration as a rise in serum creatinine of at least 25% from baseline in the first postoperative week, representing a fall of at least 20% in GFR (10). Considering the increasing recognition of the prognostic impact of postoperative renal dysfunction (1,3,9–11), future studies on this issue are needed, and these may well benefit from consensus on the criteria for postoperative renal dysfunction (12). Nevertheless, so far, despite the use of different criteria, remarkably similar results were reported with respect to in-hospital morbidity and mortality (1,3,10).

In our study, the in-hospital mortality rate was 3.4%, which is comparable to the mortality rate of 2.5 and 4.3% reported by others (7,8). In our group with renal function deterioration, the hospital mortality rate was 14.5%. Abrahamov *et al.* (9) reported a mortality rate of 30% during the first postoperative month in the renal function deterioration group. In our small group of patients who required dialysis, mortality was extremely high (83.3%). Similarly, Osterman *et al.* (13) and Chertow *et al.* (6) reported a mortality rate of 53.8 and 63.7%, respectively, for cardiac surgical patients with acute renal failure that required dialysis. Risk factors for in-hospital mortality other than renal function deterioration in our study were age, diabetes, re-exploration, postoperative stroke, and duration of operation, which are in line with other studies that found postoperative renal dysfunction (9,14,15) and cerebral stroke after cardiac surgery to predict hospital mortality (15,16). The stay in the ICU for our patients with postoperative renal function deterioration was fourfold that in patients without postoperative renal function deterioration, indicating increased hospital resources utilization, which is in accordance with recent data by Mangano *et al.* (1). Taken together, the clinical course in our population seems to be in line with that in other groups.

The main finding of our study is the difference in long-term mortality between patients with and without postoperative renal function deterioration. This analysis was performed for patients who were discharged alive. Thus, it reflects true long-term risk, rather than a lasting difference between groups elicited by differences in early risk, which underlines the impact of our observation. We have no data on cause of death, so our analysis applies only to all-cause mortality; further exploration of the underlying mechanisms and possible strategies for intervention would benefit from more detailed data on cause of death.

In all patients, long-term mortality was associated with preoperative creatinine clearance. The long-term prognostic impact of preoperative renal function is in line with recent studies showing that renal function impairment—even if mild—is an independent risk factor for cardiovascular and overall mortality, in several populations with cardiovascular disease (17–19). Accordingly, if postoperative renal function deterioration would lead to a persistent loss of renal function, then the resulting renal function impairment could account for the increased risk. However, this does not seem to apply to our data, as the increased risk was similarly present in patients in whom the renal function deterioration was transient, as evidenced by a return of serum creatinine to baseline.

Which mechanisms could be involved in the increased long-term risk in patients with renal function deterioration? First, renal function deterioration might reflect the more complicated perioperative course and the consequent more severe insults on the patient's condition. Postoperative renal function deterioration was associated with poor cardiovascular performance as indicated by low cardiac output state and increased need for intra-aortic balloon pump support. These postoperative events of hemodynamic instability and poor cardiac performance may further compromise renal perfusion and probably enhance the effect of renal ischemic insults that occur during CPB (20,21). If the severity of the insult would explain the impact on mortality, then one would expect that the difference in prognosis becomes manifest already from the start, whereas in fact the differences in mortality become manifest only after 4 to 5 yr of follow-up. However, selection of the patients who were eligible for long-term follow-up, as a result of the difference in in-hospital

mortality, may account for this. Second, the renal function deterioration might reflect the overall vulnerability of the patient who is faced with the challenge of complicated surgery. Here, the same considerations on time course and the potential impact of selection apply. Finally, it is logical to assume that a combination of both factors is involved.

We conclude that not only short-term mortality but also long-term mortality is enhanced in cardiac surgery patients with postoperative renal function deterioration. Thus, postoperative renal function deterioration identifies patients who are at an increased long-term risk—which could serve to identify patients who require specific preventive measures during follow-up (1,3). Preferably, however, high-risk patients should be identified before operation, as this might allow prevention or amelioration of renal function deterioration by adaptation of the treatment regimen. Several risk factors identified in the present study (age, IABP, emergency operation, and type of procure) may be useful to that purpose. Prospective studies will have to elucidate whether preventive measures—either adaptation of surgical or anesthetic procedures or specific intervention aimed at renal function preservation—will succeed in preventing postoperative renal function deterioration in cardiac surgery patients and, moreover, whether this will have an impact on short-term and long-term morbidity and mortality.

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See related editorial, "Acute Renal Failure and Cardiac Surgery: Marching in Place or Moving Ahead?" on pages 12–14.